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The Microscope in its Relation to Medicine

BY DR. JAMES CARROLL, U. S. ARMY, WASHINGTON, D. C.

Mr. Chancellor, Gentlemen of the Board of Regents, Members of the Faculties and Graduating Class, Ladies, and Gentlemen:

I have chosen for my theme to-night a subject of great importance to the whole medical profession and to the communities who rely upon its members for the preservation of their health and happiness. The subject of "The Microscope in its Relation to Medicine" is one that appeals to me, because my daily work is with the microscope in its bearing on medicine; it appeals to you, members of the graduating class, because you come fresh from your laboratories where with the aid of the microscope you have learned the mysteries of the structure of the human body and have seen the infinitely minute living organisms that attack and frequently destroy it; it will appeal to the members of the various faculties present, because they all have used the microscope and must continue to use it more or less in their daily routine; it will appeal to the members of this intellectual audience who from their daily reading know that the microscope has revealed to us secrets of nature that without its aid would have remained impenetrable mysteries. To fully appreciate the value of this little instrument let us pause for a moment to consider what our condition in the world would have been without it. If this instrument had never been constructed, man would never have become familiar with those minute vegetable organisms that we well know to be the causes of cholera, plague, tuberculosis, typhoid fever, diphtheria, surgical gangrene, blood poisoning, and many other disease conditions so fatal to the human race. Imagine the world still overrun by those devastating epidemics and pestilences that formerly arrested progress, limited populations, and restricted intercourse, and it will be quite apparent that under such conditions man must necessarily have remained very close to the brute. When attacked by disease he would lie helpless, and his companions, being ignorant of the nature of the cause of his affliction, could do nothing more than flee from the locality of danger. The fascinating secrets of germ life would have remained a sealed book. The use of antiseptics and germicides would be unknown, and the majority of men engaging in war would die of blood-poisoning, gangrene, typhoid and typhus fevers, plague, cholera, or some other of those pestilences that ravaged the armies of the ancients. What is the actual condition to-day? Instead of fleeing from disease, man seeks it out, in order that with the aid of his microscope he may try to find its cause, and, having found it, learn its mode of attack and protect his fellow men against it. Compare the conditions cited with those in the contending armies in the late war between Russia and Japan, where the mortality from disease was trifling and the deaths from surgical affections so small as to astonish the world. Would that we relied more upon the microscope, for it was through the use of this little instrument the lessons were learned that enabled the Russian and Japanese surgeons to preserve the lives and health of their respective armies. We were much less successful in our Spanish war, and so were the English in South Africa, as will be seen from the frightful mortality rate of that commonest of camp and city diseases, typhoid fever. When our surgeons and physicians have received the training in bacteriology necessary to render them thoroughly familiar with the morphology and biology of the bacillus of typhoid fever, and not until then, can we put large armies into the field with the assurance that our sons and brothers shall be protected from that wholly unnecessary and preventable disease. Let us pause a moment to consider the benefits we have derived from the microscope in the enjoyment of the comforts of every day life. The immortal discoveries of Pasteur have disclosed the nature of fermentation and the fact that it is brought about by living vegetable organisms. It was he and Koch who showed that these organisms can be separated as individuals and the progeny of an individual be retained as a pure culture of the type of its species. He taught us that these living producers of ferments are widely distributed in nature, and that while many are beneficial, others are harmful and may even destroy life. He showed that with pure cultures of these vegetable organisms, called yeasts, beer of varying quality and flavor can be brewed, the quality depending upon the variety of yeast that predominates. On the other hand, he showed also that when the beer had become bitter or otherwise disagreeable the objectionable feature was due to the presence in the mash of an undesirable yeast or bacterium. He made it plain that the production of wine from grape juice was a fermentation brought about by a yeast already present, in nature, upon the grape. He further showed that by the action of bacteria upon the wine it could be converted later into acetic acid or vinegar, and that the leaven of our daily bread, the yeast, is a vegetable organism. To the researches of Pasteur we owe our knowledge of the fact that all putrefactions and decompositions in nature are brought about by the activities of bacteria already present in the soil, and which are the actual producers of the ferments through which these changes are effected. We know now, thanks to him, that the putrefactive changes which take place in our bodies after death are the earliest stages in the transition from highly organized animal tissues into elementary mineral substances, gases, and water. The complete change is not brought about at once by a single species of bacterium, but it is effected gradually, step by step, each step in the process representing the activity of a particular species, which, finding the conditions favorable for its multiplication, increases at a prodigious rate until it greatly exceeds in numbers and activity all the other organisms present. This species soon exhausts the special pabulum best suited to its growth and its rapid proliferation then ceases. It is now succeeded in turn by another species for which the changed conditions are more suitable, and this in turn dies out or diminishes in number to make room for the members of a third species, and so on, until the whole supply of material available for the nutrition of any form of bacterial life has been exhausted. Thus the complete disintegration of all dead organic material is provided for through many species of bacteria, capable as a whole of splitting up all the different forms of organic matter and of living under the most varying conditions while doing so. To many of these bacteria the presence of free oxygen is necessary, therefore they live best upon or near the surface of the earth. But it is a fact that some of them can live where free oxygen is entirely absent, so long as they are supplied with certain chemical substances in solution, and these they attack and split up to obtain their supply of oxygen directly from them. These so-called anaerobic bacteria live several feet below the surface of the soil, and they subsist upon the soluble mineral substances carried down to them chiefly by the rain absorbed from the surface. This is a beneficent provision of nature through which certain constituents of the dead bodies of animals are returned to the soil in a form suitable for absorption by the members of the vegetable kingdom, many of which are in turn consumed by the animal kingdom to enter again into the composition of their tissues. With the death of these animals, the putrefactive and decomposition changes are repeated, and the elementary substances return to mother earth once more, in primitive form, for reabsorption by the plant kingdom. The individual members of the vegetable kingdom also undergo decomposition after death in order that their primary mineral constituents may be carried by the moisture into the soil for reabsorption by other growing plants.

