5-1-1941

Present concepts of the mechanism of edema

Jerome J. Hollister
University of Nebraska Medical Center

The Present Concepts of the Mechanism of Edema

by

William Gray Hollister

Announcement

Senior Thesis Presented to the College of Medicine, University of Nebraska, Omaha

1941

Table of Contents

Introduction and Definition

"Ah! Make the most of what we yet may spend
Before we too into the dust descend."
Rubaiyat of Omar Khayyam

Too long have prophets, psalmists, and cynics proclaimed man's descent "into the dust," for if the truth were spoken and man were to return to his elements, he would resolve into an ignominious puddle of mineral water! But a charitable mind can understand both how the ancients, and many moderns too, can fail to comprehend the idea of a solid structure, such as the human body, consisting of seventy percent water by weight. Indeed it can be doubted that science itself knows much of the real story of body water.

Approximately twenty-five percent of this mass of water is extracellular fluid, one-fourth of which is within the vascular channels and three-fourths of which is extravascular. Physiologically there is balance between the vascular and extravascular fractions of the free body water. But in certain pathological situations this balance can be disrupted. If the balance is upset in favor of the accumulation of fluid outside the blood vessels, edema is said to result.

Edema has been defined by Achard (1) as "an effusion of serous fluid into the serous cavities and spaces of connective tissue." To follow our analogy of the balance of these two free components of the body water, we would more exactly say that edema is the excessive effusion of

serous fluid into the serous cavities and spaces of connective tissue.

Disturbances of water balance of the edematous type can occur in both inflammatory and non-inflammatory pathologies. Fully aware that at all points the line of demarcation between these two types of edemas is not well defined, this paper wishes to concern itself with the so-called "non-infla matory" edemas. These include the edemas of heart disease, nephritis, nephrosis, malnutrition as well as the lymphatic obstruction, hereditary (Milroy's disease), and angioneurotic types. From among these our attention will be centered upon the mechanisms concerned in the cardiac, renal and malnutritional types.

History

In order to gain a clear concept of the history of the works designed to uncover the mechanism of edema, two approaches will be used. First, there will be a "Historical Survey" in order that the progress of thought, and the influence of personalities on the problem can be depicted in proper historical perspective. Secondly, there will be a "History of Specific Investigations," a relatively detailed series of accounts on each of the individual factors in edema, in order that the continuity of thought, in each of these various lines of research, can be portrayed in its logical sequence.

Historical Survey

Concern over the cause of edema dates back into the Hellenic Period, when Erasistratus (310-250 B. C.) first proposed that dropsy arose from a disturbance of the liver. Galen (131-201 A. D.) later concurred in this theory, but felt that edema was fundamentally a disturbance of blood formation. Since he believed that blood formation was a liver function, it was natural for him to point out the liver as the site of this dysfunction. We cannot discuss the history of edema without also mentioning two other men whose anatomical discoveries made possible the contributions of those who followed: Harvey's discovery of the

circulation of the blood, and Pinel's discovery of the circulation of the lymph. In fact, Pinel himself suggested that edema was a disorder of the lymph circulation.(1)

Although others before him had reported the association of edema with various diseases, Bright (2) in 1836 was the first to explain the mechanism of an edema. In his reknowned work upon the renal pathology that bears his name, he noted that the fall of serum protein was coincident with the loss of protein in the urine. From this clue, he deduced that the water content of the blood, hydremia, had increased, lowering the viscosity of the blood and so lowering its concentration that it was able to filter through the walls of small blood vessels. By this mechanism he explained both the albuminuria and the edema, and his proposal became known as the Hydremic Theory of Edema.

Another basic factor in edema was proposed by Senator (3). Basing his work on previous knowledge that venous stasis and occlusion leads to loss of fluid into the tissues, he connected the fall of serum proteins in heart and renal edema cases to the possibility that the capillaries were capable of becoming permeable. He thus explained edema as a loss of fluid and serum protein into the tissue due to some toxic agent increasing the permeability of the capillary. To this theory of the toxic

cause of capillary permeability Reese (4) in 1850 added the thought that the rise of these toxins in renal disease was due to the failure on the part of the kidney to eliminate injurious substances.

Both of the theories born in the first half of the nineteenth century, proposed the passage or filtration of fluid through the c apillary wall, one because the blood was so diluted and thinned that it could pass through and the other because the capillary became more adaptable to the passage of fluid. The second half of the century early contributed still another factor to be considered. Taking Bright's ideas, Johnson (5) in 1852 and later Bartels (6) and Stewart (7), combined their clinical observations of high blood pressure with the concept of hydremia and concluded that this increased pressure was driving the excess intravascular fluid into the tissues.

Even Virchow (8), the great pathologist, entered the field. Concerned as he was with the changes of tissue in pathology, he offered an opinion in 1854 that alterations within the tissues themselves were responsible for drawing water into the tissues. Unfortunately his opinion did not find attention until the end of the century.

The eighteen seven ties introduced two more lines of thought on this problem. 1877 found Cohnheim and Lichtheim's (9) report on the production of edema by a great intake of salt and water and the consequent conclusion

that salt was an etiological factor in edema. In the year following, in a bout of pure eclecticism, Bernard (10) proposed that the whole problem was a matter of central nervous system control. Another line of inquiry started early but unheralded was Landerer's (11) experiments in 1884 to ascertain the pressures to which the tissue fluid rose within the tissues in edema.

The theory that edema might arise from a disturbance of lymph circulation had been heralded by Pinel (1), the discoverer of lymph circulation, but in 1891 Heidenhain (12) definitely erected the theory that edema was due to a hypersecretion of the lymph. In the years that followed he searched for the point of lymph secretion but was unsuccessful. As the controversy over the formation of lymph by Magnus, Karangi, Starling, and Heidenhaim finally led to the decision that lymph was born of blood by mechanical transudation, this above concept of edema vanished(13). Also in 1891 Csatary (14) first differentiated that the loss of protein in renal edemas was mainly serum albumin, a thread of information that did not rise to prominence until 1925. This finding, as well as others, suffered relative intellectual burial, under the wave of enthusiasm that greeted the well known contribution of Starling in 1896.

Starling (15) hypothesized a balance of forces operating continuously to allow intravascular fluid to be ex-

changed with tissue fluids at the capillary. He visualized the normal hydrostatic head of pressure forcing fluid out through the walls of a standardly permeable capillary. Opposed to this force was a lesser force, the osmotic pressure of the colloidal protein, constituents of the blood, exerting a force through the semipermeable membrane of the capillary wall to bring water back into the capillary. Knowing the hydrostatic pressure fell considerably below that of the osmotic pressure, during the course of passing through the narrow constricted capillary, he proposed: That during the passage of blood through the arterial half of the capillary, where the hydrostatic pressure exceeded that of the blood colloids, transudation of fluid into the tissue spaces took place; and that in the venous half of the capillary, where the hydrostatic pressure fell below the osmotic pressure of the blood proteins, fluid filtered back into the vascular channels.

Upon the basis of this normal mechanism, Starling explained edema in this fashion: "Either a lowered osmotic pressure, as would occur in a protein loss like albuminuria, or a rise in the hydrostatic head of pressure, as in heart pathology, would upset the balance in favor of filtration and thus cause edema." This theory was widely accepted and its acceptance conferred favor on the concepts of an

inert non-factorial capillary and upon the role of hydrostatic pressure. It also should be noted that Starling mentioned that the pressure built up in the tissues was a factor in the return of fluids to the capillary. Also in 1896 Winter (16) revived the theory of the salt etiology of edema, propounded by Cohnheim and Lichtheim in 1877. He proved an interchange of chloride between blood and tissue fluid and with Reichel (17) provoked a series of studies which showed a definite relation between salt intake and the intensity of edema in the clinical course. Out of their work came the foundation for the researches of Achard and Widal in 1903.

Before the century ended one more prominent contribution was made. Taking up the idea of tissue change first stated by Virchow in 1852, J. Loeb (18) in 1898 proposed that an increase in the osmotic pressure of the cell constituents was the basis of edema. But when confronted by criticism and demands for clinical confirmation, Loeb abandoned his theory and the possibility of tissue change lay dormant until the era of Fischer.

The young years of the twentieth century bore fruit in the investigations as to the role of sodium chloride in edema. Widal (19) in 1903 came out definitely with a theory proclaiming failure of the kidney to eliminate salt and the consequent salt retention as the cause of edema. He himself and subsequent investigators produced proof of

abnormal amounts of salt retained in the tissue, but those repeating his experiments could not agree that the failure of the kidney to excrete salt was the prime cause. It is interesting to note how the confirmation swung instead to a work by D. Achard (20) who found wide fluctuations of blood chlorides with and without edema, leading him to believe that the majority of the salt poured into an individual and not lost by way of the urine must be deviated to the tissues. He therefore exonerated the kidney from being a factor in salt edema.

The next outstanding set of proposals were those of Fischer (21) in 1910. Taking up the clues of Loeb and Virchow, he drew an analogy between the hydrophilic properties of colloids and the drawing of water into tissue. Colloids, whenever the ph is lowered or raised beyond ph 7 take up water. Accordingly the tissue of the body, which are colloidal in character, naturally become edematous when subjected to the acidification of tissue, catabolism or of insufficient circulation.

The year 1918 saw the rise of concern over the role of edema fluid or tissue fluids, in dropsy. In an effort to see if the tissue fluid was capable of exerting osmotic pressure Volhard (22) began analyzing the fluid and found it only a physiological salt solution with a small amount of protein. The researches that followed noted a striking similarity in specific gravity, content, color, and

physical properties of all edema fluids, a sign heartening those attempting to visualize a common basic mechanism for all edemas. During the same year Kollert and Finger (23), basing their conclusion on plentiful reports of the existence of a hypercholesteremia with renal edema, theorized that edema was the result of the kidney's inability to eliminate cholesterol.

During the interim since Starling's publication of his hydrostatic-osmotic pressure balance upset theory of edema in 1896, many workers confirmed the existence of low blood protein levels in the various edemas. Into the midst of this dominant line of thought came a report by Govaerts (24) that the specific osmotic pressure, the amount per gram of blood protein, was different in the hypertensive individual than in the patient with cardiac failure. Again the discovery was too early for the psychology of the moment, and was briefly passed over as a mere change in concentration of blood plasma. Later recapitulation and clinical observation caused this explanation to be re-examined.

By 1921, we had had seven principle theories in the literature. The hydremia theory of Bright; the tissue change proposals of Virchow, Loeb, and Fischer; the salt retention theory of Achard; the hydrostatic-osmotic pressure upset theory of Starling; the Kollert and Finger hypercholesteremia theory of edema; Senator's theory of

increased capillary permeability; and Heidenhaim's theory of hypersecretion of lymph. Besides these theories, speculation and observations on the role of hydrostatic pressure, edema fluid, tissue fluid, tissue pressure, and the central nervous system had entered the literature. By this time the hydremia theory of Bright was in the decline as Bock (25) in 1921 and others later found no evidence of the change of plasma volume in nephritis, and Heidenhaim's theory had fallen by the wayside when the lymph was found to be an end product of capillary filtration. In a review of 1922 Epstein (26) summarized by declaring that capillary damage had been demonstrated by experimenters but that we had no information that increased permeability was operable in edema. He felt that the major factor in edema was still the colloid osmotic pressure.

In the same year two lines of thought on the permeability problem became strongly developed: One, that there were substances of a non-toxic nature that altered permeability; and the other, that capillary permeability was mechanical and subject to intra-capillary pressure. Krogh, (27) who introduced the latter theory, proved that a capillary can not hinder or accelerate the absorption of sodium chloride and water. To him, transudation was a purely mechanical process, the amount dependent on the force brought into play. The other school established by Hamburger (28), found that the electrolyte content of the

blood changed the amount of transudation. He and his followers proposed a substance capable of increasing permeability of cells and lowering surface tension of the blood in the blood of an edema patient.

An advance in the evaluation of the role of salt in edema came in 1923 when L. Loeb (29) confirmed the prerenal deviation hypothesis of Achard and proved by using various salts; potassi um chloride, calcium chloride, and sodium chloride, that only the sodium ion was the functional one in salt edema.

The year 1924 contributed the observations of Schade and Clausen (30). After a long series of experiments they concluded that under the pathology of edema the tissue fluids did not exert a significant osmotic pressure. They also made another contribution in that they were able to isolate a substance in the urine of an edematous person which increased the pe rmeability of a collodium membrane. In this they strengthened the Hamburger school of nontoxic agents as the cause of permeability of capillaries. This year, also marked the rise of opposition to pure acceptance of the theory that lowered blood proteins and its lowered osmotic pressure brought on edema. Linder, Jundsgaard and van Slyke (31) found that blood protein level curves were not always parallel to the appearance of edema. Their report was followed by a wave of similar clinical reports which led to Verney's work in 1926.

Verney (32) in 1926 proved conclusively that the osmotic pressure of a given amount of serum changed more upon dilution than mere dilution could account for alone. Thus, the discrepancies previous searchers like Govaerts had tried to explain away were turned into fact and a new line of research in edema, "the physio-chemistry of serum proteins" was initiated.

E. M. Landis (33), whose name figures prominently in this field, published the first of his long series of observations in 1928. Accepting a cue from the edema of venous stasis, he set about to find if the ph of the blood or carbon dioxide tension of blood affected capillary permeability. He found these factors operable in altering not only permeability but also colloid osmotic pressure, but not within the ranges of values of these factors that occurred within the human body. In the same year a second significant idea of hypercholesteremia in edema appeared. Fishberg and Fishberg (34) produced evidence toward the conclusion that the high blood lipids and high blood cholesterol, as occurring in cases of nephritis, were a part of the body's mechanism to compensate osmotically for the fall in serum protein.

Elwyn's (35) theory of the central nervous system control over edema highlights 1929. He erected a theory on the basis of works showing disturbance of water balance by brain lesions and by endocrine disturbances. He pro-

posed that the electrolytes of the blood system were under the control of nervous impulses and that endocrines of the posterior pituitary played pressor and diuretic roles in edema. The conclusion was that edema was essentially and basically founded on a nervous system functional pathology.

Year 1930 brought important additions to the literature. C. Achard (1) brought forward research in three fields of inquiry. He abetted Elwyn's endocrine participation concepts by recording an increased permeability with the presence of adrenaline. He checked tissue fluid for chlorides and found them in excess of blood chlorides, a finding which was mitigated by Caune et al (36) who found them in excess but not consistently so. Achard also reported that the fatty acid-cholesterol ratio had a direct bearing on the fluid taken up by the individual cell. In fatty acid predominance the cells resist water but in hyper-cholesteremia the cells take up more water. Even this lead in the task of evaluating the mechanisms of edema was somewhat modified by Murphy's (37) thesis of 1930 showing that edema incidence and hypercholesteremia do not parallel one another. This year also is known for the dye passage experiments of Underhill (38), in which dye particles passed out of the capillary along its entire length, thus upsetting Starling's concepts of capillary absorption.

Leiter (39) in 1931 headed a movement of reaction against Fischer's 1910 hypothesis of colloidal tissue changes

as a cause of edema. He stated that the changes Fischer claimed were not compatible with microscopic changes showing most edema to be in the interstitial spaces, not the cells. He pointed out that edema does not develop in acidosis, and that Fischer had not taken into account the role of sodium chloride. This same Leiter also led a counter-attack, aided by others, against Elwyn's central nervous system hypothesis of edema formation. He claimed the concept was too "Teleological" to explain the edema from a slight glomerular damage or from a decompensated heart. He felt Elwyn had assumed too many important steps in his hypothesis.

