NUTRITIONAL EDEMA IN THE DOG

II. Hypoalbuminemia and the Augmentation of Tissue Fluid

By A. A. WEECH, M.D., E. GOETTSCH, M.D., and E. B. REEVES

(From the Department of Diseases of Children of Columbia University College of Physicians and Surgeons, New York)

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Edema in the human being is known to exhibit a variety of manifestations. The regions prone to greatest swelling are not the same in all patients, and in the same patient the swelling often shifts from day to day and sometimes even from hour to hour. In some individuals with marked subcutaneous dropsy effusion into the serous cavities fails to occur or at least does not express itself clinically, whereas in others ascites is marked and edema of the subcutaneous tissues slight or absent. Finally diuresis and loss of edema may occur spontaneously and when no provoking cause isapparent. Because these phenomena and others which characterize edema in the human being have been observed in the dog, because in the dog the events preceding the development of symptoms are capable of being controlled, and because investigators elsewhere may wish to utilize the experimentally induced edema to study other problems, it appears worth while to describe from the symptomatic standpoint the development and course of edema in the group of dogs discussed in the first paper of this series (1). It is evident that caution is necessary in interpreting vagaries of symptomatic expression as due to identical causes in the dog and in man; nevertheless, the very similarity of the vagaries lends support to the belief that the motivating forces are similar in the two species.

Characteristics of the Edema

When dogs are maintained on the protein-deficient diet which was described in the first paper of this series (1) it is generally observed after several weeks that the tissues of the abdominal wall, groin, and extremities have become fuller. At this stage normal body symmetry is not disturbed and pitting edema is not demonstrable. When true edema does appear after maintenance on the diet for from 1 to 3 months, the development is often sudden and always at a rate disproportionately rapid in relation to that of the previous pre-edematous fullness. The first edema is usually inconstant. It is often present in the afternoon after the animal has stood through the day and absent the following morning after a night in the recumbent posture. With each reappearance the symptom tends to become more marked and daily fluctuations in degree become less striking. With a few animals there has been a noteworthy tendency toward spontaneous and periodic loss of edema. With these animals the symptom has appeared and developed progressively for a week or 10 days and then suddenly, and in association with diuresis, vanished. The subsequent course has been marked by further edema and periodic diuresis. The first edema does not involve all of the body nor all four extremities either equally or simultaneously. Among twenty-two animals the first edema involved only one extremity eleven times, it was present in two extremities seven times, in three extremities once, and in all four extremities three times. It appeared first in one or both hind legs fifteen times and in one or both fore legs three times. That the hind legs are more susceptible than the fore legs is undoubtedly due to the presence of relatively loose subcutaneous tissue about the Achilles tendons and it is here that the earliest signs are generally seen. Edema of the fore legs has always appeared first over the dorsa of the feet and in this region both front and hind legs seem to be equally susceptible. As the process progresses all four extremities usually become involved in the dropsy. Among twelve dogs in which the edema began in the hind legs, involvement of the fore legs had appeared within 3 to 14 (average 7) days. In two instances the fore legs remained free of edema even after the process had extended to otherwise generalized anasarca with massive ascites. That the fore legs are usually involved sooner or later has been mentioned specifically because in our experience these extremities have been spared in the acute edema which follows plasmapheresis. With further passage of time the edema tends to become more and more massive, the toes become swollen and spread apart, the swelling extends upwards to involve the extremities through their entire length, and finally bag-like sacks of edematous tissue, sometimes resembling mammary glands, may be seen hanging from the chest and abdominal wall. In several instances edema of the scrotum has been massive, now and again the face and eyelids have appeared swollen, and in one case there was marked chemosis of the bulbar conjunctivae. Ascites, which may or may not be present, will be discussed presently.

