The Journal of the

American Medical Association

VOL. XXXII. CHICAGO, ILLINOIS, JANUARY 14, 1899. No. 2.

ORIGINAL ARTICLES.

A HISTORY OF THE THEORY OF EDEMA.

BY RUSSELL BURTON OPITZ, M.D., S.M.
CHICAGO, ILL.

The history of the theory of edema shows a striking similarity to the development of the theory concerning secretion and absorption. The latter theory, however, has gained a firmer basis at an earlier time, and the research pertaining to secretion and absorption has shown the way to that concerning edema. The two theories traveled almost identic paths until, through the work of Ludwig and Haidenhain, the theory of secretion and absorption reached pretty firm ground, leaving the solution of the question regarding the production of edema in the rear. Much less good work has been done on the theory of edema during the time following the publication of Cohnheim's first investigation in 1877. Indeed, the theory of edema has been a neglected problem, if we may judge by the few papers which have been published on this subject during the last six years. Still, within the last months, the theory has taken an important forward step through the work of Professor Loeb of the University of Chicago. At last, a firm physical and chemic basis has been given to the theory.

In secretion and absorption as well as in edema, solutions of organic and inorganic substances pass through animal membrane. To determine the driving force, has been, and is today, one of the greatest problems of physiology. Secretion and absorption took a decided step toward their solution when philosophic explanations—a speculative basis—were cast aside and rigid physical and chemic investigations were instituted which promised better results. Capillary pressure and filtration seemed then sufficient to explain the phenomena. A new area appeared after the investigations of C. Ludwig. His researches on the secretion of saliva put the driving-force not outside of the cell membrane, but inside of it, and showed that those complex units of the body, the cells, are not passively but actively engaged in the secretion of saliva. Of equal importance is Haidenhain's work on absorption and on the flow of lymph. Even lymph flow, seemingly the most simple case of the passing of fluid through animal membrane, can not be explained upon the basis of filtration and diffusion alone.

Much time could have been saved to the theory of secretion, if comparative physiology had been taken into consideration. Even in animals, insects, for instance, where blood-pressure is at a minimum, secretion is well marked. If physiology had not ignored the facts of comparative physiology, filtration and diffusion could not have been considered as explanations of secretion or allied processes.

Finally, we are forced to acknowledge "vitalismus," or the "vital force" of the cell. We may call it that, provided we bear in mind that this term has lost all of its metaphysic meaning, and that by it we mean only peculiar chemic and physical properties of the cell. Of course, we must acknowledge that the chemistry and the anatomy of the cell are only in their infancy today. Let us call to mind here the illustration of the steamship, with which Haidenhain opens his classic paper on intestinal absorption. As soon as we will have passed the difficulties which Haidenhain enumerates, we will be enabled to look more clearly into this matter, and a complete solution of the problems of secretion, absorption, and allied processes will be the consequence.

In 1827, Richard Bright showed beyond doubt that the presence of albumin in the urine pointed to a diseased kidney. According to him, edema finds its origin in blood poor in albumin. The "thinned" blood reaches the tissues by filtration, while the normal blood is too thick to pass through the vessel wall. Although this theory retained its place for the next fifty years, modifications of it were put forth as a consequence of observations. Albuminuria, for instance, exists without kidney lesions. Albuminuria, as found in scarlet fever and diphtheria, shows another fact. Although, in these diseases, the urine often contains a large amount of albumin, edema at the same time being very extensive, nevertheless, the urine is discharged in such small quantities that the extent of the edema and the discharge of albumin are not at all proportional. Again, in some lesions of the kidney, the discharge of albumin may go on for years, the quantity of urine be large, and yet edema may never complicate matters at all, or at least not until the final stage of the disease has been reached.

These facts modified the original explanation of Bright, so that the loss of albumin was not supposed to be the cause of edema, but only a favorable factor for an easy transudation of the fluid constituent of the blood. The principal cause of edema was supposed to lie in the retention of water in the blood, which even led to a thinned condition of the serum, and increased the amount of other fluids of the body.[1] Filtration, therefore, played the principal part in the transudation process.

It is undoubtedly true that the amount of urine is increased, if large amounts of fluids are taken into the body. It is also known that during edema, the urine is diminished, while again, during the absorption of the edematous fluid, the urine increases in quantity. This phenomenon takes place during inflammatory processes also. Might it not be true that the urine-quantity depends upon the transfusion of fluids, and not vice versa? These are two entirely different conditions.

All the complicating facts and suggestions originating from Bright's theory about the dependence of edema upon the quantity of albumin in the blood,

[1] Bartels: Ziemssen's Handbuch d. spec. Path. und Therapie, x, 1.

finally led Cohnheim and Lichtheim [2] to institute an investigation which should settle this controversy. Until the appearance of their research, the filtration theory had held undisputed sway. Although this theory was not disproved by their work, still, many facts showed that other factors besides filtration are involved in the production of edema. Their results have been the starting point for the modern theory of edema.