In the year 1934, Youmans and his associated workers, in measuring the tissue pressure in edema noted that in standing there was a significant rise in tissue pressure. This, at first, was rapid then gradually became slower and slower as the swelling became maximum. This increment of pressure within the tissue, they felt, was a definite and important factor in limiting edema. Also, in 1934, the problem of the lymph system's participation in edema reappeared from the obscurity it had known since the day of Starling. Weech et al. found that lymphatic flow was increased in times of edema and high venous pressure. He confirmed Starling's idea that escaped plasma proteins were returned to the blood system by way of lymph channels. The invention of the ultracentrifuge

and its use by Swedish scientists made a contribution to the edema problem in 1935. In this year, MacFarlane (42) found reason for the alteration qualitatively of the osmotic pressure exerted by a given amount of serum protein. He found that although the globulin was equal in amount to the albumin in a given specimen, when these were whirled they split apart into a heavy fraction of twenty percent and a light fraction of eight percent, and that dilution changes the percentages resulting. Here was evidence that the heavy globulin molecules were capable of splitting up into lighter molecules and thus increasing the osmotic pressure. Since their work many confirmations of the dissociable properties of protein systems have complemented our knowledge.

In 1937 Landis (43) gathered up the threads of inquiry into a review and revisualization of the problem. He pointed out the value of our understanding colloid osmotic pressure, but that we had evidence that edema incidence did not always correspond to blood protein levels. He described the capillary as an inert/non-secreting membrane permeable to electrolytes but normally impermeable to protein. Thought he recognized that protein did pass through and had been isolated in amounts from one to six percent in edema fluid, he said that "we as yet do not know the mechanism for the passage of protein under physiological conditions." Possible distension of the capillary

and anoxemia were factors to be investigated. Again he issued caution to over-emphasizing the free diffusion of fluid through the capillary wall, for should fluid be diffusing freely at the maximum rate the capillaries are capable of producing, the blood system would be emptied in ten seconds. Surely, there must be retaining factors to be evaluated. As a possible mechanism of protein transudation, he offered recent research of his own showing that dye particles too large to diffuse out of the capillary escaped when intra-capillary pressure rose above normal by minute break-downs of the capillary wall. The dye was seen to spurt out at points along the capillary, and examination of these points revealed no capillary damage. He concluded by listing the following as the factors considered significant in edema in 1937: Raised capillary pressure, low colloid osmotic pressure, capillary wall damage, lymph obstruction, low tissue pressure, high salt and water intake, heat, and disturbed innervation giving vasodilatation or loss of muscle tonus.

In both 1937 and 1938, Burch and Sodeman (44 and 45) presented findings showing that tissue pressure rose in accordance with venous pressure, and could be computed. In a limb in which transudation had reached an end point, the intracapillary pressure equalled the colloid osmotic pressure plus the tissue pressure. They noted that distension of skin decreased its elasticity and caused it to

lose tone, allowing for a still greater amount of transudation before the above end point of transudation or equilibrium could be reached. Holling et al (46) in this same year reported that lymph flow, as an index to transudation, rose significantly when venous pressure was elevated clinically but did not rise when arterial pressure rose, thus formulating a question as to the qualitative difference between intracapillary pressure raised from the venous side or from the arterial side. They claim no significant changes in oxygen tension in the saphenous blood.

Kerkhof (47) ended the theory that sodium chloride was a dynamic etiological egent in edema in 1938. McClure and Hinman (48) before him found that the sodium ion was not in the cells in edema and was not pulling water into the tissues by being concentrated there. Kerkhof himself was able to pull the sodium chloride out of tissues by artificailly raising the colloid osmotic pressure of the blood. Thus the passage of sodium chloride and water into the tissue was relegated to mere passive diffusion. It was natural that the kidney could not eliminate rapidly the sodium chloride thus diffused into the tissue spaces for the rate at which the salt was brought to the kidney to be excreted was subject to the slow diffusion of fluid back to the blood stream which in turn is subject to the law of mass action.

From 1938 to 1940 there was a sequence of discoveries on the effect of hormones on edema. Aykroyd and Zuckerman (49) in 1938 reported edema of sex skin from oestrogenic hormone which led Thorn and Emerson (50) in 1940 into experiments which proved that progesterone, as well as adrenal cortical extract, were capable of producing edema. The mechanism was not explained. The year 1940 also brought a conclusion by Maurer (51) that the qualitative difference between increased intracapillary pressure derived of hypertension or venous stasis was definitely traceable to chemical differences in the blood, namely the carbon dioxide tension and the oxygen tension.

Perhaps most spectacular contribution of the year came from Danielli (52) of Yale who proved that blood platelets were functional in closing the pores of the capillaries and that the pores normally remained occluded by the surface layers of protein molecules that clings to the capillary wall. He went on to show that when this layer is broken, say by introducing a substance with a higher surface activity than protein, that filtration and edema resulted, and that reestablishment of the protein layer arrested the process. Complementing this was a report by Cristal et al (53) showing that in nephritic edema the amount of diamino acids in the blood was elevated, an index to the fact there is protein breakdown in process. Chambers and

Zweikach (54) also brought out that the sodium-calcium ratio in the blood regulated the cohesive power of the intracellular cement of th e endothelium; a loss of the calcium component weakening the cement and thereby the wall, resulting in increased filtration.

This year, 1941, finds still many challenges and points of confusion. Workers now have a clue as to how the pores of the capillary open but have not the agent. The osmotic power of the protein systems has now proved itself to be variable, quantitatively and qualitatively, thus complicating its evaluation . Pressure changes that operate physiologically have resolved into physical and chemical differences of the two conditions: Hypertension and venous stasis. The role of salt as a dynamic entity in edema has been partially ruled out as have tissue fluid changes. The lymph system has come to be a limiting factor along with the skin tonus and its corollary, tissue pressure. Still as yet unevaluated are the roles of cholesterol, intracellular changes, the endocrines and the central nervous system. In sh ort there is a need for correlation of findings and redefinition of the problem to meet the new horizons brought about by recent investigation.

History of Specific Investigations

The second part of this consideration of scientific attempts to find the mechanism of edema, will be given over to rather a detailed consideration of the progress of thought along each of the factors of edema that have proved themselves of importance. The term "History of Specific Investigations" is used to denote this longitudinal approach to the important lines of research. Such a procedure is warranted as a basis for proper evaluation of the significant discoveries for a conclusion.

Considered in order will be the following factors: Capillary permeability; blood constituents; hydrostatic pressure; sodium chloride; lymph, tissue change and tissue fluid; the central nervous system and endocrines; and tissue pressure.

The Factor of Capillary Permeability in Edema

The evaluation of the role of the capillary and the question of its permeability to fluid, of course finds its roots in the discovery of the circulation of body fluids discovered by Harvey. Out of the knowledge of this vascular system, within which fluid was constricted, grew experiments and conclusions that here was the source of dropsical fluid. Notable among these observations were those of Lower, in 1622, who produced edema by ligating

the inferior vena cava and the jugular veins of experimental animals, and those of Boerhaave and Hoffman who confirmed the role played by venous disturbance in dropsy (1).

Having thus associated the blood vascular with edema, the problem of discerning the mechanism of the transfer of fluid from blood vessel to tissue spaces naturally followed. Becquerel's and Rodier's (1) detection of the fall of albumin in the blood of a case with cardiac edema and Well's (1) 1812 report of edema and albuminuria following Scarlet Fever led Senator (3) to propose an increased permeability of the capillaries due to toxic agents, explaining the loss of albumin and protein on the basis of the increased permeability. Reese (4) in 1850, confirmed this proposal and added the thought that the cause of this "toxic dyscrasia" was a failure on the part of the kidney to eliminate these injurious substances. These two opinions provoked a search for these causative toxins (called variously nephrotoxins, nephrolysins or nephroblaptins) by Castaigne (55) in 1905, and Timofeew (56) in 1909. This line of inquiry proved to be unfruitful at that date.

Pursuing in another line of inquiry, the hypothesis of increased permeability, Magnus (57) in 1897, conducted a series of experiments in which he injected veins with various irritants to increase the permeability of these blood vessels. Unable to thus produce direct edema, he was

able to prove, to his satisfaction, increased permeability by measuring the increased rates of withdrawal of hypertonic liquids injected into muscles of the same limb. From this experimental foundation it was possible to believe that the permeability of the capillary was definitely capable of alteration; but the operation of this mechanism in edema was still not ascertained.

In order to prove that increased capillary permeability occurred in edema, the hypothesis that definite passage of blood constituents into the tissue spaces would have to be substantiated. Accordingly, inquiries on the character of the edema fluid as compared with normal tissue fluid were initiated. Findings here as listed in the section of this paper on tissue fluids, demonstrated definite differences between tissue and edema fluids in protein, glucose, and chloride concentrations. However, counter to these findings was evidence collected between 1914 and 1916 by Chisolm (58) and Boycott and Douglas (59), Bogert et alia (60) that in nephritis there were no significant changes in blood volume or tissue fluid concentrations. They concluded that the capillary permeability was actually decreased in this disease. Further dissenting evidence was advanced by Beckman (61), in 1921, to the effect that in acute nephritis the high blood protein levels also pointed to a less permeable capillary wall. These findings

plus the prominence of the colloid osmotic theories led Epstein (26) to summate the findings up to 1922 by concluding that the existence of capillary wall damage had been proved but that there were not yet enough evidences to say that such damage was the cause of edema.

In the same year, 1922, two other modes of inquiry with their consequent hypotheses were developed: One, that there were substances of non-toxic nature that altered the capillary permeability; and the other, that capillary permeability was mechanically related to intracapillary pressure. Krogh (27), who introduced the latter theory, proved that the capillary cannot hinder or accelerate the absorption of the sodium chloride or water--that these electrolytes diffuse through at all times. On these findings he was inclined to place the transudation of fluid through the endothelium of the capillary on a purely mechanical basis, as in the Starling hypothesis (55). This idea of the inert role of the capillary in edema was further promulgated by C. Achards'(1) conclusion, in 1930 that capillary wall damage was not actually proved as the cause of edema and by the conclusion of Leiter (39) in 1931, that the decreased blood albumin, blood protein, and consequent fall of colloid osmotic pressure was sufficient and that the capillaries did not have a part of it at all.

Despite the deterrent effect of these last opinions,

the group seeking the non-toxic agents, altering capillary permea ility, collected some pointed evidence. Hamburger (28) in 1922, first found evidence that permeability of the capillary was influenced by the electrolyte content of the blood. Marriott, (62) in 1924, after a series of experiments on the passage of electrolytes into the tissues concluded: "There is a substance in the blood of an edema patient capable of changing the surface tension of the blood and the permeability of cells. This substance is produced in the body in infection and is excreted in the urine." He even hypothesized that this substance operated in the kidney. Clausen (63) in 1925 continued in the attempt to prove the existence of this substance by pointing out the following facts: That when a kidney is removed there is no edema, 2. That kidney degeneration does not give edema, 3. That edema can exist without albuminuria, and that in parenchymatous nephritis there has been observed a marked lowering of the surface tension of the blood and urine. It has also been demonstrated that urine containing this "substance" possesses the ability to increase the permeability of a collodion membrane in vitro. From the facts above, they proposed an extra-renal source for this unknown substance.

It was natural that a search for this substance should follow. E. M. Landis (33) undertook experiments in 1928

to ascertain the role of the ph of blood or the carbon dioxide tension of blood in edema. After working on frogs he concluded that, within the physiological limits of ph and CO2 tension, there was no significant alteration of capillary permeability. But beyond physiological limits there is definite alteration, for permeability increased three times with anoxemic blood and the osmotic pressure of the blood colloids even lowered, allowing fluid to escape. He found this permeability reversible if not too lengthy. Confirming this in 1931 were additional works by Essex (64) showing altered permeability of all animal tissues with anoxemia, and a paper by Drinker and Field (65) showing production of permeability changes in tissues with the ph and CO2 tension occurring with exercise. Landis, Jones, et al (66) repeated the early conditions of Lower, in 1932, and reported that stasis and dilation produced transudation of protein through the capillary wall and included as a factor the CO2 tension and ph of the blood associated with such congestion. Landis (67) in recapitulation in 1937 of his work, doubted if the ph and CO2 tension changes operated under physiological conditions and was inclined to think of the capillary wall as an "inert non-secretory and impermeable to protein." He insisted that the above experiments only should urge works to discover

forces comparable in effect to ph and CO2 tension changes, forces capable of altering colloid osmotic pressure to the same degree. He felt the blood was too strongly buffered and too constant in ph to permit the changes he had observed to actually occur physiologically. Yet Maurer (51) in 1940, using lymph flow as an index to permeability reported that decreased oxygen tension and increased carbondioxide tension gave increased permeability as evidenced by increased lymph flow, increased lymph protein and red blood cells in the lymph.

C. Achard (1) in looking for this "substance" causing permeability in 1930, thought the changes in the capillary wall after adrenaline injection proved increased permeability. With this move came the hint given by Elwyn (35) and others (see section on nervous-endocrine control of edema) that endocrines were active in altering endothelial cell permeability. As late as 1939 Duran (68) of Yale found that permeability of capillaries, as demonstrated by the passage of dye particles, was increased after bull testicle extract was injected intravenously.

Within the last year even new agents causing permeability have come to light. In a series of perfusion experiments Chambers and Zweikach (54) altered the permeability of the capillary by changing the ph and mineral content of the perfusate. Most significant were their

observations that if the perfusate is low in calcium the intracellular cement loosens, and reversal to a high calcium content makes the cement sticky again. An acidic ph in the perfusate also gives a softened cement. They go so far as to conclude that edema is "related directly to the physical change in the physical state of the cement." They state that the endothelial cell secretes this intercellular cement, the chemical stability of which controls the permeability of the blood capillary.

Even more interesting are the contributions of Danielli (52) who measured the ability of various physiological blood constituents to relieve edema. When he perfused the blood vessels of his edematous tissue with inert colloids he got some reduction in edema as might be expected on the basis of osmotic pressure. But he received an even greater reduction of edema when he added blood platelets to the inert colloid. The same results were received when blood protein was substitued for the inert colloid. This led to his first conclusion that the platelets were functional in arresting edema. He proposed the idea that there were still pores capable of passing protein when the platelets were not present, and that the introduction of platelets led to mechanical clogging of those pores.

Continuing, he measured pore size by noting the size of protein molecules they would pass and he showed that, in the

dilated capillary, the pores in the capillary were 6 mm across, while in the contracted capillary they were only 4 mm. In a second group of experiments he demonstrated that a given perfusate had quite a bit of leakage into the tissues until this loss was arrested by the addition of serum. This, he contended, was due to the blockage of pores by adsorped protein. He points out that the surface tension properties of blood proteins allow them to build up a protein layer on the pore wall 4 mu thick, sufficne tneough to block even a 6 mu pore. Should a substance with a high surface tension come along, it would displace this protein of lower surface tension; and lay down an adsorped layer on 1 mu thick on the pore wall thus opening the lumen in the pore, allowing edema to start again. He proved this action by introducing cluepin, a higher surface tension substance, at a time when the pores were proved impermeable to gum acacia and noted a distinct change of permeability to the extent that gum acacia was once again leaking into the tissues. These observations have been further strengthened by Cristal and Fourcades' recent work with diamino acids in normal and pathological blood in which the amount of polypetides (of higher surface tension activity than blood proteins) have been found to be increased in nephritis.

Concomitant with this search for agents altering permeability, have been a series of experiments with the passage of dyes through the capillary wall. Underhill et al (38) in 1930, in studying the mechanics of water exchange in burned people noted that intravascular dyes passed

out of the capillary and would not re-enter. It was found in studying normal capillaries that dye often passed out as much, if not more, at the end of the capillary as it did in the first part, tending somewhat to upset the Starling hydrostatic-osmotic pressure balance hypothesis. Further investigations by Parsons, and McMaster (69) in 1938, showed that dye spreads into the tissues fast and slowly later as intra-tissue pressures build up, leading to the conclusion that the dye passage was subject mainly to a mechanis analagous to diffusion; further buttressing the concept of an inert capillary. Landis (67) in another experiment in 1937 with India ink injected into a capillary blocked at both ends showed that as the pressure rises this dye will spurt out at certain weak spots and collect outside the wall. The pressure needed to do this in the normal capillary is well above normal hydrostatic pressure (55-80 mm Hg) but if the capillary is inflamed a pressure substantially below that of the normal hydrostatic pressure (20-30mm Hg) was efficacious. The openings thus occurring are most prominent in the venous side of the capillary. Peculiarly enough, the capillary is not torn in this process for there is no later evidence of permanent injury.