The experimentalist who plans to study this form of edema may wish to know whether all animals which are maintained on the diet develop the symptom, the time required for its appearance, and the time during

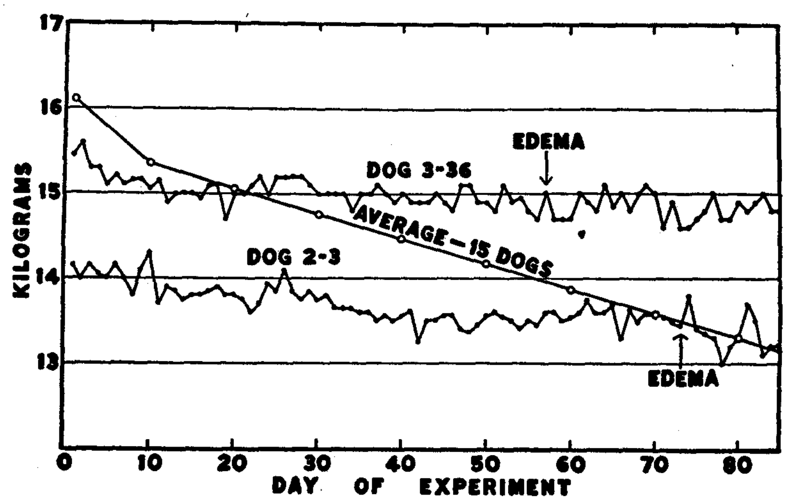

CHART 1. Behavior of body weight during maintenance on low protein diet.

which observation and study are possible. To date twenty-eight dogs have been started on the diet and of these twenty-two developed edema. Of the remaining six experiments five were terminated prematurely, three times because the animals contracted distemper and twice because of anorexia with refusal to eat the diet. In a single instance only edema had not developed after a hundred days of maintenance on the diet and the animal, which had developed severe jaundice, was sacrificed. In this case, however, the serum albumin, although it had declined progressively, had not fallen to a level which was reached with many other dogs before edema appeared. Among twenty dogs whose course was not complicated the edema appeared in from 35 to 100 days or in an average of 60 ± 15 (S. D.) days. One might expect that the interval could be shortened by initial periods of plasmapheresis. In two instances in which this was tried, the attempt was not successful and edema developed after 53 and 60 days, respectively. The period of survival after the appearance of edema or more properly the time over which edema has persisted and been available for study cannot be evaluated accurately from our data because the course has been complicated by various experimental procedures which have included transfusions, diuretics, and changes in diet. Some of the animals have been sacrificed and some have been allowed to recover. With these limitations in mind it may be stated that edema was present in the twenty-two dogs from 1 to 77 days or for an average time of 27 ± 17 (S. D.) days. In individual animals it is possible with experience to estimate the period of survival more closely from consideration of the physical state, the appetite, and the serum protein concentrations. Experimental studies can be planned accordingly.

Behavior of the Weight Curve

In the majority of experiments the animals have exhibited a progressive decline in weight during the period of maintenance on the diet, the loss being greatest during the first week or 10 days and thereafter more gradual. The extent of the loss can be gauged from Chart 1 in which has been plotted the average weight curve of fifteen dogs which received the diet containing cod liver oil. Inasmuch as the food consumed by most of the dogs was deficient both in nitrogen and total calories, we have thought the loss of weight to be due to destruction both of body protein, *i.e.* muscle, and of body fat. The destruction of tissue protein is proved by the consistently negative nitrogen balance (1). That loss of body fat has also contributed to the decline in weight is suggested by the repeated observation with individual animals of a rapid loss in weight following voluntary reduction in the quantity of diet consumed and by the fact already reported that such reduction does not greatly affect the magnitude of the nitrogen loss. During periods when the appetite has remained normal and the total diet has been consumed, we have been impressed again and again by the absence of conspicuous loss of weight. In an experiment which was described in an earlier paper (2) observations extending through 42 days before edema had developed revealed a loss in weight of 620 gm. During the same period studies of the nitrogen balance indicated the destruction of 1059 gm. of muscle. In two additional experiments, the details of which are given in Table I, studies of nitrogen balance again showed that the animals lost less weight than would have been expected from the magnitude of the nitrogen loss. With two more animals, whose weight curves are shown in Chart 1, the appetite remained good and the loss in weight was so slight as to suggest at once a discrepancy with nitrogen loss even though the latter was not measured. It may be mentioned that the serum proteins of these animals declined as rapidly as in other experiments and that no correlation has been found between the rapidity of the fall in serum albumin and either the weight loss or the quantity of food consumed. Under the circumstances, we have interpreted the discrepancy between weight loss calculated from nitrogen balance and that actually observed as due to a continual retention of water during the period of