It is true that Magendie tried to disprove Bright's theory some time before these authors, by injection of distilled water into the circulation of dogs. By this means, however, the red corpuscles were destroyed, and Magendie's results were not at all conclusive.

Cohnheim and Lichtheim on the other hand, used 6 per cent. NaCl solutions in their experiments, by this means doing no injury to the solids of the blood. Dogs were used most frequently, and the injections were made into the jugular vein. Often enormous quantities of the solution were injected; in one instance, 64 per cent. of the dog's weight without fatal results. When the dog's abdomen was opened previously, 92 per cent. of the dog's weight could be injected before death took place.

A lasting increase of pressure in the arteries did not occur, a temporary rise of pressure, however, was unmistakable. This rise occurred immediately after injection and lasted for a time, possibly until the superfluous fluid had found a space by means of the elasticity of the vessel wall. Venous pressure remained close to zero throughout the experiments. The great power of the circulatory system to accommodate itself to a change in the amount of fluids present played surely an important part in these experiments. The pulse waves were increased in strength, and continued thus for some time after the injection. Undoubtedly, much depended upon the already injected fluid. All these phenomena were less marked at the beginning, and became more pronounced as more fluid was injected into the body. When the pressure rose, pulsation of the veins took place. These waves traveled from the heart to the periphery. The blood became lighter in color and thinned to a higher degree than that of a person afflicted with any disease of the kidney. Both blood and lymph flow were increased. A large amount of light-colored urine was discharged and often slight albuminuria was present.

In all the experiments, however, the injections were never followed by anasarca. Even after the injection of enormous quantities of the NaCl solution, the skin and underlying tissues were perfectly dry; however, dropsical effusions in certain parts of the body did occur. Ascites was produced in most of the dogs; also edema of the submucosa of the stomach and intestines. The pancreas showed a high degree of edema; the liver and kidney also. The organs and cavities of the thorax, on the contrary, were normal. Only in some cases, and toward the end of the experiment did edema of the lung occur. The glands in nearly all parts of the body were edematous.

The edema produced in these experiments has a peculiar distribution. In general, the organs which become edematous during kidney disease, showed no such indications during or after the injections of NaCl solutions. The reverse is also true. As far as an explanation of this phenomenon could be given Cohnheim has done so. All the facts point to peculiar conditions which result from the injections. There is, therefore, no connection between the edema following or accompanying kidney disease and the one produced by the injections. The latter has an origin peculiar to itself, while for the former new causes must be sought.

These authors, however, put to rest the old idea of Bright and others. The results of their experiments disprove the idea that the production of edema depended upon the amount of albumin in the blood. The claims that the lining cells of the vessels could not hold the "thin" blood, but allowed it to filter through the vessel wall into tissues and tissue spaces could no longer be considered. The filtration theory received a hard blow by these investigators.

The authors concluded, moreover, that an alteration of the vessel walls was necessary to allow the transfusion of fluid to take place. They were able to produce anasarca in certain parts of a dog by subjecting the part to irritants before the NaCl solution was injected. Whether these changes were thought to be chemic or physical is not definitely stated, but the latter is more likely to be true.

Gaertner [3] repeated the experiments of Cohnheim and Lichtheim, frequently getting opposite results, namely, considerable and extensive edema of the skin and underlying tissue. He attributes the results of Cohnheim's and Lichtheim's investigations to a too rapid injection of the NaCl solution. With Bartels, Stewart and Grainger, he holds that the principal cause of edema lies in the excessive amount of water in the system.

Fleischer [4] suggested that the normal kidneys removed the superfluous fluid from the circulation. He repeated Cohnheim's experiment of injecting a solution of NaCl after having litigated the ureters. No increased blood pressure nor edema of the skin resulted; however, dropsical effusions into the tissues and cavities of the body as enumerated by Cohnheim took place.

X. Francotte's [5] results again went against the results of Cohnheim, namely, in his investigations on eleven dogs and two rabbits, edema of the skin followed the NaCl injections.

The research of O. Lassar, made under the direction of Cohnheim, and published in 1877, concerns itself with inflammatory edema. The author endeavors to show whether during inflammation, an obstruction to the absorption of inflammatory material occurs, aiding thereby the production of edema, or whether a rapid lymph flow really frees the tissues of an accumulation of edematous fluid.

For his experiments he used the posterior extremities of dogs, in which an inflammatory process had been produced. For this latter purpose, applications of hot water or croton oil were made. Often injections of .5 to 1 c.c. of turpentin were used to bring about the same result. As a rule the leg was constricted, and placed in hot water. As soon as an inflammation set in the constrictor was removed.