Before leaving the resume of works covering the permeability of the capillary wall it might be well to guard against conceiving the mere act of opening and closing

of the "gates" of the capillary wall, whatever they may be, as the only instrument of edema. Krogh (70) has shown us that the total surface area of the body's capillary walls amounts to about 68,000 square feet and Landis (67) in 1937 reminds us that if the human capillary wall was as permeable per square unit of surface area as that of the frog, in experiment, our total plasma volume could be filtered through in ten seconds. So we must consider other retaining forces to be also at work. In addition Conklin (71) has proved that local differences in capillary permeability exist. Liver capillaries permit protein to pass, skin capillaries only a bit, but mesenteric capillaries not at all. So when we come to our correlation of factors later in this paper we must be cautious in recognizing that permeability has not been proved to be standard in both the dimensions, time and position.

Blood Constituent Factors in Edema

Another group of causative factors in edema are those blood constituents tha t exercise an influence on the fluid exchange between tissues and vascular channels. From this group we must of necessity eliminate those blood elements whose effect is upon the capillary wall directly, in altering the permeability of that structure. These last have been discussed under the consideration of capillary permeability.

Falling directly into the classification of blood constituents factorial in edema are the actual blood water content, the serum proteins; fibrinogen, albumin and globulin, as well as the blood chlorides, blood sodium, and the blood lipids and sterols.

It was Bright (2) in 1836 who laid the foundations in this line of inquiry, a work which led to his recognition of the syndrome now known as "Bright's Disease." He was the first to associate albuminuria with edema, and to note the fall in serum protein concomitant with urinary protein loss. From this basis, he concluded that a relative hydremia existed as the result of kidney damage. Because of this hydremia, he visualized a blood of lower viscosity, of lower concentration that would now filter through the walls of small vessels. In reality edema was thus the result of water retention and the consequent dilution of the blood.

Johnson (5) in 1852, as well as Bartel's (6) and Stewart (7), concurred in this theory of hydremia but modified the mechanism producing the actual edema to agree with the clinical rise in blood pressure. They, accordingly, proposed that the increased vascular pressure drove the excess blood fluid of hydremia into the tissues. They called attention to the accompanying oliguria as evidence of kidney's inability to excrete water. This hydremic theory of edema reigned unchallenged until 1898 when Koranyi (72) accumulated evidence, that in the process of explaining renal edema on the failure to eliminate water, that in nephritis there was no hydremia or edema with acute kidney failure. After this turn of the tide, only Volhard (22) in 1918, and Briggs (73) in 1932, supported the hydremic hypothesis. As those before them, they associated the oliguria, loss of albumin, and the accumulation of nitrogenous waste products in the blood as evidence of hydremia. Briggs even hypothesized increased readsorption of water by kidney tubular epithelium. But Bock, 1921 (25), Linder, Jundsgaard, Van Slyke and Stillman (74) 1924, Brown and Rowntree (75) and Barker and Kirk (76) 1930, all found no change in the plasma volume in nephritis. Barker and Kirk, in studying nephrosis, found edema with oliguria but no hydremia. Thus, the general conclusion arose that the oliguria occurred only because

less water was actually brought to the kidney to be excreted.

Another blood constituent which has played a prominent role in the literature of edema is the serum protein. It was Bright who first associated low serum protein with edema, but interpreted the observation only in terms of hydremia. It was not until 1896 that Starling (15) announced the hydrostatic-osmotic pressure hypothesis for the cause of water exchange. He conceived the idea that the colloidal serum protein was capable of exerting a pressure, called the osmotic pressure, upon the fluid through the capillary wall, which he claimed was functionally a semi-permeable membrane. When the hydrostatic pressure within the capillary exceeded the osmotic pressure, fluid passed out of the vascular channels, but when that hydrostatic pressure fell below the osmotic pressure there was a movement of fluid back into the capillary in proportion to the difference between the hydrostatic pressure and the osmotic pressure of the proteins. He proposed that there was a delicate balance between the water thus forced out and thus returned to the capillary, creating in the mind's eye a mechanism for a constant fluid exchange between tissue space and vascular channel. He further extended this concept to explain renal edema on the more basis of a reduction in the amount of plasma protein and the consequent

loss of osmotic pressure to remove fluid from the tissues.

To Starling's explanation of the mechanism of edema on a low protein basis has come a host of clinical confirmation not only from workers in the field of renal disease, but also from investigations in the field of nutrition, tuberculosis, surgery and cardiac disease. Epstein (77) in applying the principle clinically, thought he was successful in lessening the edema of nephritics with high protein diets while Moore and Van Slyke (78) found that edema occurred in nephritis when the total protein fell below 5.5 to 3.0 gms or if the albumin fraction was below 2.5-2.2 gms. Kerkhof (47) in 1937, working at a date after the discovery of the ability of individual protein to change its osmotic power, (as will be detailed later) finally set the critical point below which edema occurred at 15 mm of mercury of osmotic pressure exerted by blood proteins.

Edema arising from the low blood protein of malnutrition was first reported by Denton (79) in 1918 and was confirmed by Harden and Zelva (80) in 1919, Mayer (81) in 1920, and Kohman (82) in 1920. Frisch et alia (83) produced a definite edema in rats by diets low in protein in experiments conducted during 1929 and Shelbourne and Egloff (84) confirmed the results with a low protein diet in dogs in 1931. Edema from low serum proteins in cachexia and in malnutritioned tubercular patients were re-

ported by Bruckman with Peters (85) and Landis with Leopold (86) respectively in 1930. Celiac disease with a low blood serum protein producing edema in infants was mentioned by Mariott (87) in 1930, while edematous complication of the nutritional disturbance provoked by a fecal fistula was reported in the same year by Wolferth (88). Leiter (89) in 1928 and Barker and Kirk (76) in 1930 produced edema in a dog by replacing its serum protein with ringer's solution (plasmaphoresis). Cirrhosis of the liver causing emaciation and malnutrition edema was reported by Peters et al (90) in 1931, giving a clue thereby to the source fo blood proteins. It is of interest to note that when criticism of the Starling theory, as being unapplicable to cardiac edema, arose an investigation of the blood protein of cardiac patients was made. Payne and Peters (91) both noted that frequently, though not always, the serum protein of cardiac patients with failure is decreased, especially the albumin fraction. They felt this deficiency was referable to malnutrition only.

During the process of the accumulation of this mass of clinical confirmation of the association of low blood proteins with edema, that has been sketched above, there developed lines of research tending to show that of the three important blood proteins, it was the albumin fraction that was the most influential in the p roduction of osmotic press-

ure. Csatary (14) in 1891 first noted that serum albumin was lowered more than globulin in nephritis. Govaerts (24) in 1921 and van Farkas (92) in the year following both pointed out that in renal disease the serum protein deficit was mostly albumin, and that albumin exerts more colloid osmotic pressure than globulin. Peters et al (90) in 1931 also believed albumin to be the most important fraction--being the first to be lost--because of its smaller size and also being less readily replaced, tended to fall in blood level sooner.

But contrary to the men whose works we have just listed, who had come to believe as Colvin and Goldberg (93) 1931 summarized it, "that a low blood protein was the trigger mechanism of edema" there arose observations that the amount and occurrence of edema was not always proportionate to the serum protein concentration. Linder, Jundsgaard and van Slyke (74) as early as 1924 noted two salient facts: One, that the lost protein of the blood did not correlate with the greater urinary loss; and two, that the greatest decrease of plasma protein was not coincident with the most edema. They found instances in which low proteinemia was not accompanied by edema. These observations led them to conclude that there must be unknown undiscovered alterations in the production of blood proteins or that the protein itself was capable of change. In 1926 Salvesan (94)

in study of the nephrosis of syphylitics found cases with low serum albumin but no edema. He tried to rationalize this by proposing that the slight globulin increase compensated osmotically for the low albumin.

Caune, Jarvis, and Cooperstock (36) found cases in 1930 of low protein, even reversed albumin-globulin ratio, without edema; while in 1931 McClure, deTakats, and Hinman (48) found cases in which edema disappeared spontaneously without serum protein change; provoking a conclusion that doubted the paramount position of colloid osmotic pressure in the production of cure of edema. Reports that edema occurred with nephritis with normal protein were published by Peters et al (95) in 1932. They felt that hydrostatic pressure and increased permeability of capillary were the factors functional in nephritis.

When these clinical observations challenged the efficacy of the lowered colloid osmotic pressure causation of edema, the investigators, convinced of the role played by the proteins, gave more credence and energy to the possibility that the osmotic power of the proteins could be altered. In reality this line of thought was heralded as early as 1921 when Govaerts (24) noted that the osmotic pressure exerted per gm % of protein nitrogen was higher in the blood of hypertensive individuals than in the serums of patients with edema. He was inclined to place

the cause of this in the concentration of the blood and the dilution of proteins. We have mentioned above how Linder et alia (31) tried to explain in 1924 the discrepancies in blood protein levels and edema on the basis of a possible change in the protein production or protein itself. Verney's (32) experiments, which he conducted in 1926, quite conclusively showed an alteration in the osmotic ability of proteins. He diluted plasma with Ringer's solution and found a fall in the osmotic pressure of the resultant fluid to be greater than the fall of protein concentration. This, he concluded, proved that the protein not only might undergo quantitative changes in edema but also qualitative change. Fishberg (96) expressed it, "as the protein decreases in arithmetical progression the osmotic pressure decreases in geometric progression."

Investigation into the physio-chemical properties of the serum proteins began to shed light on the character of this acknowledged change in the proteins fractions. Sorenson (97) in 1936 discovered that the two principal serum proteins were constructed of a large number of non-dissociated components. Precipitation studies by Goettsch and Lyttle (98) noted abnormalities in the protein fractions in nephritis. There was evidence that both of the important proteins were somehow altered. Block (100) et alia in 1934 in attempting to chemically analyze the

serum proteins, found that the fractions of albumin and globulin precipitated by the accepted procedures were artifacts and not actually the proteins as present in the blood. They found that by merely heating the serum the amount of globulin would increase at the expense of the albumin and that the ratio of proteins in nephrotics (who clinically display considerable edema) was not altered from the normal ratio. In other words, the albumin fraction was not, by measurement, reduced as had been so stringently supported by analyses of the urinary protein loss. Was there some internal compensation for the loss of urinary albumin? To answer this Yanagi (101) examined the physical properties of serum protein in 1935. He observed that both serum from normal and pathological individuals, when studied at levels of concentration comparable with normal blood levels, were stable in the osmotic power they exerted. But both sera, normal and pathological, showed a relative instability in this osmotic ability when diluted to concentration analagous to edema. These results were used to explain the wide differences in figures for colloid osmotic pressures as measured by Starling, Krogh, Govaerts, Landis, Sorensen, and Schade.

But most dramatic proof of the heterogenous character of the serum proteins came with the application of the ultracentrifuge technique of molecular weight analysis

to this problem. Svedberg and Sjogren (102) in 1930 in analyzing the molecular weights of albumin and globulin found the molecular weights of their sera unstable in dilution, a fact which provoked McFarlane (103) to make the following observations: "Sera taken from a horse and centrifuged at tremendous rates divides in a light fraction and a heavy fraction. Eighty percent of the serum is in the light fraction while twenty percent is in the heavy fraction, despite the fact that the albumin globulin ratio is 1:1. Further, if the serum is diluted and then centrifuged the fractions become fifty percent heavy, fifty percent light, and yet concentration of the same proteins reverses the ratio of light to heavy back to the original percentages." Experiments with altered ph and salts in the solution did not in any way alter the above facts. Basing his conclusion on Svedberg and Sjogren's work showing the protein molecules can be made to break into smaller molecules with a lowering of the ph, this author McFarlane states, "the important fact is that in some manner the interaction. . between albumin and globulin . . involves a reduction in molecular size of a part of the globulin fraction to the size of the albumin . . molecule." The mechanism of this is unknown, but the force must be commensurate to the action observed by Svedberg and Sjogren, of an altered ph on proteins. It is of interest to note that the latter

investigators showed that the molecular weight of globulin was approximately 103,800 plus-minus 3000 and that of albumin 67,500 plus-minus 2000, demonstrating that should this conversion of molecular weight be true the globulin molecule must just about break in half.

Other evidence of the idea of internal compensation for loss of osmotic pressure by the blood protein systems was collected by Melnick and Cowgill (104) in 1936. They showed that even with hypoproteinemia and a relative fall of the albumin fraction as measured by precipitation test that the plasma volume increased. This, they felt, was explainable on the basis of a breakdown of protein into smaller molecules. They concluded that the albumin-globulin ratio was not an index to oncotic pressure in vivo, but that it did show the presence of pathological alterations in the relative amounts of two independent protein systems in the blood in each of which the protein molecules were capable of reversible dissociation into fractions of many small light weight molecules or fewer large heavy weight molecules. Bourdillon (105) noted a difference in lower molecular weights of the albumin and globulin occurring in the urine from the larger molecular weights of the same two proteins occurring in the blood of the same individual affected by nephrosis.

The concept, that in pathologies characterized by edema, there was a dissociation of protein molecules was further strengthened by Cristal et al (53) who discovered that the presence of diamino acids and polypeptides was higher in the blood of nephritics, which they considered evidence of protein break-down. Jameson, Alvarez, and Tostodo (106) applied 135 volt current in electrophoresis experiments to vitro solutions of blood serum at normal ph and obtained a division of the serum into one albumin and two globulin fractions. Application of 250 volts separated each of the two globulin fractions into two more fractions. Thus the concept of alteration of the osmotic ability of the plasma proteins has been buttressed by both clinical and experimental evidence of a fluctuation of molecular size of proteins under various environmental changes.

Accompanying these investigations on the physio-chemical character of the plasma proteins, the influence of such factors as posture, and specific gravity, on the protein osmotic pressure have been investigated. Thompson et al (107) as early as 1927 studied the effect of posture on the peripheral blood. They reported that in quiet standing the blood volume decreased by 400 cc. which they ascribed to filtration loss to tissue. They claim, however, that as the process continues the protein percent of the blood rises, thus elevating the colloid osmotic pressure and

diminishing proportionately the rate of filtration at a given intra-capillary pressure.

This clue was followed by Youmans et al (40) in 1934 whose works showed that standing one hour caused an increase of from 18 to 40 percent in the concentration of serum protein in the capillaries of the foot, and an increase of from 24 to 65% in the osmotic pressure. The increase in total protein and in the two protein fractions was proportionate. All these processes were increased in the feet about twice the amount in the arm, and patients with hypoproteinemia showed the same changes. Youmans, Akeroyd and Frank (108) a year later, pointed out that the osmotic pressure rise in standing was also aided by a decrease in blood volume as shown by the fall in skin temperature and decreased velocity or longer circulation time of the blood. They did not explain fully this mechanism.

Moore and Stewart (109) 1937, evaluated the question of plasma concentration by measuring the specific gravity of plasma. They found this index to be accurate and noted that ingestion of water or fats, bleeding, and intravenous fluid dilution affected the specific gravity of proteins themselves, confirming [illegible] the works showing the effect of dilution on protein systems. They found the plasma specific gravity and concentration higher in cardiac patients than in nephritics.