TABLE I

Comparison between Observed Loss of Weight and Loss of Weight Calculated from Negative Nitrogen Balance

Dog 8-4*a* Initial weight 15.68 kg.			Dog 8-06 Initial weight 15.45 kg.		
Metabolism period	Calculated weight loss	Observed weight loss	Metabolism period	Calculated weight loss	Observed weight loss
days	*gm.*	*gm.*	*days*	*gm.*	*gm.*
1–6	338	380	1–7	328	320
7–13	350	480	8–14	283	240
14–19	270	20	15–21	265	180
20–25	153	190	22–28	259	−120
26–32	217	140	29–35	265	20
33–39	200	−250	36–42	171	80
40–46	226	150	43–49	253	290
47–53	185	90	50–56	250	410
Total......	1939	1200	Total.......	2074	1420
Edema appeared on 65th day			Edema appeared on 92nd day		

pre-edema. It is realized that such a discrepancy would also occur if fat were being stored while tissue protein was undergoing destruction and it is true that many of our animals have shown at autopsy abnormal infiltrations of fat in the liver. Nevertheless, the panniculus and omental fat have never been more abundant than in normal animals and indeed these stores have usually appeared to be depleted to such a degree as to suggest a considerable loss rather than an increase in total body fat. Furthermore, physical signs of pre-edema which were described in the last section favor the interpretation that has been given. It is interesting as well as confirmatory that a similar observation was made by Bischoff and Voit (3) as long ago as 1860. These investigators maintained a dog exclusively on bread for a period of 41 days. They found that although the nitrogen loss corresponded to 3,717 gm. of muscle, the animal lost only 531 gm. in weight, and concluded that water retention must have taken place. In other experiments in which cats were fed exclusively with bread they found the water content of the muscles and brain to be from 3 to 4 per cent higher than in control cats fed with mixed food.

In the majority of experiments the development of edema was not preceded by definite fluctuation in the weight curve. In a previous publication (2) this fact was noted and interpreted to mean that the state of pre-edema gradually merged with that of true edema in such a way that sudden accumulation of fluid in the tissues did not occur. Subsequent observations have shown that this interpretation was at least partly in error. For reasons given in the preceding paragraph we are still convinced that fluid does accumulate in the tissues for some time preceding the appearance of palpable edema; nevertheless, from inspection alone it has become clear that the development of palpable edema represents a sudden local increase in the rate of accumulation.[1] It seems likely that the amount of fluid required to

[1] Because they believed that the onset of edema was not associated with a sudden increase in the rate of accumulation of fluid in the tissues, Weech, Snelling, and Goettsch (2) suggested that the term "correlation level" rather than "critical level" be used to refer to serum protein concentrations below which edema is usually present and above which it is not. From the above discussion it appears that the reason for the suggestion was not valid and the expression "correlation level" will not be used in this report.

produce dependent edema in one or two extremities of the dog is too small to produce an obvious change in body weight. It may be that the phenomenon is associated with an internal shift in the distribution of fluid already in the body inasmuch as studies of salt metabolism have failed to indicate a significant retention of either sodium or chloride at this time. In either case the fact that palpable edema does not develop in all regions of the body at the same time but rather by successive steps over a period of several weeks, tends to obscure whatever effect there might be on the weight curve.