In all instances, Lassar found that the amount of lymph, coming from a lymph-vessel of the inflamed extremity, was greatly increased. From a normal lymph-vessel of a dog's leg, hardly one drop in ten minutes escapes. From the inflamed extremity, on the other hand, the lymph dropped spontaneously and 20-40 c.c. of it could be obtained in a short time.

[2] Virchow's Archiv., 77.

[3] Wien. med. Presse, Nos. 20-21.

[4] Sitzungsb, der physik. med. Ges. von Erlangen. No. 1, Juli.

[5] Bull: Belge, 4 Ser. T. 11.

The greater the edema, the greater was the lymph flow. We might conclude, therefore, that the large mass of exudated fluid in the tissue produced, by mere pressure, the rise in lymph flow. Normally, the weight of the tissues, aided by muscular movements, pushes the tissue plasma into the lymph stream. According to this explanation, the rise in lymph flow would take place later in the process, after a sufficient exudation has occurred to exert pressure. Lassar, however, found that the lymph flow is increased from the beginning of the process when there is no sign of an exudation. An increase in the transudation must occur from the time the inflammation begins, and the lymph flow rises long before an accumulation of fluid could take place.

Emminghaus [6] has shown that the same is true in obstruction edema. Thus he constricted the leg of a dog sufficiently to obstruct the venous circulation and the flow of lymph from the leg was greatly increased. After relieving the constriction, physiologic conditions set in again. There is, therefore a striking similarity between edema produced by inflammation and obstruction. In both instances, there is a disturbance of the circulation, accompanied by edema and increased lymph flow. By a number of analyses, Emminghaus showed that there is a great difference in the characteristics and chemic composition of the fluids drawn from a leg which is inflamed and one in which stasis has taken place.[7]

This author also raised objections against Arnold's [8] idea that in diapedesis the blood corpuscles escaped through preformed stomata. A different explanation must be looked for as a consequence of the fact that the fluids of inflammation and obstruction edema differ so much in composition. If stomata did exist in the vessel walls, the difference in the composition of the two fluids is to be explained; moreover, the absence of a transudate even after an increase of capillary pressure. All the facts, therefore, point to changes which determine the permeability of the vessel wall.

In 1878, Professor Welch [9] of Johns Hopkins University, published the result of his investigations regarding edema of the lungs, made under the direction of Cohnheim in Breslau. After reviewing the prevailing causes of this type of edema, such as atrophy and hypertrophy of the heart, local inflammations, hyperemia, etc., he came to the conclusion that none of the causes serve as a sufficient explanation. Welch produced edema of the lungs experimentally in dogs and rabbits. He brought about this condition in rabbits after ligating the arch of the aorta, between truncus anonymus and left subclavian artery; all branches except one of the former had to be ligated also. In dogs, edema of the lung occurred after ligature of the aorta between heart and truncus anonymus. When he wished to produce edema of the lung by venous obstruction, it was necessary to ligate all veins of the left lung and those of the upper lobe of the right lung. Only after resorting to such measures was he able to produce edema of the lung in these animals. In man, such heroic measures would, of course, be out of the question. The author concluded, therefore, that an explanation of edema of the lung upon the base of active and passive hyperemia was entirely insufficient.

In other experiments, Welch was successful in producing edema of the lung by digital compression of the left ventricle, hindering its action thereby. If the right ventricle acts normally while its fellow does not, one of the principal conditions for the production of this type of edema may have been produced.

Mayer [10] made similar experiments. He produced edema of the lung in rabbits after ligating the large arteries of the neck. According to him, this type of edema is produced by an obstruction to the return of the blood from the lungs, and by the driving of blood into the organ by accessory forces, such as: 1, increased tonus of the vessel wall; 2, increased pumping force of the thorax; 3, spasms of muscles, principally of abdominal muscles and diaphragm.

Colin [11] concluded from experiments which he performed in 1883, that moderately complete venous obstruction was sufficient to produce edema, and that vasomotor nerves took an unimportant part in its production. Ranvier, on the other hand, said that vasomotor paralysis was a necessary factor in conjunction with venous obstruction. In order to reach some conclusion, Sotnischewsky [12] examined the question again. Edema was produced in the extremities of dogs and rabbits by simple constriction, no matter whether the nerves were divided or not. The constriction, or ligature, of course, had to be made in such a way that the afflux of blood was not disturbed. Venous return alone, had to be interrupted entirely, otherwise, collateral branches would carry on the circulation. Like Ranvier, this author found that even after obstructing one vein, edema resulted, provided the nerve supplying the vein had been previously cut. He explains this fact upon the ground that the vasomotor nerves are paralyzed, the amount of blood in the involved region is increased and the collateral branches are no more able to transfer the blood.