Thus by specific gravity measurements and clinical evidence we have proof that erect posture, concentration of the blood from transudation of fluids into the tissues, and the alteration of the protein system's osmotic power in serum concentration all play a part in raising the osmotic power to compensate for fluid loss.

The role of the blood constituents of lipoid and lipid nature constitutes a story in itself. As early as 1827 Blackwell and Bosteck (110)noted the unusual milky appearance of the serum in renal edema. Christisen (111) in 1839 proved this was fat. Kaiserling and Orgler (112) in 1902 found double refractile lipoid bodies in the urine of renal patients and Adams and Aschoff (113) proved these were esters of cholesterol,four years later. Both Port (114) and Chauffard and associates (115) announced in 1910 that the blood lipoids were high in the blood and urine of renal patients, and distinguished it as a hypercholesteremia.

These findings led to a period of theorizing as to the cause of these lipoid materials in blood and urine. For a while they were considered granules of lipoid from the fatty degeneration of the kidney tubules, but Epstein (77) called it a generalized disturbance of fat metabolism. It was Kollert and Finger (23) in 1918 who finally accociated hypercholesteremia with edema. He stated that in-

ability of the kidney to excrete cholesterol led to edema. Lowenthal (116) and Bennett (117) both concurred later in this theory of edema caused by cholesterol retention.

Added confirmation was afforded by C. Achard et al (118) in 1919 when he noted that cells take up water easily when cholesterol is present. In fact the hydrophilic property of cells increased as did the ratio between cholesterol and fatty acids in the blood. Later in 1928 Fishberg and Fishberg (34) in studies of haemorrhage in rabbits felt that the increase of blood lipids and lipoids in haemorrhage was a device to compensate for the loss of osmotic power from loss of blood plasma. Barker and Kirk (76) in 1930 noted that as the protein levels fell the cholesterol level rose.

In opposition to the papers portraying cholesterol as a key factor in edema, arose some findings to the contrary. Lowenthal (116) confirmed the high lipoid levels in edema in 1926 but in feeding cholesterol to experimental animals got hypercholesteremia but no edema. Maxwell (119) in 1928 asserted that hypercholesteremia and edema were coincident but not related and Murphy (120) in 1930 admitted their occurrence together but stated that on close observation the highest hypercholesteremia and the greatest amount of edema did not coincide. He felt the two factors were not truly parallel in occurrence.

The Factor of Hydrostatic Pressure in Edema

It was early recognized that the mechanical and gravitational heads of pressure were forces to be reckoned with in the analysis of the mechanism of edema. As early as 1852 Johnson (5) and his later corroborators Bartels (6) and Stewart (7) gave their support to Bright's original hydremic theory of edema and proposed that the increased blood pressure in nephritis was the force driving the excess fluid in the vascular system into the tissues.

Although the hydremic theory fell into disrepute in the latter part of the nineteenth century, the announcement by Starling (15) of his hydrostatic-osmotic pressure balance theory of edema upheld the role of intra-vascular pressure in the transudation of fluid. As has been presented previously, the normal hydrostatic pressure here was considered and later proved to be in excess of the osmotic pressure exerted by the blood colloids. As long as this latter difference occurred within the capillary, fluid would be filtered out. The development of this theory brought the idea that in the first half of the capillary, hydrostatic pressure gradually fell due to friction to about the level of the osmotic pressure, thus forcing out fluid, and in the second half of the capillary the hydrostatic fell increasingly below the osmotic pressure, creating the difference necessary to admit fluid back from the tissue spaces. Later workers confirmed with experimental

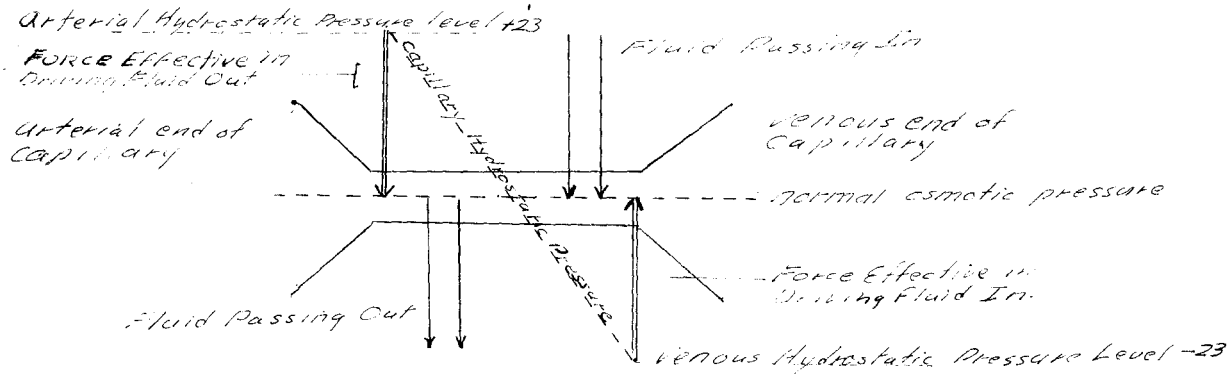
evidence the pressure relations involved. Krogh et al (121) in review of the literature and by personal investigation established the pressure at the arterial end of the capillary at 43 cm. of water. The osmotic pressure at 35 to 36 cm. of water and the hydrostatic pressure at the venous end ranging from 24 to 34 cm. of water. Christian (122) pictorializes this pressure relation as follows: * He points out that with a lowering of the protein there would create an advantage for the force causing filtration. This same disruption of balance could come from an increase in hydrostatic head or intracapillary pressure at the venous end. * See Illustration page 47a

Starling applied this theory to the two main clinical edemas. Renal edema was a resultant of the lowering of the osmotic pressure, from loss of protein in the urine, to the extent that there was a greater force driving fluid out than there was drawing fluid back into the capillary. Cardiac edema, he explained in 1909 (23) as a case of only slight loss of protein osmotic pressure, as from the albuminuria and low dietary intake, but mainly of a preponderance of filtration due to increased hydrostatic pressure.

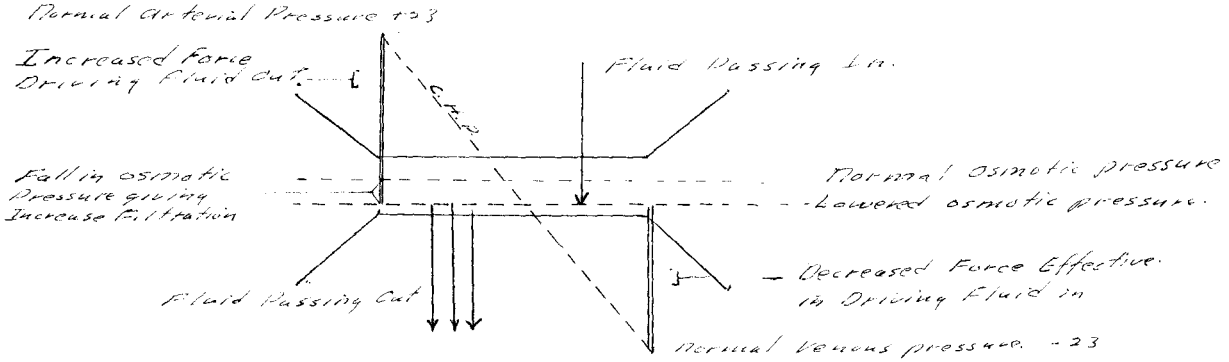
This concept so captured the imagination of men and so thoroughly mastered the available data, that not much new research in this line was done until 1922 when Krogh (70) began to feel that capillary permeability was a factor to

Hydrostatic Pressure Relations

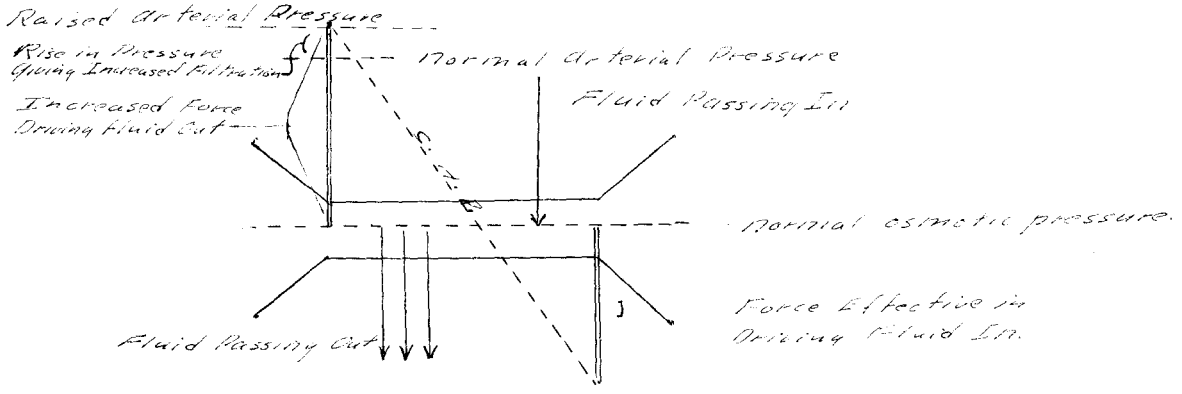
A. Normal Water Exchange



B Low Blood Protein Mechanics



C. Increased Hydrostatic Pressure Mechanics



be considered, as well as the efficiency of lymph flow and possible metabolic activity by the tissue cells. Not soon after E. M. Landis (33) and associates began a series of experiments that utilized the techniques of micro-injection and microscopic visualization of capillaries in order to ascertain certain relationships of pressure with the capillary. In 1927 they reported the following observations on the frog: If the flow of the blood stream through a capillary is stopped by a glass rod, the corpuscles are at first distributed uniformly in the capillary. If the hydrostatic pressure is 11 cm. of water (equal to the osmotic pressure of the frog) the corpuscles stay uniformly distributed but if the hydrostatic pressure is higher the corpuscles move toward the obstructing rod and concentrate there. These corpuscles can be seen to move more and more slowly as the concentration of corpuscles at the rod rises, and more fluid is filtered out. If however, the hydrostatic pressure is low, there is absorption of fluid from the tissue spaces, occurs, for the corpuscles separate and move away from the rod as the fluid comes into the capillary." He felt that here he had an index to filtration rate which by these observations is high at first and lower at the end. He also demonstrated the effect of hydrostatic pressure on filtration rate and direction of flow quite clearly.

With micro-injection osmometers, Landis in 1930 (24) went on to measure the intra-capillary pressure as it varied with posture. In a finger raised above the suprasternal notch both the arterial and venous capillary pressures were less than the colloid osmotic pressure and below the notch both pressures exceeded the osmotic pressure, provoking the thought that if such observations were true the body above the shoulders would be in relative tissue dehydration and the body below the notch would be relatively edematous should only the simple factors proposed by Starling be operative. Surely other forces must be considered. In the same year Landis also measured by this new technique the intracapillary pressures. He found the arterial end to be about 32 mm of mercury and the venous end 12 mm of mercury, and the fall to be gradual along the capillary.

With co-workers Jonas, Angevine and Erb, Landis (66) continued in 1932 to demonstrate the effect of intracapillary pressure on fluid filtration. They found the volume of fluid filtered proportional to venous pressure as detected by the rise in red blood cell count, hemoglobin concentration and protein concentration in the capillary. Their computations showed that at 20 mm of mercury the capillary lost 3 cc. per 100 cc. and at 80 mm mercury lost 20 cc. per 100 cc. Figures on the efficiency of capillary demon-

strated that the capillaries of the human forearm and 90 percent efficient in retaining protein at 60 mm of mercury. Incident to this protein loss the colloid osmotic pressure drops from about 26 mm of mercury to about 24.5 mm of mercury.

This latter work was in principle corroborated by Krogh et al (121) in the same year, who in using a cuff on the limb to occlude all blood vessels and thus mechanically increasing intracapillary pressure, found the rate of filtration also proportional to venous pressure. Filtration even occurred at venous pressures as low as 15 to 20 cms. of water, indicating that man is constantly very close to edema. The fact that lowering colloid osmotic pressure 1 cm. of water increased filtration to the same amount as raising venous pressure 1 cm. of water, shows the reciprocal function of these two forces.

The association of edema with varicosities, incompetency of valves of veins, and orthostatic edema with the problem of pressure, has led to some recent literature. In 1938, Holling, Beecher, and Linton (46) set down the following notation: "(1) Edema develops more readily in the legs of patients with varicosities than in normal patients. (2) This tendency is greatly increased when the valves of the communicating veins are incompetent. (3) Studies of the saphenous blood oxygen tension offer no significant changes of tension associated with valve incom-

petency. Allen and Hines (125) of the Mayo Clinic in 1940 contributed further evidence that erect posture gives increased colloid pressure in the veins of the feet and they feel that edema is normally prevented in standing by this latter fact, and by the decrease in volume and velocity of the blood in the legs, and by the increase of tissue pressure from accumulating fluid in the tissues.

Recently Swindle (126) in examining the mechanical factors in edema ran across a phenomenon he has termed "arterial looping." Under normal conditions of circulation the most conspicuous feature of the pulsatile movements of the systemic arteries is a systolic arterial looping," a sort of looping contortion of the small arteries with the passing of the systolic impulse. He further notes "Some of these arteries loop into veins." It is his idea that this dams venous blood back, raising first the intra-capillary pressure then later the intercapillary pressure as fluid is thereby filtered through the capillary wall. As soon as this systolic rise in intracapillary pressure dies, fluid filters back into the capillary.

The Factor of Sodium Chloride in Edema

The historical sequence of the series of discoveries relating sodium chloride to edema commenced with Cohnhein and Lichtheim (9) in 1877. In that year these co-authors reported that they obtained edema by inundating the organism with large quantities of salt solution in different concentrations. Then Winter (16) showed that the molar concentration of the blood was maintained by the exchange of water and chloride between blood plasma and tissue. On the basis of these two studies he arrived at the conclusion that sodium chloride was a more important factor in edema than was colloid osmotic pressure.

These early investigations precipitated studies by many others. Reichel (17) in 1898 reported that edema from sodium chloride injection lasted longer in patients with nephritis, while Chaufford (27) in 1900 noted edema in a jaundiced patient treated with sodium chloride injections. Magnus (57) in 1901 confirmed Cohnheim and Lichthiem's original basic observation but it was Widal (19) in 1903 concurring with Chaufford and later confirmed by Strauss (128) who finally stated the hypothesis that edema was due to a kidney failure to eliminate sodium chloride. Widal stated directly that increased sodium chloride intake increased edema directly in proportion to the amount taken. Widal even pointed out that the failure of the kidney to excrete water was associated with the failure to eliminate sodium chloride.

This theory of the sodium chloride retention mechanism in edema, and the associated kidney inability to excrete water won many confirmations. Muller (129) in 1905, Volhard and Fahr (130) in 1914, Epstein in 1922 (26) and Munk (131) in 1925 all noted sodium chloride and water retention in their studies of edema. Thus the 1903 observations of Widal upon these retentions were well accepted, but his pointing specifically to kidn ey failures to excrete these substances, was mortally attacked within the same year. Attempting to confirm his assertion with Loeper of the year before, that sodium chloride retention was not due to kidney changes, D. Achard (20), in examining the blood chlorides, demonstrated that the sodium chloride content of the blood varies widely in edema. He found excess blood chloride both with and without edema. From this the conclusion arose that sodium chloride retention was not renal, but an extrarenal problem, possibly occurring in the tissues. So accepted became this extrarenal causation of salt retention, that Ambard and Weill's (132) suggestion that the kidney threshold for salt was elevat ed never received much consideration.