And so we have a continuance of these cycles of alternate growth and decomposition by means of which the mineral matter of the surface of the earth is kept in circulation, passing alternately from the vegetable to the animal kingdom, and *vice versa*. And how is this change brought about? By bacteria, which exist everywhere in nature for the purpose, and which possess the power, under favorable conditions of food and environment, to multiply with incredible rapidity and bring about the changes designed by nature to render the world habitable. Let me impress upon you, if I may, one important fact, namely, that without the presence of bacteria the existence of man upon the earth would be impossible so soon as the vegetable kingdom had exhausted the available supply of nutriment in the soil, because, in the absence of bacteria, decomposition of dead animal or vegetable bodies could no longer take place, and they would accumulate upon the surface. How do we know that these changes are brought about by bacteria and only by bacteria? Through the wonderful researches of Pasteur and Koch as pioneers with the microscope. Is this knowledge of any value to us? Most assuredly; the thousands of empty tins scattered over your western prairies within the last forty years show one of the benefits that man has derived from this knowledge. It has enabled him to transport various articles of food long distances, preserving their soundness and flavor when they are hermetically sealed and sterilized by a degree of heat sufficient to destroy the bacteria necessarily present upon them. The means relied upon for the preservation of our fresh food substances are simply those that destroy bacteria, or at least restrict their growth.

Our knowledge of bacteria obtained through the microscope enables us to treat milk in such a way that we can preserve it almost indefinitely; it has enabled us to impart to cheeses the particular flavor that we desire by adding to the curd pure cultures of certain bacteria or molds, also to protect our milk from a disagreeable bitterness and to hasten the ripening of cream. It has taught the farmer the secret of the proper preservation of fodder and the preparation of fertilizers; it has taught us why strong solutions of sugar and salt are good food preservatives; and in innumerable ways it has aided us in the enjoyment of nature's luxuries. We have learned that we can ordinarily preserve milk, meat, and fruits better at low temperatures, because under such conditions the growth of the bacteria of decomposition is retarded. It is even said that to a common grade of tobacco the genuine Havana flavor can be imparted by fermenting the green leaves with pure cultures of a certain organism obtained from a high grade of Havana tobacco.

The entertainment to be derived from the use of the microscope is not the least of its attractions; it opens up an entirely new world to us in the animal, vegetable, and mineral kingdoms, and to this fact we are probably indebted for the work of the older investigators. A study of the minute individuals of the animal kingdom is one of the greatest interest and importance, and in this I am sure of the concurrence of Professor Ward, who has taught you young gentlemen of the graduating class the extreme value to the physician of a certain familiarity with the microscopic as well as the grosser forms of animal life. To the man of leisure, even without technical training in biology, the microscope, as a means of recreation, will afford endless amusement and instruction. In the present state of perfection of the instrument and the low price at which it can be manufactured, it is surprising that the microscope is not more generally used.