In 1883 Jankonski[13] took up the same question under the direction of Cohnheim. First he determined the question of how far nerve section and vasomotor paralysis influenced inflammation. In a normal dog, the lymph flow from the posterior extremity remained the same after the sciatic nerve of the involved limb had been divided. When, however, both extremities were inflamed, by the methods previously mentioned, and the sciatic nerve of one limb was divided, the lymph flow from the paralyzed extremity was increased. Upon the physical and chemic properties of the lymph, nerve section had no effect.

After this determination, the author added venous obstruction to the inflammation. This was produced either by constriction of an inflamed posterior extremity or by injections of plaster of Paris into the veins leaving the leg. The result was, that by the combination of the two conditions, the lymph flow from the leg was greatly increased, and the amount of lymph was larger in this case than if inflammation or obstruction had been used alone. If the sciatic nerve was divided in such an instance, the amount of lymph discharged from the leg became still larger.

NaCl injections were made in a number of instances to determine what effect upon the lymph flow would then be produced by nerve section. About one-half the mass of the blood of a dog was substituted by a solution of NaCl. (The amount of blood was figured at

[6] Arbeiten des phys. inst. zu Leipsig, viii Jahrgang.
[7] See Hoppe-Seyler, Physiologic Chemistry.
[8] Virchow's Archiv., 58 and 62.
[9] Virchow's Archiv. 72, xx.
[10] Sitzungsberichte der Akad. der Wissenschaften zu Wien. lxxviii. Abth iii.
[11] Bull. de l'Acad. de Med., No. 51.
[12] Virchow's Archiv., 77.
[13] Virchow's Archiv. Bd., 93, p. 259.

one-thirteenth of the body weight.) Three days later section of the sciatic nerve was made and the lymph flow observed. Simple obstruction to the lymph flow had no effect, but, after division of the sciatic nerve, a considerable increase in the amount of lymph followed. This result shows that a change in vasomotor action is a sufficient cause for the production of edema in an animal with "thinned" blood. This fact, seemingly, is of great importance in explaining the edema of cachectic individuals. The afflux to the paralyzed leg produced by enlargement of the blood-vessels, is not so considerable after nerve section as during inflammation; still, in the former case, the edema is more extensive. From this fact, the assumption follows that by the loss of nerve innervation, the walls of the blood-vessels are changed in an unknown way, and allow the fluids to escape.

A. Landerer's[14] investigations about the influence of the pressure of the tissue spaces upon lymph and blood flow have an important bearing upon the theory of edema. In order to see to what extent tissues possessed elasticity, the author used Braun's method upon different tissues, and found that they possessed this quality in a high degree. The tissues surrounding the capillaries, therefore, are of the same importance as are the media for the arteries. They serve as a reservoir to the capillaries. Edematous tissues on the other hand, have little elasticity, but possess expansibility in a marked degree. Of course the formation of edema may be due to a second cause, namely, continued expansion of the tissues as occurs during obstructions to the circulation.

In inflammation, the elasticity and firmness of the tissues and vessel walls is impaired. According to this author, alterations in the elasticity of the tissues is the primary factor in the change of the circulation of the blood and lymph. The phenomena of inflammation, therefore, follow the loss of elasticity of the tissues and not vice versa. By weight lifting, he demonstrated that inflamed tissues possessed marked expansibility, and little elasticity. To this loss of elasticity is added a greater pressure of the fluids within the tissue. This rise in pressure of inflamed tissues has been previously demonstrated by Quincke. The circulation is quickened by the loss of elasticity of the tissues, and Landerer hopes to have found in this a simple physical explanation for hyperemia. The dilatation of the capillaries is also a consequence of the loss of elasticity, and a condition favoring stasis. In general, Landerer considers inflammation and resulting edema as an impairment of the elastic equilibrium of the circulating fluids of the body. Wound healing and traumatic inflammation the author explains in the same way.

G. Salvioli[15] performed experiments in a similar manner as Cohnheim. His work, published in 1885, has given the following results:

Under constant pressure, NaCl solutions were injected which did not exceed 10 per cent. of the body weight of the animal. Hardly any effect was noticed, the superfluous fluid being removed by the kidneys. When solutions of a strength of 30-40 per cent. of the body weight were injected, different results were produced. Already during the experiment, all secretions of the body were increased. The amount of urine and saliva was large, tearing resulted, and the stomach often contained a large amount of water. These symptoms were followed by swelling of the abdomen, impaired circulation and respiration, and finally death. Postmortem examination showed an edematous condition of the intestinal walls, stomach, pancreas, liver, spleen and kidneys. The pleural cavities and the pericardium were free from fluid; moreover, edema of the lung did not always follow the injections. The skin, with the exception of the region around the eyes, the neck, and inguinal regions was perfectly dry. Practically the same results as those arrived at by Cohnheim and Lichtheim followed Salvioli's experiments.