Considerably broader work on sodium chloride retention was reported by Loeb (29) in 1923. He found this phenomenon occurred not only in kidney pathologies but also in heart disease, pneumonia, pernicious anemia, trypanosomiasis, and also some of the other anemias. He also picked up a clue

from Widal, that sodium acid sulphate was less effective in producing edema than sodium chloride, that led him to believe, as had Magnus Levy (135) and Blum (134) before him that it would be necessary to differentiate the roles of the chloride and sodium ions in this process. After experimentation he noted that potassium chloride and calcium chloride did not give edema, but that all the sodium salts he employed, like sodium bromide and sodium phosphate, produced edema. To substantiate this, he gave nephritics alternate courses of potassium chloride and sodium chloride and checked the edema by weight measurements. There was an exact parallel of the occurrence of weight gain with the intake of the sodium salt and a fall with the intake of the potassium salt. The elimination through the urinary tract of one always took place upon administration, orally, of the other. It was easy therefore for Loeb to assume that the sodium ion is responsible for edema and he was subsequently confirmed in this by Veech and Ling (135) 1931 and Basset, Eldon and McCann (136) in 1932. He even went so far as to surmize that the action of the sodium ion was on the osmotic pressure in the tissue spaces.

With the impetus thus given to the tissue and tissue space site of the actions of the sodium by both Widal and Loeb, it was natural that Marriott (137) should come forward in the following year with this analysis: "Edema arises from a change in the permeability of vessels and cells. Fluid and salts pass through the vessel walls into cells and

cavities, and by this method fluid and salts are held back so that even the normal kidney can not excrete them. The kidney is not a party to edema, for kidney removal does not give edema. Krogh (70) added his approval to this concept of the peripheral loss of salt and water by pointing out that at any time, normal or pathological, the capillary could not hinder or accelerate the absorption of sodium chloride or water, that they were free as crystalloids to diffuse through at all times.

The above findings focused the attention of two later experimenters on the actual proof of increased sodium content in tissue using chloride detection tests, our best index, to sodium levels by virtue of the chlorides relationship to sodium. C. Achard (1) in 1930 was able to demonstrate a greater salt content of edema fluid than in blood. Caune, Jarvis, and Cooperstock, (36) in the same year, showed that the chloride of ascitic fluid were significantly higher than blood chlorides, but felt that tissue chlorides were not consistently higher in edema. In the course of these experiments Achard also noted that a muscles' ability to take up water was augmented in solutions containing an excess of sodium and decreased in solutions containing calcium. He then showed that when the calcium and sodium ratio fell to less than .04, edema resulted. Barker and Kirk (76) in 1930 and Kirk (99) in 1932 reported blood chlorides

were increased in dogs undergoing protein loss, but that gastric chloride, both total and free was reduced.

Equipped with the knowledge of Hastings and Eichelberger (138) that sodium does not normally occur in the cytoplasm, McClure, Terakats, and Hinman (48) got down to the task of specific measurement of the sodium, potassium and water content of a specific tissue. They found that the total muscle sodium content was such as to be accounted for by the concentration of sodium that was in the extracellular fluid alone and that the total muscle potassium content was such as to be accounted for by the concentration of potassium known to be in the cells. Thus, normally sodium stays extracellularly and potassium intracellularly, and in this equilibrium thus established, the sodium and potassium were not capable of pulling water into the tissues. Studies of this conducted during edema showed slight increase 5-8 percent in the concentration of these bases, but these concentrations were not beyond physiological limits.

Thus, the trend of thought on the role of sodium chloride has culminated in a concept of the passive deviation of sodium chloride to the tissues in the transudation of water. In a series of studies during 1937 and 1938, Kerkhof (47) substantiated this interpretation by a new method. In the course of experiments employing gum acacia injections

on the therapeutical rationale of raising the intravascular osmotic pressure, he found that the method not only pulled the water out of the tissues but also the salt and that the kidney was perfectly able to excrete this salt in both nephritics and nephrotics provided the colloid osmotic pressure was high enough to draw it from the tissues. He thereby proved conclusively that retention of salt was not due to renal insufficiency but a consequence of a pre-renal deviation in to the edema fluid. A lowered osmotic pressure without salt intake results in no edema, but a lowered osmotic pressure with salt intake gives edema. If however, the colloid osmotic pressure is kept high no edema will result with or without salt.

Despite these conclusive-appearing results, there is one other group of findings to be considered. Stein (139) reports in 1940 on a case in which the globulin fraction was diminished, indicating a severe capillary damage. This case developed an edema upon the administration of intravenous sodium chloride. Quoting a conclusion of Eppinger, Kounitz, and Popper (140) that "Edema fluid rich in proteins interferes with normal nutrition," Stein felt that the intracellular edema he found at autopsy was explainable on a cell nutrition basis. He proposed that in some manner the capillary permeability was somehow altered, probably by the sodium chloride, so that the protein escaped and damaged

the cell walls. This damaged cell then permitted the entrance of salt, and the intracellular sodium produced the intracellular edema. It is of interest that the colloid osmotic pressure in the case was not lowered, as determined by measurement, and that the albumin was 8.2 grams percent and the globulin only 0.52 grams percent.

Chambers and Zweikach (54) recently demonstrated that a rise in the blood sodi um at the expense of blood calcium led to destruction and loosening of the intracellular cement of the endothelial cells of the capillary. If this if so the sodium ion may be factorial in creating permeability of the capillary.

The History of the Research on the Role of Lymph, Tissue Fluid, and Tissue Factors in Edema.

Virchow (8), the noted pathologist, was the first to propose that the mechanism of edema was dependent on factors arising in the tissues. In 1854 he thought that edema was due to an attraction of water to the tissue that arose as the consequences of malnutritional disturbances. Since then workers have entered into research purporting to explain the role of sodium chloride retention, the part played by the lymphatic system, the relation of tissue and edema fluid, and the possibilities of actual tissue change in edema.

D. Achard (20) in 1903 found no relationship between the ability of the kidney to eliminate sodium chloride or the retention of salt and edema. From this he concluded that sodium chloride retention was an extrarenal matter, most likely a tissue change. With this conclusion he linked the sodium chloride factor with tissue factors, a subject which merits an individual section elsewhere in this paper.

Beside the proposal of sodium chloride retention as as a tissue factor in edema there appeared another idea, fostered by Pinel (1) the discoverer of the lymph circulation, that edema was, at least in part, due to disturbance of the lymphatic system. Later Cohnheim and Lichtheim (9) in 1877 suggested that variations in the pressure of blood and lymph changed the amount of water in the tissues.

Heidenhain (12) in 1891, developed the concept that edema was a hypersecretion of lymph by the tissues, and set about to search for the lymph secreting structures; which, however, he never found. But the line of investigation he initiated led to recognitions of the common basis of lymph and tissue fluid, and the fact that edema fluid directly entered and altered both the lymph and tissue fluid.

Except for Starling's (15) (1896) suggestion that the proteids of tissue fluid were observed by the lymphatics, the evaluation of the lymphatic systems'role in edema lay dormant for some time. Meech, Goetsch, and Reeves (141) revived the problem seriously in 1934. In their experiments on dogs, they found an increase in lymph drainage during muscular activity in both normal and edematous dogs and that with venous return prevented, dogs were able to walk edema out of their legs. Coupled with this White, Field, and Drinker (142) also noted that high venous pressure was accompanied by an increased lymph flow. With these hints toward the fact that the lymph system was a route for the evacuation of edema fluid, Drinker et al (143) added to the picture by demonstrating, later the same year, that lymph obstruction raises the protein content of edema fluid to as high as five percent. The albumin-globulin ratio is even higher in edema fluid than in blood, and the

proteins represented show a fair degree of similarity to blood proteins. The conclusion from above and from their own research, that the lymphatics ducts drained the escaped protein in edema, was made by Lawson, and Hampden (144) in 1938. Studies that they made pointed to the conclusion that the lymphatics only aided in the removal of fluid in pathological extremes, and that normally the fluid which escaped the blood capillaries was exactly balanced by the fluid returning to them. They also attempted to measure the tissue fluid protein osmotic pressure and found it as high as 10 mm of mercury, a significant finding if corroborated and standardized to meet the new knowledge of the ability of protein systems and their osmotic power to alter. In addition to this Lawson and Hampden record this finding: When the blood pressure is elevated and, the capillary pressure also elevated, the lymphatics compensate for the increased filtration and no edema occurs; but if the venous pressure is high and the capillary pressure elevated, edema occurs. Although this hints of a qualitative difference between the high intra-capillary pressure due to high arterial pressure and the high intra-capillary pressure derived of elevated venous pressure, these authors are inclined to deny that the anoxia accompanying venous stasis might be causative of edema in this instance. They rebuttaled with the finding that the amount of tissue protein is not increased, as it would be if the anoxemia were to have

increased the permeability of the capillary wall. Their explanation is on the basis that ~~in~~ a steady increased pressure, as in elevated venous pressure, the lymphatics, is not as efficient in removing extravasated fluid as they are when the pressure changes due to arterial pulsation which help to keep tissue fluids and lymph flowing.

Directly contrary to this latter interpretation of the qualitative difference between high arterial-born pressure in the capillary and high venous-derived pressure in the capillary are Maurer's (51) Recent 1940 observation that increased carbon-dioxide tension and decreased O_2 tension in the blood gave an increased lymph flow. Paradoxically in this experiment the percent of protein in the lymph went down yet red blood cells appeared in the lymph and capillary permeability increased. He found a compensatory rise in colloid osmotic pressure in the blood which he felt might account for part of this paradox.

Meanwhile other investigators became interested in the analysis of edema fluid in order to shed light on not only capillary permeability but also ascertain if the fluid within the tissues space was exerting any osmotic pressure to draw fluid into the tissues. In 1918, Volhard (145) found edema fluid to be essentially a physiological salt solution with .02 to .05 percent protein. It was described as a thin colorless non-coagulable fluid with a specific gravity below 1.018. Later, in 1922, Epstein (26) also studied the protein content of edema fluid. He found the protein content much lower than the blood protein, but did note that the

protein content varied by disease. In nephritic patients the edema fluid possessed from .09 to .17 percent protein while in heart conditions the protein content was as high as .1 to .4 percent. Schade and Clausen (146) concluded in1924 that edema fluid had no measurable osmotic pressure. A. C. Kerkhof (47) checked and confirmed Epstein's finding in 1937 but felt that the possibility of increased colloid pressure in the tissues themselves could not be excluded.

On the chance that other constituents of edema fluid might be factorial in edema, C. Achard (1) in a series of determinations in 1930 collected data showing that the glucose concentration was lower than the blood concentration, that the urea concentrations were the same but that edema fluid chloride concentration was above that of the blood. This was somewhat confirmed by Caune, Jarvis, and Cooperstock (36), who in the same year, reported that the chloride concentration os ascitic fluid was higher than blood chloride, but claimed that this was not a persistent finding.

As early as 1898 the possibility that the tissue cells themselves might be functional in the production of edema was brought forward by J. Loeb (18). He found that frog muscle would take up water if perfused or bathed in acid or alkalie. The conclusion he drew was that edema formed secondary to the interference of oxidative processes in the tissues, as the result of this cell injury there was

an increased colloid osmotic pressure in the tissue. He later abandoned his theory because he could not correlate his osmotic pressure changes with other factors in edema.

Taking up the same line of thought, Fischer (21) in 1910 called attention to works proving the formation of lactic acid, succinic acid, and other organic acids in the course of muscular activity. He also pointed out that muscles anoxemic from activity, or from being bathed in anoxemic blood (as in heart disease) underwent acidification. Then likening a muscle to a colloid, he demonstrated by analogy the ability of colloids, like gelatin and fibrin, to take up water when acidified. From this basis, he proposed a process analogous to this one just mentioned called syneresis, as the mechanism of edema. Chemical changes, namely acid forming, within tissues provokes their colloidal property of taking up water, thus causing edema. He was inclined to place these hydrophilic properties mainly in the proteins. Ort and Moskowitz (147) proved that heart muscle edema varies with the ph just as does the hydrophilic properties of colloids.

Further fuel was given to this school of thought by C. Achard's (118) contribution in 1919 and which was based on the bio-chemical discovery that tissues absorbed water i n proportion to the lipocytic index of the tissue, i.e. the ratio of cholesterol to fatty acids. He studied the indices of patients, finding the index significantly elevated in

renal edema but normal in heart patients. There was evidence collected that the fatty acids resisted the cells intake of fluid, but that cholesterol lessened a cell's resistance to take up fluid, throwing the problem into the realm of the physical chemistry of surface tension. The observation by Aldrich (148) that toxic substances may change a cell's affinity for water, suggested to him that a toxic substance from an infected area might be instrumental in causing edema. Combining these two authors' contributions with the finds of Barker and Kirk (76) of a high cholesterol content in nephritic blood leads to an interesting challenge.

Despite the fine later work in this field the wave of reaction against Fischer's hypothesis has practically swept this factor out of consideration. L. Loeb (29) in 1923, Osman (149) in 1926 and Frisch, Mendol and Peters (83) in 1929, criticized Fischer by pointing out that microscopically edema was mostly in the interstitial spaces not the cells, that edema does not run parallel to the occurrence of acidosis and that Fischer's theory does not include the action of salts. Leiter (37) in 1931 also joined in the criticism quoting Schade and Clausen (146) to the effect that the colloid osmotic pressure of tissue fluid had then proved so low that it was unable to pull water out of the blood vessel: therefore, once the tissue (as assumed

by Fischer) started exerting osmotic pressure, it would have to exert it through a wall of tissue fluid of practically negligible osmotic power. Thus the tissue fluid would be a buffer between cell and blood vessel. Leiter himself added that if the tissue had affinity for water then there would be no free edema fluid in the interstitial spaces, but all of it would be taken up by cells or blood vessels, a condition contrary to the facts.

The Central Nervous System and the Endocrines As Factors in Edema

The possibility that the central nervous system was the key force controlling the water balance of the body was suggested by Bernard (10) as early as 1878. It was not until 1929, however, that a direct relationship of the central nervous system to edema was stated. At this time Elwyn (35) proposed that edema arose from a disturbance of the central nervous system control of water balance. He discounted the efforts of others to explain the entire mechanism on the basis of mere chemical and physical systems as osmotic pressure or hydrostatic pressure.

He drew on many previous reports to substantiate his contention nervous control over body water. He quoted Bernard, 1878 (10) Kahler (150) 1886, Eckhard C. (L51) 1903, and Jungman and Meyer (152 1913, to the effect that polyuria had been observed in high ventricular puncture. Aschner (153) in 1912, had shown polyuria from hypothalamic injury while Camus and Roussy (154) in the same year wrote up observations on a polyuria from a luetic involvement of the infundibulum and tuber cinerum. More applicable to Elwyn's thesis were facts presented by Pohle (155) in 1920 who was working on the frog. He observed that after extirpation of the bigeminal bodies that more water was taken up by the frogs' skin. But most of all, removal of the hypophyses actually gave peripheral edema. In the year just

preceding Elwyn's work, 1928, Baily (156) recorded a polyuria and polydipsia associated with a tumor of the third ventricle.

Upon this foundation Elwyn elaborated his thesis that edema resulted from a disturbance of the hypothalamic centers and the hormone pituitrin resulting in a change of the physical and chemical forces of the "peripheral constellation of electrolytes" which they control. He quotes Hamburger (28) on the statement that capillary permeability is influenced by the electrolytes sodium, calcium, He felt that potassium and magnesium in the blood are subject to nervous impulses.

He strengthens his endocrine participation in the mechanism by mentioning the following works: that Eppinger in 1917 (157) and Ascher in 1926 (158) found that thyroid gland changes upset the water balance of the individual, notably based on clinical experience of edema recession after administration of thyroid.

Klein (159) reported in 1926 that insulin also affects water balance. By quoting these Elwyn assumes that he has grounds for a generalized endocrine mechanism for edema on the basis of the interdependence and interrelationship of the endocrine glands. To this picture he adds observations demonstrating that a h rmone from the pars inter media and posterior pituitary gland has an inconsistent but definite effect on capillary t on us and the rate of water movement.