In one circumstance, however, the development of edema may be associated with a marked rise in body weight; namely, when fluid is accumulating in the peritoneal cavity. In one instance the rise began before subcutaneous edema had appeared; in six other instances it followed within 1 to 15 days after palpable edema had first been demonstrated. When ascites is fully developed the total gain in weight is sometimes enormous. Dog 1-91 showed an increase from 9.85 to 12.95 kilos over a period of 13 days, the increment of 3.10 kilos representing 31.5 per cent of the previous body weight.

Edema and the Serum Proteins

The concentrations of albumin, globulin, and total protein in the serum at the time of the first appearance of palpable edema are shown in Table II for twenty-one animals. With albumin all values are below the range of normal variation and are distributed between 1.04 and 2.17 gm. per cent. The globulin values are normal so that the reduction in total protein obviously results from the albumin deficits alone. However, although the total protein is usually reduced below normal levels, concentrations within the range of normal are not infrequent, and a satisfactory correlation cannot be drawn between it and edema. A positive correlation with edema exists for the albumin fraction only but even in the case of albumin the variations encountered among different animals are fairly wide. To investigate the possibility of defining the critical level for edema in less variable terms, we have calculated both by the formula of Wells and his associates (4) and by the method of Govaerts (5) the colloid osmotic pressure of the several sera. The results are included in Table II. The coefficients of variation for either of the osmotic pressure tabulations and for albumin alone do not differ significantly. Evidently the critical levels vary just as widely when expressed in calculated units of osmotic pressure as in grams per cent of albumin. Unfortunately,

TABLE II

Serum Protein Concentrations Associated with First Appearance of Edema

Dog No.	Albumin per 100 cc.	Globulin per 100 cc.	Total protein per 100 cc.	Colloid osmotic pressure	
				Wells	Govaerts
	gm.	*gm.*	*gm.*	*mm.* H_2O	*mm.* H_2O
8-4*a*	1.04	1.93	2.97	82	116
2-06	1.04	2.94	3.98	110	136
1-91	1.15	2.48	3.63	102	135
8-4*b*	1.29	2.48	3.77	109	146
8-4*c*	1.29	3.32	4.61	134	162
8-38	1.30	2.61	3.91	114	149
8-06	1.35	2.99	4.34	127	160
3-87	1.37	2.13	3.50	103	145
2-07	1.38	2.55	3.93	116	154
5	1.40	2.00	3.40	101	145
1-90	1.47	2.90	4.37	131	167
2-3	1.52	1.90	3.42	104	152
4-49	1.59	4.06	5.65	174	199
5-89	1.63	2.80	4.43	137	178
3-36	1.75	3.12	4.87	155	193
4-30	1.79	1.97	3.76	120	173
2-93	1.79	3.22	5.01	160	198
5-97	1.85	3.16	5.01	162	201
1-89	1.95	2.51	4.46	147	196
2-05	1.95	3.53	5.48	180	216
5-65	2.17	2.70	4.87	167	216
Average......	1.53	2.73	4.26	130	168
S.D.*........	0.31	0.56	0.70	27.1	27.9
C.V.†........	19.9	20.4	16.5	20.8	16.6

* S.D. = standard deviation of average.
† C.V. = coefficient of variation.

the calculation depends upon formulae which were derived from measurements of human serum. Analogous formulae for canine serum do not exist. It is possible, therefore, that a narrower range of variation in the critical levels may be demonstrated when direct measurements of the osmotic pressure have been made. At the present time, however, it is reasonable to assume that the levels actually are quite variable and to suspect the existence of other factors of importance in determining the exact time of appearance of the first edema. That other factors must exist is apparent when it is recalled that a considerable interval may intervene between the onset of edema in the fore legs and in the hind legs in the same experiment, a circumstance which means that different critical levels might be recorded for the first appearance of edema in different regions of the same animal.