Small quantities of injected fluid are of course easily removed by the kidneys. When larger amounts are injected, other organs must contribute to the removal of the superfluous fluid. Probably the intestinal canal serves as an eliminator of some of the fluid, if too much intravascular pressure follows the injection. The action may be similar to that produced in morphin poisoning. In general, however, the organs of the body vary greatly in their reaction to the increased mass of fluid, the variations being due to their difference in structure.

In order to determine how much depended upon the quality of the NaCl solution and upon the intravascular pressure in the production of edema, Salvioli made the following experiment: The author produced artificial circulation in the intestines and posterior extremities of different animals, using NaCl solutions with 40 per cent. resp. 10 per cent. of blood, under a pressure of 76-120 mm. mercury. While edema of the intestines was produced almost immediately, after injecting the second solution under low pressure, it took one to two hours and higher pressure for the appearance of the edema, when the first mixture was used. Edema of the extremities occurred much later, and only after increasing the pressure still more and obstructing venous return. By irritants, heat for instance, the edema was made more extensive.

Salvioli suggests no other force than filtration as an explanation for edema, however, one fact which the author puts forth should not be overlooked. He cautions investigators against applying the facts found by experiments upon animals, to man, without using some reserve in doing so. That the skin and underlying tissues in man become so easily involved in edema is undoubtedly due to their structural peculiarities. While the skin of man is such an important excretory organ, the same is not true in dogs. Cohnheim has already shown that horses died quickly of edema of the lungs, accompanied by hypersecretion of sweat, if NaCl injections were made. We see, therefore, that different animals are affected in different ways by these experiments, and the problem of edema in man will require different investigation and explanation for its solution.

According to Salvioli, the transudation is dependent upon the nutrition of the animal, the concentration of the injected fluid, and the pressure. His belief in the filtration theory becomes much more pronounced when he puts down as the principal cause of edema the permeability of the vessel walls, and endeavors to explain the problem upon a mechanical basis.

Similar to Landerer, von Basch[16] finds the cause for edema of the lung in the rigidity of the walls of the alveoli which has been brought about by a hyper-

[14] Die Gewebspannung in ihrem Einflusse auf die Örtliche Blut und Lymphbewegung, Leipzig, 108 S.

[15] Edrema et edimi idremici. Arch. per le Scienze med., Vol. viii, No. 21.

[16] Wiener med. Blaetter, No. 15.

emia of this organ. The elasticity of the tissue is lost, giving rise to edema. The appearance of edema of the lung in muscarin poisoning, M. Grossman[17] attributes to blood stasis, produced by spasms of the heart muscle. The spasms are stronger in the left than in the right half of the organ, increasing venous pressure in the right auricle, in the pulmonary artery and the left auricle.

That edema of the lung is due to an obstruction is denied by H. Sahli.[18] Neither the experiments of Welch nor those of Grossman are sufficient proof to him for such an assumption. From pathologic, anatomic and clinical facts, he assumes that edema of the lung has a local cause which lies in an alteration of the capillary walls. What this change is, whether physical or chemic, he does not state. According to him, impaired action of the left auricle (Welch) and spasm of the heart muscle (Grossman) can never cause a rise of blood pressure in the circulation of the lungs, necessary for the production of edema. This is undoubtedly well proven by later experiments.

The anasarca of the lower extremities occurring during ascites and cirrhosis of the liver is undoubtedly an obstruction edema, produced by pressure upon the inferior vena cava. In order to see what influence the pressure of the ascitic fluid has upon anasarca of the lower extremities, G. B. Queirolo[19] measured the lower limbs before and during withdrawal of the dropsical fluid from the abdominal cavity. With the removal of the fluid the size of the limbs decreased. This certainly shows that in this and all similar pathologic conditions of this locality, an obstruction edema is formed by impairing venous return and the lymph flow from the leg. Undoubtedly, anasarca of the lower limbs does not always accompany ascites; this fact compelling us to believe that other factors must play an important rôle. It may, moreover, be true that the pressure exerted by ascitis or any other similar condition is not at all great enough to produce anasarca of the limbs, and that its primary cause lies in an impaired action of the heart. In the light of modern research, however, both conditions can be looked upon as exciting causes only, mere secondary causes as far as their importance is concerned. Obstruction, inflammation and similar conditions only pave the way for the real phenomena of edema.

As late as 1893, W. Dickenson[20] investigated the question whether filtration or diffusion played the principal rôle in edema. From a comparative chemic analysis of the blood and dropsical fluids, he concludes that diffusion is the principal factor in the interchange of salts, while blood pressure determines the escape of the albuminous constituents of the blood. The explanation of the fact that frequently we do not have edema during acute nephritis or renal calculi, this author finds in an impaired action of the heart, and in low blood pressure. When edema does occur the pressure is always high. In chronic nephritis, with or without edema, the blood pressure increases on account of hypertrophy of the heart and arteriosclerosis, accompanied very frequently by complications in the lung which lead to blood stasis. The occasional absence of edema in this disease, Dickenson attributes to an increased discharge of urine.