Elwyn's proposal met with a wave of criticism both in defense and on the basis of merit. Leiter (39) 1931, perhaps epitomized the opposition when he stated "Elwyn's . . theory is based too much on assumption, too highly teleological in concept to explain its upset at a slight glomerular damage." He was willing to admit the observations but the concept of this specific central nervous system--endocrine response in malnutrition, heart disease, and nephritis appeared too top-heavy.

Although Elwyn's proposals fell by the wayside, allergists and later endocrine investigations did not abandon the idea of an endocrine role in certain edemas. In 1938, Aykroyd and Zuckerman (160) proved that it was estrogenic substance that caused the swelling of sexual skin. In fact the protein of the interstitial fluid rose to 2.5 grams percent in phases of oestrogenic stimulation, which he accounted for on the basis of most cells discharging granules into the interstitial fluid (thus raising the osmotic power). It is of interest to note too that both cells and intercellular space swelled in this edema. Urged by the long standing observations of premenstrual edema, Thorn and Emerson (50), knowing that this edema was occurring in the presen ce of both estrogenic+corpus leuteum hormones, set about to find which hormone was responsible. Their 1940 article demonstrated that progesterone was the causative agent. Knowing that adrenal cortical

hormone gave edema upon injection, they gave the two ovarian hormones to adrenalectomized dogs. Only the progesterone was able to keep the dogs alive and the performance of the same functions as the adrenal cortical hormone.

It is also known that the posterior pituitary extract contains an antidiuretic principle. Silvette (161) in recent experiment 1941, found he could produce ~~anuria~~ diminished urine flow, but no pressure or oxytoxic actions in smooth muscle, thereby not being able to also affect blood vessel tonus.

He could get a repeated antidiuretic effect with repeated injections of post. pit. But repeated injections of the pressor substance loose their ability to raise B.P.

The Factor of Tissue Pressure in Edema

Starling (15) in his original proposal of the hydrostatic-osmotic pressure balance theory of fluid exchange recognized that the pressure built up by extravasated fluid being forced into the inter-spaces of an elastic tissue must be a factor in the control mechanism of edema. His personal idea was that normally the process of backward filtration in the connective of limb muscle and glands was impossible as the pressure of outside forcing water in would tend to collapse the blood vessel. But if the intra-tissue pressure is built up, absorption becomes possible because capillaries each have radiating fibers into the surrounding tissue and swelling in the tissues would distend the fibers and keep the capillary open. Only two years previous to Starling's publication, Landerer (11) measured the tissue pressure in edema, arriving at a figure of 550 mm of mercury. Subsequent workers have refuted this high figure. Geldenmeister and Hoffman (162) in 1922 found the subcutaneous pressure in edema patients to build up as high as 130 mm of mercury. Landis and Gibbons'(163) findings refute Geldenmeister and Hoffman, and are inclined to place greater credence on the technique and these results of Meyer and Holland:(164) 55 to 85 mm of mercury intracutaneously and 20 to 40 mm of mercury subcutaneously as read by direct manometer. By indirect methods Youmans and al in 1924 found the figures between

311 to 489 centimeters of water and Smart in the following year found figures from 40 to 180 cms of water in cases of heart failure.

Youmans et al (40) found that in standing there was increase in leg volume and that pressure increased three to five times. They concluded that the rise of tissue pressure was an important in the limiting the loss of fluid as was any compensatory increase in the colloid osmotic pressure. These authors attempted to formulate mathematically the loss of fluid from a capillary but as Smart (40) pointed out beside the three factors of hydrostatic pressure, blood protein, osmotic pressure, and tissue pressure (which they included as variables in their study) should have taken into account such factors as filtration rate, capillary vaso-dilitation, osmotic pressure ot tissues, and lymph flow.

Burch and Sodeman (44) reinvestigated the problem of the estimation of subcutaneous tissue pressure in 1937 in an attempt to eliminate factors not that were unevaluated in previous experimentation. They measured subcutaneous pressures at heart level and found they differed by the tissue involved. Their readings ranged from 17.9 to 37.1 cm of water, but in no tissue was the tissue pressure ever more than the accepted values for capillary or venular pressure. In testing the effect of raising venous pressure on tissue pressure, they found a very slow slight rise, confirmed by measurements on cardiac failure patients dis-

playing a slightly raised tissue pressure. In receding edema, the tissue pressures seem to fall below normal for a while, then gradually return to normal, a phenomenon which they explained as did Landis and Holland (165) on the collapse of a distended tissue and its gradual return to tone. In a summary they claimed that tissue pressure is the resultant of four factors: venous pressure, filtration ratio, skin distensibility and the lymph removal of fluid. It is significant that they found no increase in tissue pressure with the rise of arterial blood pressure.

In 1938 the problem of skin distensibility was attacked both by Burch and Sodeman (44), but also by Wells, Youmans, and Miller (166). The latter found that the sum of the osmotic pressure of blood colloids plus the tissue pressure of muscle of a standing individual was equal to the venous pressure, and that there was no myoedema. But in the same individual upon the moment of standing the tissue pressure of his skin plus the blood protein osmotic pressure was considerably less than the venous pressure, and that filtration of fluid into the tissue started. This transudation did not stop until, in two and one-half hours, the tissue pressure rose so as to balance the difference that had been originally existant. They felt that changes in osmotic pressure and tissue tension were sufficient to account for the gradual slowing of capillary filtration rate. Sodeman and Burch observed followed these observations

with reports that skin distensibility decreased in edema, returned with a lag after the recession of edema. They concluded that skin distensibility was definitely a limiting factor in edema.

In 1940, Allen and Hines (125) expressed the opinion that edema in standing was limited by increased tissue pressure and that if tissue tone is poor more fluid will escape and diffuse before the tissue pressure rises high enough to balance the filtration pressure. Sodeman and Burch applied the same idea to explain postural syncope. They found that patients suffering from syncope of this nature were suffering from a poor muscle and skin tonus.

The Problem

The force that motivates this particular paper is the hope that a survey of the literature on the mechanism of edema will afford a rational applicable concept of the factors at work. Further than that, there is the desire to discern if there are any general principles behind these factors that would enable us to better orient our clinical and research endeavors.

Accordingly then the problem of this paper is to examine and evaluate the research reports, to sketch any principles discovered as conclusions, and to formulate challenges for future research and clinical effort. The examination has been afforded by the two historical techniques in previous sections of the paper. An evaluation is now in order.

The Discussion

On the basis of a perspective gained by both a historical survey and an examination of the specific lines of investigation, there will be an attempt to delineate the significant aspects of the problem today. Since personal opinion and the exercise of prejudice will color these opinions, even more so than the personal choice factor in electing the research to be listed, it is best for the reader's evaluation to distinctly identify this section as personal.

In full realization of these limitations, let us first sketch the 1941 concept of capillary permeability. The capillary is now considered to be a structure normally impermeable to objects the size of a protein molecule, but relatively permeable to water and electrolytes. It is limited to the term relatively permeable because we know that water is not diffusing freely at the maximum rate possible through the pores of the capillary, that there are factors retaining most of the diffusible water within the capillary.

There seems to be two methods by which the capillary can become completely permeable: one, by the actual weakening of its intra-cellular cement from lack of the calcium ion; and two, by the opening of the capillary pores which are normally partially occluded. The first, of these above methods of opening to capillary wall to the passage of larger amounts of fluid and larger particles depends upon the effect on intra-cellular cement formation of the electrolytes in the blood. Prime illustration of this is a decrease in calcium ion occurring with an increase in the sodium ion that arrests the ability of the endothelial cells to secrete cementum enough to maintain their tissue continuity. This immediately reopens the case of the sodium ions role in edema. Perhaps the accquittal it has received in the last ten years has been premature.

The second method by which the capillary can be made more permeable is by the opening of the normally occluded pores in the capillary wall. These pores are kept closed or partially closed to the transudation of large amounts of fluid or large particles by two blood constituents; the blood platelets and the blood serum protein

The platelet action in occluding the pores can be compared to the action of a butterfly valve, closing the pore when pressure within the capillary is higher by covering the lumen and opening the pore when higher extravascular pressure forces it aside. Illustrations of this function can be seen in the minute localized capillary haemorrhages of thrombocytopenic purpura in which the platelet count is decreased, and in the partial arrest of edema that occurs by adding platelets to the blood stream.

The action of the blood serum protein in occluding the pores of the capillary is a surface activity phenomenon, depending on the physical property of the protein to line the capillary wall with a single molecule thickness layer, which because of the the size of the protein molecule would be about 4 mu. thick. This layer is of sufficient thickness to at least partially occlude the capillary pores which in their maximum size in vaso-

dilatation have been measured and found to be about 6 mu. wide. The displacement of this protein layer by substances of a higher surface activity and lesser molecular size would open these pores wider, allowing more fluid to escape and particles of larger diameter to be lossed from the blood stream.

Consequently, the question of capillary permeability has resolved itself into three challeneges: one, the role of the calcium ion in edema must be studied with emphasis on detection of falls in blood calcium ion levels below that compatible with endothelial continuity; second, the blood platelet count must be followed in the various edemas and the possibility of whole blood transfusions be reconsidered; and third, the search for substances of high surface activity and smaller molecular size in the blood of the edematous patient must continue. This latter substance has been proven to exist, but now it must be identified. Perhaps it is the same force that is etiological in changing the protein dispersion and molecular weights in the albumin or globulin protein systems? The polypeptids appearing in the blood and the hypercholesteremia of nephritics must also be investigated as possible causative agents here, as should be the question of blood oxygen tension and carbon dioxide tession.

Though the above challenges are vital, they are by no means the whole story. We still must be aware that capillary permeability is only one of several doors that may be opened before tissue gathers water. We have still to show that brief periods of increased intra-capillary pressure do not cause the "blow-out" phenomenon recorded by Landis. We have still to evaluate the vasodilatation of the capillary by nerve or endocrines and the whole question of the relation of capillary tonus to permeability. In addition, we must also remember the possibility that enough fluid, protein free of course, could filter out of the normal partially occluded pores to cause an edema. This must be what occurs when the normal individual stands for a long period. Information showing the low protein content of the edema fluid of nephritics and the higher protein content of the edema fluid of cardiac patients leads to the suggestion that when the colloidal osmotic pressure is reduced enough fluid can diffuse out of the normal partially occluded pore to cause edema, but that in heart disease some qualitative change in the blood opens the capillary pores so that fluid and protein may escape. Thus, a different mechanism is erected as the general pattern of mechanism for cardiac and the low blood protein edemas.

In considering the part played by the blood constituents in edema, we can not, as others before us, throw aside the hydremic theory in full. We now know that the stage of dilution of the blood has a direct effect upon the transudation of fluid into the tissues, that dilution is immediately and automatically eliminated by a mechanism designed to keep the plasma volume constant. When a relative hydremia does exist, we know from studies of the physical properties of the protein systems in the blood, that the osmotic pressure exerted per gram of protein receds to levels beyond that accountable from pure dilution itself. In other words there is some form of internal compensation within the protein systems in which light weight molecules within the systems combine to form heavier molecules, the reduction in number of molecules lowering the colloid osmotic pressure exerted by each gram of protein. By this method fluid is freed to filter into the tissue resevoir or to be excreted.

If the above can be considered to be the body's normal mechanism of handling excessive intake of water, how then does this effect the concept of edema. In normality, the blood protein system thus sheds unwanted water and the excess is demonstrably emptied from the vascular channels thorugh the kidney though some may deviate to

the tissues temporarily to await their turn for excretion by a kidney which has a limited maximum capacity. On the other hand in pathology, the loss of the kidney outlet or the failure of the circulation to carry excess fluid to the kidney combined with some increase in the permeability of the capillary would result in the excess water being diverted into the tissues. Thus, we do have a rationale for limiting water intake, for we must appreciate the tendency of the blood protein systems to internally compensate for too much water by lowering the specific osmotic pressure.

The recognition of the internal compensation mentioned above as a qualitative alteration of plasma protein osmotic pressure does not in any way lessen the significance of quantitative alterations of osmotic power by protein loss or inability of the organism to compensate for chronic loss es. For the clinical problem of arresting such losses we must mobilize the information on capillary permeability given above and for the problem of increasing the regeneration of plasma proteins we should utilize the vital information in recent literature. Madden et al.(167) show that the curve of plasma replacement follows the protein intake curve, quantitatively and qualitatively, once the body protein stores have been depleted. They show that cystine, tryptophane, lysine and glycine are the essential

amino acids for plasma protein regeneration, that animal protein is more effective than vegetable protein, and that a diet of casein, liver, rice and potatoes gives the best results. They feel that in renal disease especially, the regeneration of plasma protein is a major problem for often that part of the body protein available for conversion into plasma protein is exhausted. It should be noted incidentally that during the conversion of body protein to plasma protein the protein breaksdown into polypeptids before resynthsis, a fact that may have bearing on the problem of permeability where already the polypeptids are under suspicion.

Recent work also should open our minds to the possibility that this internal compensation mechanism of the plasma proteins might be impaired pathologically in favor of a continuous low specific osmotic pressure, thus creating an edema. It is entirely possible that both the albumin and globulin systems might be so dispersed that their components would be combined into the heaviest molecular weights possible for each respective system. MacFarlane (42) has already noted that besides dilution, the factors of aging and the presence of other proteins can change the state of protein association, and he has emphasized that only slight environmental

changes were needed to reap large variations in the proportions of molecular weight fractions. Electrophoresis experiments show that measureable forces can alter by degrees the state of protein dispersion. Perhaps here lies the answer to those paradoxical cases of normal blood protein levels associated with clinical edema.

The very same background can be postulated to explain the paradox of low protein plasma level and no clinical edema. It is also possible that the dispersion state of proteins in each of the two systems, the albumin system and the globulin system, could be altered so that the lightest molecular weight fractions would predominate. As this would divide each gram of protein into the maximum number of particles the osmotic pressure would consequently be raised. Hoitink (168) found the specific osmotic pressure high after haemorrhage despite the plasma loss but could not correlate it with changes in albumin-globulin ratio, salt concentration, ph, lactic acid, or non-protein nitrogen. Perhaps here we have an example of internal compensation altered to the side of high osmotic pressure in order to better defend the body and prevent edema.

It is natural for us now to face the challenge of finding the forces, beside those given above, that

control the dispersion state of the two protein systems in the blood. Once we are equipped with this information we shall be able to give to the clinician tools so that he may not only aid regeneration and prevent the loss of plasma proteins but also obtain the maximum osmotic ability of those self same proteins. Here again, as in permeability the increased polypeptids and hypercholesteremia of edema patients must be related to proteins and their physical properties.

The problem of evaluating the role of hydrostatic pressure in edema is one of discerning just what conditions are physiological and just what conditions are experimental. Many of the investigators in this particular field have suceeded in demonstrating increased edema or increased lymph flow by raising the intracapillary pressure, but in obtaining these results they have resorted to techniques for raising the intra-capillary pressure that interrupt the blood flow and thus alter physically and possible chemically the conditions of their experiment. The question rises, "Does the pressure within the capillary ever physiologically rise to heighths sufficient enough tocause edema?"

We know from Griffith et al. (169) that in hypertension the intracapillary pressure is raised, if only slightly. Yet it is known that hypertensive individuals do not

develop edema except upon decompensation of the heart. Lawson and Hampden (144) confirm increased lymphatic flow in hypertension, but claim that it is the intermittent pulsatile pressure changes of a strong arterial pulse that milks the venous and lymphatic channels, keeping the drainage adequate enough to prevent edema. Thus, we do have evidence of an elevated intra-capillary pressure of arterial origin though the theories explaining the lack of edema under this condition are unconfirmed. But does intra-capillary pressure ever rise due to strictly venous conditions? Many experimenters have raised venous pressure and thus the intra-capillary pressure, but have they duplicated physiological conditions? Some have claimed that capillary pressure rises beyond normal in incompetency of the valves in the veins and also in venous stasis. An examination of the hydrodynamics of the system involved would question these claims.