From the standpoint of the investigator who wishes to utilize the method of diet for producing experimental edema, it is apparent that in general the time (T) which must elapse before edema appears will be short when the edema develops in association with a high concentration of serum albumin and relatively long when the critical level (A_e) for the individual animal is low. The extremes of our experience show that Dog 5-65 developed edema after 40 days of maintenance on the diet and in association with a serum albumin concentration of 2.17 gm. per cent, and that in contrast 100 days had elapsed and the serum albumin had fallen to 1.04 gm. per cent before Dog 2-06 became edematous. One would also expect to find some degree of correlation between the albumin concentration at the start of the experiment (A_s) and T; that is, it should require a greater time to deplete the albumin to edema levels when the initial concentration is high. Actually a positive correlation has been demonstrated between T and A_s but an analysis of our data by the method of partial correlation indicates that A_e was approximately twice as important as A_s in determining T. On the average, lowering the initial level of albumin by 1 per cent decreased by 11 days the time required for producing edema, whereas lowering the critical level by 1 per cent increased the time by 23 days. However, the coefficient of multiple correlation, which measures the combined effect of A_s and A_e on T was only 0.49 and it is evident that other unknown factors were operative in determining T. Among them we have considered the possible influence of the original nutritional state, the amount of weight lost during the experiment, and the quantity of food ingested, but have failed to demonstrate that importance can be attached to these factors.

When the serum albumin is raised by appropriate measures the edema will disappear. When the rise follows interruption of the low protein diet and return to adequate feeding, the elimination of edema usually occurs in association with concentrations of serum albumin within the same range as that described for the first development of edema. Now and again, however, conditions have been encountered under which the edema has not disappeared until the albumin had regenerated considerably above this range. An experiment which exemplifies this happening was illustrated in Chart 5 of the first paper of this series (1). In the experiment Dog 3-36, which developed edema in association with an albumin concentration of 1.75 gm. per cent, did not become free of edema until an adequate diet had been offered for 19 days and until the level of albumin had risen to 2.75 gm. per cent. In two instances in which discrepancies of this magnitude existed between the critical levels for the appearance and disappearance of edema, the dropsy had existed for more than a month when the change in diet was instituted. In other experiments in which the albumin concentration has been raised abruptly by means of transfusion we have not always observed an immediate disappearance of edema with concentrations above the critical level.

Protein Content of Edema Fluids

Thirty samples of edema fluid from the subcutaneous tissue of the extremities of fourteen dogs have been analyzed for total protein. The results appear in Table III. The range of protein concentration was from 0.02 to 0.72 gm. per cent. The average protein level was 0.230 gm. per cent and the median level was 0.165 gm. per cent. The discrepancy between the average and median values indicates the absence of normal frequency distribution in the results. Actually in five instances only, or one-sixth of the total number, was the concentration greater than 0.35 gm. per cent. Table III also shows the contemporaneous protein content of the serum and the number of days which had elapsed after the onset of edema before the fluids were collected. With neither of these factors has it been possible to demonstrate a significant positive correlation with the amount of protein in the edema fluid, a fact which is roughly apparent from the manner of arrangement of the data in the table. Apparently, some other factor, presumably the permeability of the capillary, is of such importance in determining the protein in edema fluid as to obscure the effect of variations in serum protein and it would seem that the circulation of edema fluid through the lymphatics is sufficient to offset the gradual increase in protein content which would be expected if the fluid remained dormant in the tissues.

TABLE III

Comparative Data Which Show Lack of Relationship between the Protein of Edema Fluid and the Protein of Serum or the Duration of Edema. Data Arranged in Ascending Order of the Protein Content of Edema Fluid