[17] Zeitschrift für klin Med., Bd. xii, S. 550.
[18] Zeitschrift für klinische Medicin, Bd, xiii, 5.
[19] Revista Clinica, No, 1.
[20] Medico-Chirurgical Transactions, vol. lvii, 317.

Finally, even diffusion seems not to be a sufficient explanation of edema. During edema, due to acute nephritis, the blood pressure is increased. When the disease becomes chronic the pressure rises even more, cardio-arterial changes set in and the edema decreases. As soon as the heart's action becomes insufficient, the edema increases again.

No history of edema would be complete without mentioning the work of H. Senator.[21] In 1868 he joined those investigators who hoped to arrive at a solution of the problem of edema by making the chemic composition of dropsical fluids the basis for further research. Although the knowledge of the composition and peculiarities of edematous effusions is not to be underestimated, it has never caused any advance of the theory of edema. On the contrary, it has served to prolong the life of the filtration theory, as a natural consequence of the results of the chemic analysis, which point rather toward filtration.

In order to show the influence of a different venous pressure upon the flow and composition of lymph, constriction of the lower extremities of dogs was resorted to, and after twenty minutes the fluid escaping from a trocar was examined. The amount of lymph was increased after constriction. In ten out of fifty cases the amount of albumin was the same as that of the blood; in thirteen cases it was increased and in seven instances decreased. Only in five of the thirteen cases, the increase in the amount of albumin was undoubtedly due to venous obstruction. The quantity of NaCl remained the same in five instances out of ten; seven times an increase and six times a decrease was noticed. An unquestionable result the method does not give, as even before constriction of the extremity a certain amount of transudation has taken place.

Senator considers the theory of Bright and Bartels to be wholly inadequate for explaining edema following nephritis. He upholds the theory of Cohnheim according to which the blood and lymph vessels not only in the skin, but also in the serous membranes, have undergone an abnormal change and have become more permeable. In edema following or accompanying scarlet fever, malaria, etc., the glomeruli of the kidneys seem to be greatly affected. It is certain, however, that as the poisonous substances continue to irritate the body, the blood and lymph vessels of other localities besides the kidney, become affected. According to this, Senator attributes the absence of edema in contraction of the kidney to a slow and small injurious influence of the disease-substances.

After having investigated the absorption of ascitic fluid, H. Hamburger[22] comes to the conclusion that the blood-vessels play the principal rôle in this process. The lymph vessels are involved in a lesser degree. The diaphragm serves as a pump by means of which the exudated fluid is forced into its lymph spaces and finally into the ductus thoracicus. The lymph vessels in the other part of the peritoneum, however, aid in the absorption. According to this author, osmosis can have no part in the process, also Haidenhain's theory can not be considered, as absorption takes place after extensive injury to the peritoneum and even after death. About the production of edema, Hamburger holds about the same view as Cohnheim. This is to be seen from his enumeration of the causes of obstruction-edema, which is as follows:

[21] Spec. Pathologie und Therapie (Nothnagel), xix, i, 1.
[22] Nederl. Tigdschr., 2$_4$ Aug. and 7 Sept., Virchow's Archiv, Bd. 141, ii.

1. Considerable venous hyperemia.
2. Increased permeability of the vessel walls (Cohnheim).
3. Disease substances which irritate the endothelium and exercise a peculiar influence upon the lymph flow.
4. Retarded absorption.

Lazarus-Barlow,[23] in his paper on the pathology of edema, tells us that the mechanical causes of edema are not at all satisfactory, but serve only as primary or exciting causes for the real phenomena of odema.

Only recently the theory of edema has taken an important forward step through the work of Dr. Loeb[24] of the University of Chicago. A physical and chemic basis has been given to the theory, and if its final solution has not been reached, at least the solution of the question must be close at hand. Just as the development of the theory of secretion and absorption is awaiting a thorough knowledge of the properties and functions of the cell, so will it be necessary for the theory of edema to await such an end before the final solution of the question will be possible.

According to Dr. Loeb, the transudation of the fluid into the tissues is greater than that of the blood and lymph. Such causes, therefore, must be at the bottom of edema as either increase the osmotic pressure of the tissues, or decrease it in the circulatory system.