At any one given point on the capillary wall, the pressure exerted against that point is equal to the column of fluid above that point, whether it be the arterial column or a venous column, plus the kinetic force of the blood in motion. This kinetic force is equal to the force exerted by the heart less the friction between the heart and the point in the capillary that is in question. Accordingly, the force against this point is always more when the fluid

is in motion than when the circulation is at rest. Thus, if the valves of the veins should become incompetent or the decompensation of the heart should dam back blood, creating a venous column above the point, the pressure against that point would still not be raised, for it is already supporting a column equally high through the arterial side of the system. Instead the pressure here would be lowered because the venous stasis would resist and thereby lower the kinetic force of motion.

On the basis of this reasoning we must assume that, clinically, edema does not arise from raised venous pressure. And further, if venous stasis is known to cause edema, then we must cease looking for some quantitative pressure change and center our attention on some qualitative change of blood peculiar to venous stasis. We must look for some physio-chemical blood change to explain cardiac edema, remembering that the edema fluid analyses of cardiac edema indicate that the substances occluding the capillary pores have been displaced. Thus, we come to the conclusion that arterial hydrostatic pressure increases do force more fluid out but that this transudation rarely goes above the limits of compensation by the lymph system; that although raised venous pressure does force out more fluid per cm. of water (144) increase than does raised arterial pressure, it does not occur

under physiological conditions. Instead it seems more logical to account for the advantage of raised venous pressure transudation over raised arterial pressure transudation, and the edema that occurs with venous stasis without raised pressures, on the basis of a change in the blood.

Having ruled out increased intra-capillary pressure as a factor in the common renal, malnutritional, and cardiac edemas, we must not overlook the fact that changes in posture still can alter the intra-capillary pressure. In standing a higher column of fluid must be supported by the capillary causing a tremendous increase in capillary pressure. This increase is accompanied by transudation of fluid into the limbs, an increase in size of the limbs, the rise of the subcutaneous pressure and an osmotic compensation by the blood proteins to adjust to the new situation. This mechanism, although it suggests bed rest in cases of edema, is not the pathology operative in renal and heart disease.

The trend of inquiry upon the role of sodium chloride in edema has culminated within the last ten years in the decision that it is passively deviated into the tissues along with other electrolytes and has no dynamic part in the causation of edema. However this crystalloid does augment edema clinically because the mechanics of its

diffusion are subject to the law of mass action.

When an individual takes in salt it diffuses equally through the free body water. Therefore one fourth of it would be still in the blood stream and the other three fourths in the tissue fluid, and the osmotic pressure exerted by the great numbers of sodium and chloride ions within the vascular system and without the blood vessels is nullified as a force in water exchange because of the free diffuseability through the capillary wall. As the kidney excretes salt it removes that in the vascular system, thus lowering the salt concentration intravascularly and causing a diffusion of ions from the tissue resevoir into the blood stream until the the intravascular and extravascular concentrations are once more equal. With this diffusion of ions into the blood vessel the is an accompanying diffusion of water molecules out of the vessel as a complementary function to equalize the concentration at all points of this electrolytic solution. Thus, the mechanics of diffusion tend to work counter to the forces absorbing an edema fluid as long as the kidney continues to excrete salt and keep the intravascular concentration lower than the extravascular. So long as there is sodium in the body above the renal threshhold salt will aggravate an edema, and it will continue to do so during the long process of diffusing the sodium of the tissue fluid into the blood stream, a process which

becomes progressively slower as the amount of salt per unit of tissue fluid falls lower and lower.

Despite this exoneration of sodium chloride as a prime factor in edema, there has been work recently that incriminates sodium as an agent causing capillary permeability. Chambers and Zweikach contribution that has been cited above points to sodium creating a weakness in endothelial continuity by suppression of the cementum secretion promotion effect of the calcium ion. The rise of the amount of sodium over calcium in the blood also has been shown to cause muscle edema. Therefore we must keep our minds open to the possibility that sodium chloride intake is doubly active in augmenting edema

The lymph system can only be evaluated in terms of a limiting mechansim in edema. It is a system capable of draining the escaped protein and excess fluid from the site of the edema. The tissue fluid, except in terms of its sodium chloride content, has not yet been proven to be factorial in edema but the same can not yet be said about the tissues themselves. Although Fischer's particular mechanism for the absorption of water by tissues has been ridiculed out of existence, there is still no proof that osmotic pressure exerted from within the cells might not be complementing some other factor pulling water into

just into the tissue spaces. Pathological examination of tissues show that not all edema is extra-cellular. C. Achards findings on the effect of the lipocytic index on the hydrophilic properties of tissue cells as well as Gaune, Jarvis and Cooperstock's report on sodium-calcium ratio, mentioned in the paragraph above, show extensive literary and experimental background to the existence of intra-cellular edema. Evidentally the story of intra-cellular edema is a chapter yet to be written.

The factor of tissue tone and tissue pressure can also be identified as a limiting factor in edema. The distensibility of a tissue determines just how much fluid will escape before the extravascular pressure will build up high enough to equal the intravascular pressure. At the point where transudation stops, the hydrostatic pressure will be found to be equal to the sum of the tissue pressure, colloid osmotic pressure, and the compensatory drainage by the lymph system.

An examination of the meagre data gathered on the relation of the endocrines and the central nervous system to edema indicates at once that the background it too inadequate for a balanced evaluation. Necessary foundation to the formulation of an opinion upon these factors demands additional information on such phenomena as the alternate constriction and dilatation

of capillaries in any given bed and the alterations of capillary flow that occur with sensory perceptions of pressure, temperature, and whatever stimuli operate in inflammatory conditions. We need correlations of academic knowledge of the nervous control of blood flow with clinical situations. In the field of the endocrines, we again need careful confirmed research and clinical experience. From the reports of allergists and others we have evidence against both ovarian hormones, the adrenal cortical hormone, and the anti-diuretic factor of the posterior pituitary body as agents causing edema in some of its rarer forms. Here again, in discretion, one awaits a greater factual background before treading upon unproven ground.

Conclusions

1. Salient findings on the factors operative in the edemas of heart disease, renal diease , and malnutrition have been examined.
2. Some capillary permeability exists normally, but permeability may be increased by electrolyte changes in the blood impairing the intra-cellular cement or by substances displacing the adsorped layer of protein molecules and blood platelets that line the capillary wall and partially occlude its pores.
3. The colloid osmotic pressure exerted by the blood plasma protein systems is capable of being altered not only by changes of the amount of protein present in the blood stream but also by internal rearrangements of molecular size within the protein systems.
4. Hydrostatic pressure increases are capable of causing increased transudation of fluid into the tissues, but they do not occur as factors in the clinical edemas. The increased transudation of venous stasis is not due to increased intra-capillary pressure but to qualitative changes in the blood.
5. Sodium Chloride passively diffuses into the tissues and mechanically slows the absorption of edema fluid

by the transudation of water into the tissues in the process of equalizing the extra-vascular and intra-vascular sodium chloride concentration, the balance between which is constantly upset by renal excretion of intra-vascular salt.

6. Tissue pressure, skin distensibility, and lymph drainage are identified as limiting factors in edema.
7. Conclusions on the role of the nervous system and endocrines in edema were deferred until more pertinent information is available.

The Challenges

In accordance with the motive of this paper to reorient and redefine the directions for future clinical and laboratory investigation, the following challenges are included:

1. What alterations of sodium-calcium ratio occur in the common clinical edemas?
2. What alterations of the blood platelet count and platelet physiology occurs in the common clinical edemas?
3. What physiological or pathological blood constituents displace the protein molecular layer lining the capillary wall? Cholesterol, polypeptids, and salt should be among those investigated.
4. What is the effect of cholesterol, blood lipids, sodium chloride level, fibrinogen, oxygen tension, carbon dioxide tension, et al. on the dispersion of protein systems as

Selective Bibliography

1. Achard, C. The Oedema of Bright's Disease New York The MacMillan Company 1930

2. Bright, R. Practical Observations of the Nature and Symptoms of Dropsy. Guys Hospital Reports 1:848 1836

3. Senator, H. Uber die Wassersacht bie Nierenkrankhieten. Berlin Klin. Wchnschr. 32:165 1895 Quoted from (99)

4. Reese, O. On the Nature and Treatment of the Diseases of the Kidney. London Longmans 1850

5. Johnson, G. On the Diseases of the Kidney London J.W. Parker and Son 1852

6. Bartels, C. Formen von Chronische Diffuse Nierentsundungen. Samml. Klin. Votr. 25:1 1871 Quoted from (99)

7. Stewart, G. Practical Treatise of Bright's Disease of the Kidney. Edinburgh 1871 Quoted from (99)

8. Virchow, E. 1854 Quoted from (1)

9. Cohnheim, J. and Litchtheim, L. Uber Hydramie und Hydramisches Oedem. Virchows Arch. 69:1 1877 Quoted from (99)

10. Bernard, C. Lecons sur le Physiologie et Pathologie. Syst. Nerv. 1:398 1858 Quoted from (99)

11. Landerer, A. Die Gewebessparnung in ihren Einfluss auf die Ortliche Blut-und-Lymph Bewegung. Leipzig Quoted from (99)

12. Heidenhain, R. Versuche und Fragen sur Lehronder Lymphbildung. Arch fur ges Physiol. Quoted from Kirk (99)

13. Howell, W. A Textbook of Physiology. New York Saunders 1937

14. Csatary, A. Uber Globinurie 1891 Quoted from (99)

15. Starling, E. Physiological Factors Involved in the Causation of Dropsy. Lancet 1:1331 1896

16. Winter, R. De la Concentration Moleculaire des Liquides de L'Organisme. Arch. Physiologie 8:114 1896

17. Reichel, O. Zur Frage des Oedems bie Nephritis. Centralb. Inn. Med. October:41 1898 Quoted from (99)

18. Loeb, J. Physiologische Untersuchungen uber Ionenwurkungen. Pflugers Arch. 71:457 1898 Quoted from (99)

19. Widal, F. La Retention Renale de Chlorures et la Pathologie de l'oedeme Brightique. Bull. et Mem. Soc. Med. 12 Juin:678 1903 Quoted from (99)

20. Achard, D. Retention des Chlorures et Pathogenie de L'oedeme. Sem. Med. 23:259 1903 Quoted from (99)

21. Fischer, M. Edema: A Study of the Physiology of Water absorption by the Living Organism. New York J. Wiley and Sons 1910

22. Volhard, F. Brightische Krankheit. Mohr und Staehelins Handbuch Inn. Med. 3:1149 1918 Quoted from (99)

23. Kollert, V. and Finger, A. Ueber das Verhalten der Lipoide bei der Akuten Nephritis im Kriege. Med. Klin. Berlin 9:840 1917 Quoted from (93)

24. Govaerts, V. Recherches Clinique sur le role de le Pression Osmotique des Proteins de Sang. Bull. de L'Acad de Med Belg. 4:161 1921 Quoted from (32)

25. Bock, A. The Constancy of the Volume of Blood Plasma. Arch. Int. Med. 27:83 1921

26. Epstein, A. Further observations on the Nature and Treatment of Parenchymatous Nephritis. Am. J. Med. Sc. 163:167 1922

27. Krogh, A. The Anatomy and Physiology of the Capillary. Page 265 New Haven The Yale Press 1922

28. Hamburger, R. Die Verunderlichkeit der Permeabilitat Zucker. Biochem. Ztschr. 128:207 1922 Quoted from (99)

29. Loeb, L. Edema. Med. 2:171 1923

30. Schade, H. and Clausen, F. Osmotic Plasma Pressure and Edemas. Zeit. Klin. Med. 100:363 1924 Quoted from (99)

31. Linder, G. Jundsgaard, C. and Van Slyke, D. The Concentration of Plasma Proteins in Nephritis. J. Exper. Med. 39:887 1924
also, Changes in the Volume of Plasma and the Absolute Amount of Plasma Protein in Nephritis. J. Exper. Med. 39:921 1924

32. Verney, E. The Osmotic Pressure of the Proteins of Human Serum Plasma. J. Physiol. 61:319 1926

33. Landis, E. Microinjection Studies of Capillary Permeability. Am. J. Physiol. 83:528 ibid 82:217 1927-8

34. Fishberg, E. and Fishberg, A. The Mechanism of Lipemia in Bleeding. Proc. Soc Exper. Med 25:296 1928

35. Elwyn, H. Edema and Its Treatment. New York The MacMillan Company 1929

36. Caune, D. Jarvis, K. and Cooperstock, M. Metabolic Studies in Nephrosis. Am. J. Fis. Child. 40:465 1930

37. Murphy, P. Chronic Glomerular Nephritis with Lipoid Changes. Arch. Int. Med. 45:23 1930

38. Underhill, F. Fish, M. and Kapsur, A. The Mechanism of Water Exchange. Am. J. Physiol. 95:302 1930

39. Leiter, L. Nephrotic Edema. Arch. Int. Med. 48:1 1931

40. Youmans, J. Wells, H. Donley, V. and Miller, D. The Effect of Posture on the Serum Protein Concentration and Colloid Osmotic Pressure of the Blood from the Foot, and the Relation of the Formation of Edema. J. Clin. Invest. 13:447 1934

41. Weech, A, Goetsch, E., and Reeves, E. The Flow and Composition of Lymph in Relation to the Formation of Edema. J. Exper. Med. 60:63 1934

42. MacFarlane, A. An Ultracentrifugal Investigation of the Serum Proteins. Biochem. Journal 27:407 1935

43. Landis, E. The Passage of Fluid through the Capillary Wall A, J. M. Sc. 193:297 1937

44. Burch, G. and Sodeman, W. The Estimation of the Subcutaeous Pressure by a Direct Method J. Clin. Invest. 16:845 1937

45. Sodeman, W. and Burch, G. Direct Method for the Estimation of Skin Distensibility with its Application to the Study of Vascular States. J. Clin. Invest. 17:785 1938

46. Holling, H., Beecher, H., and Linton, P. The Study of the Tendency to Edema Formation Associated with Incompetency of the Valves of the Communicating Veins of the Leg. J. Clin. Invest. 17:555 1938

47. Kerkhof, A. Plasmapheresis: Experiments of its Influence Upon Colloid Osmotic Pressure, Water, and Salt in Edema. Ann. Int. Med. 11:1407 1938 also ibid 11:864 1937

48. McClure, W., deTakats, C., and Hinman, W. Changes in the Water Content of Blood during the Course of Edema of Renal Type in Children. Am. J. Dis. Child. 42:725 1931

49. Aykroyd, O., and Zuckerman, S. The Factors in Sexual Skin Edema J. Physiol. 94:13 1938

50. Thorn, G. and Emerson, K. The role of the Gonadal and Adrenal Cortical Hormones in the Production of Edema. Ann. Int. Med. 14:757 1940

51. Mauer, F. The Effect of Decreased Blood Oxygen Tension and Blood Carbon Dioxide Tension on the Flow and Composition of Cardiac Lymph. Am. J. Physiol. 131:331 1940

52. Danielli, J. Capillary Permeability and Edema in the Perfused Frog. J. Physiol. 98:109 1940

53. Cristal, P., Fourcade, J. Diamino Acids and Diamino Acid Polypeptids in Normal and Pathological Blood. Comp. Rend. Soc. Biol. 131:636 1939

54. Chambers, R. and Zweikach, B. Capillary Endothelial Cement in Relation to Permeability. J. Cell and Comparative Physiol. 15:355 1940