Dog No.	Duration of edema	Protein of serum per 100 cc.	Protein of edema fluid per 100 cc.	Dog No.	Duration of edema	Protein of serum per 100 cc.	Protein of edema fluid per 100 cc.
	days	*gm.*	*gm.*		*days*	*gm.*	*gm.*
Subcutaneous edema fluid				Subcutaneous edema fluid			
8-4*b*	14	2.88	0.02	3-36	29	4.64	0.23
8-4*b*	14	2.88	0.04	5	2	3.24	0.23
8-06	7	3.53	0.06	5-89	17	3.76	0.28
8-06	7	3.53	0.07	5-97	9	4.68	0.28
8-38	16	3.29	0.08	5-65	14	4.73	0.29
2-07	41	3.63	0.08	3-36	15	5.17	0.33
5-97	23	5.03	0.10	4-51	26	4.61	0.34
1-90	40	4.32	0.10	5	1	3.24	0.36
1-90	40	4.32	0.11	2-3	16	3.38	0.48
1-90	40	4.32	0.12	2-3	16	3.38	0.56
8-06	5	3.77	0.12	2-93	12	4.43	0.71
8-06	11		0.13	2-93	23	4.72	0.72
2-06	6	4.03	0.15	Ascitic fluid			
5-97	23	5.03	0.16	2-07	44	2.57	0.01
2-3	15	3.38	0.16	8-4*b*	13	2.88	0.02
2-3	15	3.38	0.17	2-07	41	3.63	0.04
5-89	18	3.69	0.21	5-97	30	4.50	0.13
3-36	22	4.69	0.22	5-89	25	3.60	0.72

The protein content of five samples of ascitic fluid is included in Table III. In four instances the level was less than 0.15 gm. per cent and in one instance greater than 0.70 gm. per cent.

Ascites

The accumulation of fluid in the peritoneal cavity in amounts sufficient to produce a noticeable increase in body weight and signs of ascites on physical examination was observed seven times in the group of twenty-two dogs which developed subcutaneous edema. Because the majority of animals did not exhibit the symptom the protocols were examined with a view to discovering provoking circumstances. The examination showed that in five instances out of the seven the first signs of ascites followed closely an abrupt increase in the amount of salt and water in the diet. On numerous other occasions, however, similar increases failed to evoke the same response. In two instances only, the ascites developed when the salt intake had been constant at a level of approximately 5 gm. daily for longer than 2 weeks. The results are at least understandable if it is supposed that a sudden increase in dietary salt produces a stress throughout the tissues which favors distention of the intercellular spaces and accumulation of fluid. If the stress is exerted when the tissues possess a reasonable reserve strength retention will not result. When the reserve is broken fluid will accumulate in the organism. In a general way it has seemed that subcutaneous tissues and peritoneal cavity react differently to the application of stress. When the stress is increased gradually and exerted constantly or repeatedly over long periods the subcutaneous tissues yield more readily than the peritoneum. When the stress is applied suddenly the reverse is true,—the subcutaneous tissues are generally resistant whereas the peritoneal cavity, once the barrier to the accumulation of fluid has been broken, does not manifest further resistance for some time and large collections can and do develop rapidly. Although a sudden stress of this nature seems to result when the salt in the diet is increased abruptly, there are undoubtedly other factors or processes capable of effecting similar shifts in the stress on the tissues.

The difference in behavior between subcutaneous tissue and peritoneal cavity is exemplified further by contrasting the form of edema which develops rapidly in plasmapheresis experiments with that produced slowly by restriction of protein in the diet. In plasmapheresis experiments ascites is invariably present whereas edema of the extremities is less intense than in nutritional experiments. If the plasmapheresis experiment is so arranged that fluid retention, although great, is limited to a period of 24 hours or less, the contrasting responses of subcutaneous tissue and peritoneal cavity are even more striking.

Such an acute retention can be obtained by maintaining the dog on a salt-free diet during the 8 or 10 days required for depleting the serum albumin below the critical level, and then administering by gavage in the course of a few hours large volumes of physiologic saline solution. The details of an experiment are presented in Table IV. Although in this instance the final abrupt rise in weight indicated that more than 2½ liters of fluid had been retained after a period of about 18 hours,

TABLE IV

Plasmapheresis Experiment

Dog 9-92.