First, the author demonstrates the possibility of a rapid change in the osmotic pressure of tissues; showing thereby that the forces which according to the filtration theory are able to produce edema are wholly inadequate. The pressure of a 0.7 per cent. NaCl solution, which is isosmotic to the blood and the resting gastrocnemius of a frog, amounts to 4.9 atmospheres. It is twenty times greater, therefore, than the blood pressure ordinarily present in physiologic investigations. Only a trace of acid or alkali in muscle increases the osmotic pressure to such an extent that the muscle becomes edematous in an 0.7 NaCl solution. By stimulation, the osmotic pressure is raised, and water is taken up by the muscle. After tetanizing the gastrocnemius of a frog for ten minutes, the increase in its osmotic pressure amounts to 1 atmosphere. After a few hours, the muscle in a 4.9 per cent. NaCl solution begins to take up water, the reaction becoming acid. The osmotic pressure of such a salt solution is over 30 atmospheres. The author concludes that through the influence of the original loss of water, chemic changes must take place in the muscle which raise its osmotic pressure by about 25 atmospheres.

When we compare these pressures with some produced by an increase of blood pressure, the absurdity of supposing that the latter are sufficient to produce edema is striking. During the experiments on the production of edema of the lung, Welch never got a greater rise in blood pressure than 1/10 atmosphere, in the lesser circulation. A rise in osmotic pressure of 1 atmosphere, however, occurs during common muscular exercise and an increase of 25 atmospheres can be produced quickly by chemic means. That is a rise 300 times greater than can take place during a change of blood pressure. The filtration theory, therefore, can not be considered, and osmotic pressure must be the principal factor in the production of the edema.

The cause for the presence of blood corpuscles and epithelial cells in edematous fluids, the author finds in the morphologically changed blood-vessels. This change is brought about by the same chemic substances (poisons) which produce the increase in osmotic pressure. For the purpose of showing that these poisonous substances may be produced by a lack of oxygen, Dr. Loeb gives several instances of similar processes. An ameba which suffers a lack of oxygen becomes contracted. Quincke thinks this is due to a disintegration of the more solid constituents of the ameba. If oxygen is taken from the developing eggs of *Ctenolabrus*, the walls of the splitting cells disintegrate. As soon as oxygen is admitted again, the cell walls become normal. The bodies of certain infusoria become fluid in an atmosphere poor in oxygen.

In order to disprove the supposition of the filtration theory, that during edema the fluid constituents of the blood are pressed into the tissues, Dr. Loeb made the following experiment. He used a number of frogs, in which the circulation of one posterior extremity had been completely stopped by a ligature. The gastrocnemii of both legs were then removed and weighed. Although the two muscles are equally heavy under ordinary circumstances, yet in all instances the gastromemius removed from the ligatured leg was heavier. Its weight increased with the time that had elapsed since the ligature was applied. After 16 hours, the weight of the muscle of the abnormal leg was about 1 to 3 per cent. greater than that of its fellow on the opposite leg; after twenty-four hours, the difference amounted to 15 per cent., and after seven days to from 25 to 40 per cent.

In order that there might be no possibility of an increase of blood pressure in spite of the ligature, and a consequent occurrence of edema, some gastrocnemii were removed and immersed in a physiologic NaCl solution. By this means, all possible circulation of blood was stopped, and a lack of oxygen was produced at the same time. These muscles behaved in the same way as those in the ligated leg of the frog; showing conclusively that the blood pressure has very little to do with edema.

It has been shown by Araki that sugar and lactic acid are excreted in the urine if certain amounts of oxygen are withheld from an animal. The increase of weight in a muscle in the experiments enumerated is accompanied by the formation of one or several acids. The nature of the acid (or acids) has not as yet been settled, but Dr. Loeb is inclined to think that lactic acid is one of the possibly several acids formed in the oxygen-starved gastrocnemii.

The favorable influence of nerve section upon the formation of edema, this author considers as not proven. Moreover, if this statement were true, this fact could not be utilized as an argument for the filtration theory. We know that nerves exercise direct chemic influences in secretory processes, and as the nature of the nerve innervations is yet indefinite, we may justly suppose that many, if not all, nerve-transmissions are of chemic origin. Gaule thinks that the nerve gives off a special substance, but Dr. Loeb suggests a dissociation of ions, if electric phenomena play a rôle in the transmission of impulses.

Professor Welch attributes edema of the lung to an increased blood pressure, but this driving force is entirely too small in comparison with osmotic pressure. Upon one fact, Professor Loeb dwells particularly. While in rabbits, the ligation of the principal branches of the arch of the aorta produces edema, this condi-

[23] British Med. Journal, March 23-30.
[24] Archiv für die ges. Physiologie, Bd. 70, 457.

tion does not occur in dogs under similar circumstances. Walther has shown that rabbits and dogs differ greatly in their reaction toward acids. While in rabbits, a sufficient quantity of acid proves fatal, dogs are almost immune against it. The difference in their reaction toward acids is caused by the greater amount of ammonia which is produced through the influence of the acids in dogs. It is not necessary to seek the cause for edema in the formation of acids directly, but it must be acknowledged that certain chemic peculiarities exist in these animals which determine the difference in the formation of edema of the lung.