55. Castaigne, J. Le Role de Rein dans la Retention Chlorures. Sem Med 25:472 1905 Quoted from (99)

56. Timofeew, S. Zur Frage von der Pathogenese der Nephritischen Oedem Berlin 1909 Quoted from (99)

57. Magnus, R. Uber Diurese. Arch. Exper. Path u. Pharm. 31:10 1901 Quoted from (99)

58. Chisolm R. The Regulation of Blood Volume in Experimental Nephritis. J. Path. Bact. 19:365 1914

59. Boycott, A. and Douglas, J. On the Attempt to Discover the Composition of Tissue Fluid in Normal and Nephritic Animals. J. Path. Bact. 19:528 1914

60. Bogert, L., Underhill, C. and Mendel, B. The Regulation of the Blood Volume after the Injection of Saline Solution. Am. J. Physiol. 41:189 1916

61. Beckman, K. Oedem Studein. Deut Arch. Klin. Med. 135:39 1921 Quoted from (99)

62. Marriott, M. Nephritis in Children. Med. Clin. N.A. 7:1415 1924

63. Clausen, S. Parenchymatous Nephritis. Am. J. Dis. Child. 29:582 1925

64. Essex, H., Power, M. and Ort, J. Erythrocytes and Oxygen as Factors in Determining the Permeabilith of Animal Tissues in General. Proc. Am. Physiol. Soc. in Am. J. Physiol. 47:551 1931

65. Drinker, K. and Field, M. Lymphatics and Lymph Tissue Fluid. Baltimore Williams and Wilkins 1933

66. Landis, E., Jones, L., Angevine, M. and Erb, W. The Passage of Fluid and Protein through the Human Capillary Wall, During Venous Congestion. J. Clin. Invest. 11:717 1932

67. Landis, E. The Passage of Fluid through the Capillary Wall. Am. J. M. Sc. 193:297 1937

68. Duran, R. The General Permeability-Increasing Effect of a Factor of Mammalian Testicle on the Blood Capillaries, Yale J. Biol. Med. 11:601 1939

69. Parsons, R. and McMasters, P. Normal and Pathological Factors Influencing the Spread of Vital Dye in Connective Tissue. J. Exper. Med. 68:869 1938

70. Krogh, A. The Anatomy and Physiology of the Capillaries. New Haven Yale Press ed 1922, 1929

71. Conklin, R. The Formation and Circulation of Lymph in the Frog: The permeability of Capillaries. Am. J. Physiol. 95:98 1930

72. Koranyi, A. Physiologische und Klinische Untersuchungen uber dem Osmotichen Druck Thierischer, Flussig Kieten. Budapest Pallas 1896

73. Briggs, A. The Acidosis of Nephritis. Arch. Int. Med. 49:72 1932

74. Linder, G., Jundsgaard, C., Van Slyke, D. and Stillman, E. Changes in the Volume of Plasma and the Absolute Amount of Plasma Protein in Nephritis. J. Exper. Med. 37:921 1924

75. Brown, G. and Rowntree, L. Blodd Volume in the Edema of Nephritis and Nephrosis. Arch. Int. Med. 41:44 1928

76. Barker, M and Kirk, E. Edema in Dogs in Relation to Edema of Renal Origin in Patients. Arch Int. Med. 45:319 1930

77. Epstein, A Concerning the Causation of Edema in Chronic Nephrosis. Am J. M. Sc. 54:638 1917

78. Moore, N. and Van Slyke, D. The Relationship between Plasma Specific Gravity, Plasma Protein Content, and Edema in Nephritis. J. Clin. Invest. 8:337 1930

79. Denton, M. Feeding Experiments with Raw and Boiled Carrots. J. Biol. Chem. 36:249 1918

80. Harden, A. and Zilva, S. Edema Observed in a Monkey. Lancet 197:780 1919

81. Maver, M. Nutritional Edema and War Dropsy J. A. M. A. 74:934 1920

82. Kohman, E. The Experimental Production of Edema as Related to Protein Deficiency. Am. J. Physiol. 51:378 1920

83. Frisch, R. Mendel, L. & Peters, J. The Production of Edema and Serum Protein Deficiency in White Rats by Low Protein Diet, J. Biol. Chem. 84:167 1929

84. Shelbourne, S. & Egloff, W. Experimental Edema Arch, Int. Med. 48:56 1931

85. Bruckman, F. and Peters, J. The Plasma Proteins in Relation to Blood Hydration. J. Clin. Invest. 8:541 1930

86. Landis, E. & Leopold, S. Inanition Edema Associated with Tuberculous Enteritis. J. A. M. A. 99:1378 1930

87. Marriott, W. Infant Nutrition. St. Louis. Mosby 1930

88. Wolferth, C. Inanition Edema Associated with Alimentary Disturbance in Adults. Med. Clin. N. A. 8:785 1924

89. Leiter, L. Experimental Edema, Proc. S. C. Exper. Biol. Med. 26:173 Quoted from Kirk, C. J.

90. Peters, J. Bruckman, F. Eiseman, A. Hald, D. & Wakeman, A. Serum Protein in Nephritic Edema, J. Clin. Invest. 10:941 1931

91. Payne, S. & Peters, J. Plasma Protein in Relation to blood Hydration. J. Clin. Invest. 11:103 1932

92. von Porkas, A. Zum Problem der Berechnung des Kolloidosmotischen Druckes der Bluteiweiss korper Ztschr. f. d. ges Exper. Med. 1935 97:18

93. Calvin, Jr. and Goldberg, A. Cholersterol and Edema. Am. J. Dis. Child 41:1066 1931

94. Salvesan, T. Hyperproteinemia in a Case of Nephsosis. Acte Med. Scanda 65:152 1936 Quoted from Kirk (99)

95. Peter, J. Bruchman, T. Eiseman, A. Hald, P, and Wakeman, A. Plasma Protein in Relation to Blood Hydration. J. Clin. Invest. 11:97 1932

96. Fishberg, E. The Relation of the Serum Protein and Lipids to the Osmotic Press. J. Biol. Chem. 81:705 1929

97. Sorensen, S. Comp. Rend. Trav. Lab. Carlsberg 18:1 1930 Quoted from Block (100)

98. Goettsch, E. and Lyttle J. Precipitation Studies of Sera in Nephrosis and Nephritis. J. Clin. Invest. 19:9 1940

99. Kirk, E. J. Studies of Edema, Especially Edema of Renal Origin. Omaha. Theses to Nebraska College of Medicine 1932

100. Block, R. Darrow, D. & Cary, M. The Basic Amino Acids of Serum Protein, J. Biol. Chem. 104: 347 1934

101. Yanagi, K. A Clinical and Experimental Study of the Stability of the Colloid Osmotic Pressure of Serum Protein. J. Clin. Invest. 14:853 1935

102. Svenberg and Sjogren, B. The Molecular Weights of Serum Albumin and Serum Globulin. J. Amer. Chem. Soc. 50:3318 1938

103. McFarlane, A. An Ultracentrifugal Investigation os the Serum Proteins. Biochem. J. 29:407 1937

104. Melnick, D. & Cowgill G. The Serum Protein Complex as a Factor in Regulating Blood Volume. Proc. Soc. Exper. Biol. & Med. 35:312 1936

105. Bourdillon, J. Osmotic Pressure Study of Protein Fractions in Serum in Normal and Nephrotic Subjects, J. Exp er. Med. 69:819 1939

106. Jameson, E. Alvarez-Tostado, C. Qualitative Separation of Proteins of Rat Serum by Electrophoresis. Proc. Soc. Exper. Biol. Med 40:476 1939

107. Thompson, W. Thompson, P. and Bailey M. The Effect of Posture on the Composition and Volume of the Blood in Man. J. Clin. Invest. 5:573 1927

108. Youmans, J. Akeroyd, J. & Frank, H. Changes in Blood and Circulation with Changes in Posture. J. Clin. Invest. 14:739 1935

109. Moore, N. & Stewart, N. Variation of the Specific Gravity of the Blood and the Means Available to Alter it. J. Clin. Invest. 16:845 1937

110. Blackwell and Bostock Outlines of a Course of Lectures on the Practise of Medicine p. 83 London R. Taylor. 1827 Quoted from Colvin (93)

111. Chrisison. On the Granular Degeneration of the Kidney and Its Connection with Dropsy, Inflammation, and Other Disease. p. 60. Philadelphia 1839

112. Kaiserling, and Orgler. Double Refractile Lipoids in the Urine of Renal Disease. Virchow. Arch f. Path. Anat. 167:296 1902

113. Adams and Aschoff. Proc. Roy Soc. London 78:359 1906 Quoted from (93)

114. Port, F. Deutsches Arch. f. Klin. Med 99:259 1910 Quoted from (93)

115. Chaufford, A. Laroche, R. & Grigaut. Comp. Red. Soc. de Biol. 70:108 1911 Quoted from (93)

116. Lowenthal, Virchows Arch. Path. Anat. 261:109 1926 Quoted from (93)

117. Bennett, I. Davis, D. & Dodds, E. Studies in Renal Disease Lance t 1:3 1927

118. Achard, C. Ribat, A. & Leblanc, A. Le Coefficient Lipemique dans les hydropsies Comp. Rend. Soc. Biol. 182:539 1919

119. Maxwell, J. The Blood Cholesterol in Nephritis Quart. J. Med. 21:297 1928

120. Murphy Chronic Glomerular Nephritis with Lipoid Change. Arch. Int. Med. 45:23 1930

121. Krogh, A. Landis, E. & Turner, A. The Movement of Fluid through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood. J. Clin. Invest. 11:63 1932

122. Christian, H. The Mechanism of Edema. J.A.M.A. 97:296 1931

123. Starling, E. On the Fluids of the Body Chicago W. T. Keener 1909

124. Landis, E. Micro-injection studies of Capillary Blood pressure in Human Skin. Heart. 15:209 1930

125. Allen, E. & Hines, E. Lipedema of Legs. Proc. Mayo Clinic 15:184 1940

126. Swindle Mechanical Factors in Edema. Am. J. Physiol. 106:105 1938

127. Chaufford, A. Recherches de Physio-pathologie dans une cas distere infectieux. Sem. Med. 11 Avril 119 1900 Quoted from (99)

128. Strauss, H. Die Chorentziehungskur bei nier-und-Herzwassersucht, verhandl. Inn. Med. 26:91 1909 Quoted from (99)

129. Muller, V. verhandlanger der Deutscher Pathologischen Gesellschaft. Quoted from (35)

130. Volhard, F. & Fahr T. Die Brightsche Nierenkrankheit. p. 184 Berlin, Springer, 1926

131. Munk, V. Nierenkrankungen Berlin Urban und Schwarzenberg 1925

132. Ambard, L. & Weill, A. La Secretion Renale des Chlorures Sem. Med. 32:217 1912 Quoted from 99

133. Magnus-Levy V. Alkolichloride und Alkolikarbonate bei Oedemen Deut. Med. Woch. 46:594 1920

134. Blum, L. Recherches sur des sels alcalins dans la pathologie des oedemes. Press. Med. Septembre 685 1920

135. Weech, G. & Ling, S. Nutritional Edema. J. Clin. Invest. 10:886 1931

136. Bassett, S. Elden, C. & McCann, W. The Mineral Exchange of Man J. Nutrition 5:1 1932

137. Marriott, M. Nephritis in Children, Med. Clin. N. A. 7:1415 1924

138. Hastings, A. & Eichelberger, L. Bio.Chem. 117:73 1939

139. Stein, P. Phlebocylsis ædema Ill. Med. Journal 77:335 1940

140. Æppinger, H. Kounitz, W. & Popper, H. Die serose Æntrundung Vienna Springer 1935

141. Weech, A. Goetsch, Æ. & Reeves, Æ. The Flow and Composition of Lymph in Relation tothe Formation of Ædema. J. Æxper. Med 60:63 1934

142. White, J. Field, M. And Drinker, C.. On the Protein Content and Normal Flow of Lymph from the Foot of a Dog. Am. J. Physiol. 103:34 1933

143. Drinker, C. The Composition of Ædema Fluid and Lymph in edema:and Elephantiasis Resulting From Lymphatic Obstruction. Am. J. Physiol. 109:572 1934

144. Lawson & Hampden. The Physiology of Ædema Formation. Kentucky Med. J. 36:309 1938

145. Volhard, F. Bright'sche Krunkheit. Mohr und Staehelin's Handbuch Inn. Med. 3:1149 1918 Quoted from (99)

146. Schade, H. & Calusen, F. Osmotic Plasma Pressure and Ædema. Zeit Klin. Med. 100:363 1924 Quoted from (99)

147. Ort, J. Moskowitz, J. Hydrion Concentration and Ædema in the Perfused Heart of Rabbits. Am. J. Physiol. 94:60 1930

148. Aldrich, C. The Treatment of Nephrosis. Am. J. Dis. Child. 32:180 1926

149. Osman, A. A Study in Bright's Disease Guy's Hosp. Reports 77:412 1926

150. Kahler, P. Uber dauernde Polyurie als Cerebrales Herdsysptom Ztschr. Heilk. 7:105 From (35)

151. Æckhard, C. Zur Deutungder Æntstehung der vomvierten Ventriekl aus er zengbarently drurien Ztschr. Biol. 44:407 1903 Quoted from (35)

152. Jungman, P. & Meyre, E. Experimentelle Untesuchengen uber die abhangigkeit de nieren funktion vom nerven-system. Arch. Exper. Path. u Pharm. 73: 49 1913 Quoted from (35)

153. Aschner, B. Uber die function die hypophyse Pflugers Arch. 146:1 1912

154. Camus, J. & Roussy, G. Hypophysectomie et polyurie experimentales. Comp. Rend. Soc. Biol. 75:483 1913 Quoted from (35)

155. Pohle, E. Einfluss des Nierensystem auf die Osmoregulation der Amphibien. Pflugers Arch. 182:215 1920 Quoted from (35)

156. Baily, D. Some Unusual Tumors of the Third Ventricle. Bull N. Y. Acad. Med. 4:646 1928 Quoted from (35)

157. Eppinger, H. Zur Pathologie und therapie des Menchlechen Odoms Berlin Springer 1917 Quoted from (35)

158. Ascher, L. Der wasserstaffwechsel, Klin. Schnschr. 5:2385 1926 Quoted from (35)

159. Klein, O. Uber die Wirkung des Insulins und des Pituitrins auf dem wassermanschatt, Arch Exper. Path u. Pharm. 113:151 1926

160. Akkroyd, O. & Zuckerman S. Factors in Sex Skin Oedema. J. Physiol. 94:13 1938

161. Silvette, H. Renal Response to Repeated Administrations of Post Pituitary Extract Am. J. Physiol. 131:605 1941

162. Geldenmeister, & Hoffman, L. Uber Elastizital und Innendruck der gewebe Pflugers Arch. ges Physiol. 195:153 1922 Quoted from (44)

163. Landis, E. & Gibbon, J. The Effect of Temperature and Tissue Pressure in the Movement of Fluid Through the Human Capillary Wall J. Clin. Invest. 12:105 1933

164. Meyer, E. & Holland, C. Die Messung des Druekes in Geweben. Arch fur Exper. Path. u Pharm. 168: 580 1932 Quoted from § 163)

165. Landis, E. & Hilzrot Clinical value of Alternate Suction and Pressure in Treatment of Advanced Peripheral vascular Disease. Am. J. Med Sc. 189:305 1935

166. Wells, H.. Youmans, J. & Miller, D. Tissue Pressure as Related to Venous Pressure, Capillary Filtration and Other Factors J. Clin. Invest. 17:489 1938

167. Madden, S. C. Finch, C. A. Swabach, W. & Whipple, G. Plasma Protein Production and Utilization J. Exper. Med. 71:283 1940

168. Hoitink, A. Colloid Osmotic Pressure of Plasma and Composition of Blood after Acute Haemorrhage Arch Neerland Physiol. 24:169 1939 Quoted from (167)

169. Griffith, et al. Classification of Arterial Hypertension Am. J. Heart 21:47 1938