Day of experiment	Blood exchanged by plasmapheresis	Salt addition to diet	Body weight (9 a.m.)	Remarks
	cc.	*gm.*	*kg.*	
1	350	0	14.80	Serum albumin = 3.06 gm. per cent
2	380	0	15.30	
3	420	0	15.15	
4	380	0	15.30	
5	490	0	15.55	
6	300	0	15.45	
7	520	0	15.25	
8	575, 300	22.4	15.35	Serum albumin after second exchange = 0.85 gm. per cent
9	—	—	18.00	Weight gain 2.65 kg. in 18 hrs. Subcutaneous tissue everywhere fuller. Mild edema of abdominal wall. No edema of extremities. Massive ascites; at autopsy in late afternoon 1100 cc. fluid withdrawn from peritoneal cavity. Total protein of ascitic fluid = 0.01 gm. per cent

pitting edema of the extremities did not develop and the peritoneal cavity was the only large depot which could be demonstrated easily. Of significance, however, is the fact that the subcutaneous tissue everywhere was fuller, obviously contained more fluid, but had not yielded to the point of exhibiting palpable edema. It is precisely this peculiarity of resistance to acute stress on the part of tissues which yield readiy to prolonged stress which contrasts sharply with the behavior of the peritoneal cavity.

DISCUSSION

A description of the events which attend the development of nutritional edema in the dog has been the main purpose in presenting the data contained in this paper. It is desired here merely to modify and elaborate briefly concepts, previously expressed (2), of the mechanism involved in the formation of edema. Those forces which operate on the inside of the wall of the capillary,—colloid osmotic pressure and capillary blood pressure,—have been discussed frequently in recent literature. Under conditions of rest and at times when the volume of fluid in the interstitial spaces is constant these forces must be in equilibrium with others on the outside of the capillary. The extramural forces may likewise be divided into osmotic and mechanical components. Of these, in the type of edema under consideration, the effective osmotic pressure is relatively small and discussion at this time will, therefore, be confined to the other factor, mechanical pressure in the interstitial spaces. The effect of variations in this pressure on the volume of fluid in the spaces must obviously depend on the physical properties of the connective tissue framework which encloses the spaces. If the intercellular tissue were composed of a rigid non-yielding substance it is clear that no amount of pressure could result in distention and the accumulation of edema. If the tissue were perfectly elastic, equal increments of stress would result in equal degrees of stretching and corresponding increments in the volume of interstitial fluid. Obviously the tissue spaces are neither non-yielding nor perfectly elastic. The observations described in this paper indicate that the increasing stress on the tissues, which results from the declining level of albumin in the blood, does lead to expansion of the intercellular spaces for some time prior to the appearance of edema. Consideration of the quantitative relationship between weight loss and nitrogen loss as well as physical signs of pre-edema both suggest retention during this period of moderate amounts of fluid. The development of palpable edema, however, takes place suddenly in a manner which suggests that increasing stress has finally become too great to be tolerated by the elastic strength of the tissue framework. The tissues seem to be torn apart and edema fluid accumulates rapidly throughout the area involved. For the time being the barrier to accumulation is removed and the volume of transudate is determined by the extent of the involved area, by the residual strength in surrounding tissues, and finally by back-pressure from overlying skin.

In a previous paper on the relationship between lymph flow and edema (6) it was pointed out that massage, passive movement, or voluntary motion activate the pumping mechanism of the lymphatic valves, that the activation results in removal of fluid from the tissues through the lymphatics, and that mechanical pressure in the extracapillary spaces must be lowered by the process. It is, therefore, apparent that, under normal circumstances of alternate rest and activity, pressure within the tissue spaces varies in a periodic way. The higher values which under appropriate conditions lead to separation of the spaces and the accumulation of edema occur only during rest or when physical activity is extremely reduced. The magnitude of the pressure required to accomplish this effect is not known although it is clear that the force cannot be greater than capillary blood pressure. Higher pressures by collapsing the capillaries would automatically stop the process of filtration. It is further clear that those measurements which have been attempted of pressure within the tissue spaces and in which the relation between the time of measurement and previous physical activity was not controlled (7) can have no meaning in evaluating the forces involved in edema formation.