Sigmund Mayer and von Sahli demonstrated that curare lessens the liability of the formation of edema of the lung, while muscular spasms favored its production. Their explanation has obstruction, increased blood pressure, and filtration for its basis; however, Professor Loeb gives a more interesting cause for this difference. The muscles are the principal seat of the oxidation processes and, therefore, in these structures the acids must be formed which are produced by a lack of oxygen. When curare is given, the metabolic processes of the muscles are reduced, and less poisonous matter circulates through the heart and lungs. Muscular spasms, on the other hand, cause an increase of these injurious substances and are, therefore, more liable to produce edema.

According to Professor Loeb, the cause of edema lies in the chemic changes which occur in the tissues, and which are mostly due to a lack of oxygen. These changes lead to an increase of osmotic pressure, which is greater in the tissues than in the blood and lymph. Morphologic alterations of the vessels are also a consequence of the chemic exciting cause. Such conditions as blood stasis, inflammation, etc., are only the primary causes which give rise to chemic changes and consequently edema.

For fifty years after Bright and Bartels, the filtration theory has held undisputed sway. Nobody seems to have considered any other force than mere filtration as an explanation for the minute phenomena of edema. Through the work of Cohnheim and his pupils, however, a future was given to the theory. Bright's theory was disproved and new factors were found which promised to be worthy of careful research. The frequent suggestion that an alteration of the vessel walls and blood pressure are the means by which the fluid escapes from the vessels, is only a part of the filtration theory. It is hardly possible that any other change than a mechanical one was thought of when an alteration of the vessel walls was mentioned. The work of Cohnheim, Welch and others has really been done in the interest of the filtration theory, the chemic side of the formation of edema having been neglected. Only recently the theory has found a physical and chemic basis through the work of Loeb. The theory of edema stands today where the theory of absorption stood before Haidenhain's classic paper was published. In spite of the many attacks upon Haidenhain's explanation, the merits of his work have not been lessened. In fact, the criticisms of the extreme physicists have only served to strengthen the belief that the cells play an important rôle and that osmotic pressure is not the only factor to be considered in absorption. Just as important is the physiologic state of the absorbing membrane. The same end has been reached in the theory of secretion through the work of Ludwig.

Why should edema be such a passive process? Undoubtedly it is true that not so much stress can be placed upon cell activity in edema as in secretion and absorption, naturally edema would be a more passive phenomenon. Just as secretion and absorption depend upon the physiologic condition of the cell, so does edema depend upon the pathologic state of the cell. Still it is best not to conjecture, but to await further developments of the theory of edema.

RETROMAXILLARY GROWTHS.

OPERATIVE TREATMENT, ESPECIALLY OF NASO-PHARYNGEAL FIBROMATA.

BY CARL BECK, M.D.
CHICAGO.

Among the tumors of the nasopharyngeal cavities which are amenable to operative treatment, the nasopharyngeal fibromata, or so-called nasopharyngeal polypi, are the most important. Sarcomata and carcinomata of this region may also be treated surgically, but when one considers how unfavorable the prognosis is, even in the case of a very good operative result, one must acknowledge that it is inexpedient to undertake so serious an operation for the sake of such a trifling benefit. Butler, who has paid particular attention to this question, finding an operative mortality of 30 per cent. and such a small number of cases free from recurrence after three years, arrived at the conclusion that the operation must be condemned unless there is a reasonable hope of obtaining better results in the future. In addition to the nasopharyngeal polypi and malignant growths, there are a number of very rare tumors which may be extirpated. The polypi, however, are clinically the most important. Histologically they are mostly fibromata or fibroangiomata which produce grave symptoms, even endangering the life, and their removal, as a rule, is followed by a complete cure. The question as to the best method of removing them has been discussed for a long time in the past, and even now there is a wide divergence of opinion on this point among surgeons.

The difficulties of the technic lie in the obstacles encountered in obtaining access to the growths. They arise in a region which can not be attacked through any natural opening, even with instruments of special construction, without making a considerable breach in the skeleton of the face. The development of the technic of the operation shows that surgeons are more and more endeavoring to replace the operation in the dark by an anatomic preparation under the guidance of the eye. Experience shows that pieces of the growth left behind after such operations of polypi cause not only recurrences, but degenerate and even become malignant (Koenig) and, therefore, the surgeon endeavors to remove the growth radically. On the other hand, others maintain positively that such relinquished pieces disappear spontaneously, that even the whole tumor of considerable size disappears after a certain age, say twenty-five years (Lafont-Gosselin), but it can not be discovered, a priori, what is going to be their course. Besides, there is another cause which was pre-eminently noticeable in one of my cases, calling for the most radical removal of these tumors. These fibromata are often multiple, and parts are liable to be overlooked, and these remaining small growths may develop to enormous size, as owing to the removal of part of the growth,