If the concept outlined in the preceding paragraphs is correct it follows that the critical level of protein in the serum is determined by that concentration which permits the attainment in the tissue spaces of mechanical pressures great enough to break down the restraining action of the connective tissue boundaries of the spaces. Obviously such pressures can arise only when the colloid osmotic pressure of the serum has fallen below capillary blood pressure, but the effect of the fall on pressure outside the capillary is more directly the cause of edema than the disturbance of the balance between the intramural forces. Because physical activity as well as the relationship between the intracapillary forces both have an effect on pressure in the tissue spaces it is apparent that the degree of spontaneous activity exhibited by an animal will influence the exact level of the serum protein which will be regarded as critical. We have already reported the fact (6) that a previously developed edema can be eliminated by an enforced régime of activity. The reason for the elimination, however, is complicated by the fact that veins as well as lymphatics are furnished with valves and that the function of both is stimulated by muscular motion. When the veins are filled by hydrostasis with a column of blood, stimulation of their valves leads to a reduction in capillary blood pressure, and this effect will be added to that of the lymphatics in removing fluid and lowering pressure in the tissue spaces.

The concept which places primary importance on the elastic strength of the connective tissue framework of the tissue spaces in determining the site and time of appearance of edema provides a basis for understanding several of the phenomena which have been described. The singular susceptibility of the loose tissue about the Achilles tendons contrasts sharply with the resistance exhibited by the firmer tissue over the dorsa of the feet. It is unlikely that the difference in reaction can be explained by variations in capillary blood pressure for the two regions are anatomically contiguous and exposed to the same hydrostatic force. The concept allows a clear comprehension of the distinction between pre-edema and palpable edema in accordance with the discussion in a preceding paragraph. It assists in an understanding of the difference in protein levels which may be critical for the formation and disappearance of edema in the same animal. For it is conceivable that after marked edema has disturbed the integrity of the tissue spaces time must elapse and a new level of pressure conditions arise before the edema is removed. Finally there is provided a comprehensible basis for the phenomenon described in the section on ascites; namely, that a sudden fall in the colloid osmotic pressure of the serum does not have the same effectiveness on subcutaneous edema formation as a gradual decline over a number of weeks which is associated with progressive malnutrition.

SUMMARY

The manner in which edema develops in dogs maintained on a diet low in protein is described. Pre-edematous fullness of the tissues is observed for some weeks before palpable edema develops. The state of pre-edema does not merge gradually with that of true edema but rather the transition is relatively sudden. Among twenty dogs the

time required for the production of edema varied from 35 to 100 days and averaged 61 days.

With three animals in which the nitrogen metabolism was studied during the period before edema had developed, the observed loss of weight was consistently less than the theoretical loss of weight calculated from the negative nitrogen balance. Reasons are given for interpreting the discrepancy as evidence of increasing retention of fluid during the stage of pre-edema. In general the weight curve does not rise during the transition from pre-edema to edema. However, the weight does increase rapidly when fluid is accumulating in the peritoneal cavity.

The level of serum albumin which is critical for the development of edema varied between 1.04 and 2.17 gm. per cent. The range is sufficiently wide to suggest the existence of other factors of importance in determining the exact time of appearance of edema. During the phase of recovery the level of albumin which is critical for the disappearance of edema may be appreciably higher than the level which was critical for the formation of edema.

Among thirty samples of edema fluid the protein concentration was from 0.02 to 0.72 gm. per cent. The average protein level was 0.230 and the median level 0.165 gm. per cent. A positive correlation is not demonstrable between the duration of edema and the protein content of edema fluid.

A difference in behavior toward fluid retention between subcutaneous tissue and peritoneal cavity is pointed out. Subcutaneous tissue is more resistant to acute stress and less resistant to prolonged or repeated stress than the peritoneal cavity.

The rôle of tissue pressure in the etiology of edema is discussed. It is suggested that the critical level of protein in the serum is the concentration which permits the attainment in the tissue spaces of mechanical pressure great enough to break down the restraining action of the connective tissue boundaries of the spaces.

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