In an old work published in London nearly two hundred years ago, and entitled "The Wonders of the Microscope, or an Explanation of the Wisdom of the Creator," I find most interesting descriptions of such animals as the cheese mite, the vinegar eel, various protozoa, the flea, and the louse. The book is stated to have been adapted to the understanding of young persons. The familiarity with which the louse is treated there must be regarded, I am afraid, as a serious reflection upon the personal habits of our ancestors. Nevertheless the illustrations are large and wonderfully true to nature. The assertion "there are male and female lice" is an interesting exposé of the condition of knowledge of that day, and for the truth of the statement I am sure Professor Ward will be willing to vouch. It speaks of the experiments of Mr. Leeuwenhoek, who in the seventeenth century manufactured a simple microscope and with it discovered and wrote our first descriptions of bacteria. So strongly was he imbued with the spirit of investigation that he put two of the abovenamed animals into his stocking, which he wore night and day for a week, in order that he might note the rapidity with which they multiplied. I commend to you young gentlemen the self-sacrificing spirit of this investigator, whose discovery of bacteria was destined to revolutionize the whole field of medicine and surgery and save hundreds of thousands of lives. Although at the time of Leeuwenhoek it had been suspected for centuries that minute forms of life were causes of disease, it was not demonstrated until two hundred years later when, during the Franco-Prussian war, the German surgeons showed that bacteria gaining entrance to wounds, traversed the tissues of the body, and excited suppuration and infection. Prior to this time these organisms had been seen in the tissues and in the discharges from wounds, but their direct causative relationship had not been determined. Twenty years before these demonstrations, Pollender had declared that the blood of animals dead of anthrax contained rod-shaped bodies that were not present in the blood of healthy animals, and Davaine showed soon after that inoculation with this blood conveyed the disease. The discovery of the organisms of relapsing fever, of leprosy, of typhoid fever, of pneumonia, and of the specific causes of the various surgical infections followed upon Koch's discovery of a simple method for the isolation of bacteria in pure cultures. In 1882, Koch published his discovery of the tubercle bacillus, an organism which causes more deaths among the human race than any other bacterium. The discovery of the fact that the microscopic organisms which we know as bacteria were the causes of wound infections was followed, as a logical sequence, by attempts to prevent the development of these organisms in wounds, by the use of antiseptics, for which method we are indebted to Lister, whose mode of treatment of wounds first made it possible for the surgeon to operate with comparative safety. This was followed by efforts to prevent the entrance of bacteria into wounds, called the aseptic method, in contradistinction to the antiseptic method, in which it was taken for granted that bacteria must necessarily enter all wounds.

Thus we have, as the direct outcome of microscopical investigations disclosing the specific causes of diseases and infections, an effort to prevent these organisms gaining entrance to the body at all. These and similar preventive principles are the keynote of the general science of medicine to-day. To the military surgeon and the state medical officer the science of hygiene, or the preservation of health and the prevention of disease, is of the utmost importance, as it is also of vital interest to every individual. When an army is in the field its success depends largely upon its health and mobility. To be able to move promptly and to strike quickly at the proper moment, an army must be in good health, while, on the other hand, an army decimated by disease is at the mercy of its opponents. Thanks to the patient investigations of those who have preceded us, we are prepared to recognize the causes of most of our diseases and infections; we know the manner in which they gain entrance to the body, and it is in our power to guard against their invasion, and thus protect armies and communities from the inroads of disease. As the whole science of hygiene and preventive medicine is based upon a knowledge of the minute causes of disease and infections, their modes of life, habits, and powers of resistance, I can not urge you young physicians too strongly to maintain your familiarity with this branch of medicine and to keep apace with the giant strides our knowledge is making to-day. Although we can cure some diseases we can not cure them all, and prevention is the golden rule. We know that the successful operator is he who guards his patient against infection; we know how to prevent the infection known as typhoid fever; we can guard ourselves and those under our care from tuberculosis; we can protect against diphtheria, puerperal fever, dysentery, Asiatic cholera, plague, malaria, yellow fever, and many other diseases, whenever we can control the individual and his surroundings.

There are times, however, in armies, in communities, and on shipboard, when it may be beyond our power to prevent the introduction of cases of a disease; it then becomes a matter of prime importance for us to be able with certainty to prevent its extension; and let me impress upon you that the knowledge that will enable you to do this most often and most thoroughly can only be acquired through a laboratory training in the study of the morphology and biology of the organisms that produce disease, and of the best known methods for destroying them or restricting their development. Let us take for instance the matter of water supply in its relation to water-borne diseases. Of these the most important are typhoid fever, cholera, dysentery, and other intestinal disturbances. We are now able by the bacteriological examination of a given water to determine with a reasonable degree of certainty whether or not it can be safely used in the raw state. We are in a position usually to determine by inspection of the source of supply whether or not it is liable to contamination. Experience has taught us that when natural waters flowing through densely populated districts are used for drinking purposes in the raw state, they are certain sooner or later to cause epidemic outbreaks of typhoid fever; our microscopical investigations have taught us that raising the temperature of water to near the boiling point will destroy the bacillus of typhoid fever, the cholera vibrio, and the specific causes of dysentery with absolute certainty. Therefore, whenever in suspected localities we can not secure a water that is above suspicion, a good alternative is to boil the water in order to render it perfectly safe for drinking. The immunity of the Japanese and Russian armies from intestinal diseases has been justly attributed to their habit of drinking tea, which is prepared with boiling water.

Our laboratory experience has taught us that milk is a very valuable medium for the cultivation of bacteria which grow in it with wonderful rapidity. We know that the people who handle milk are sometimes careless and uncleanly, and that if they chance to be brought in contact with a case of typhoid fever or of diphtheria, if they suffer from either of these diseases themselves, or, if the water used in cleansing their vessels be not pure, the milk may become infected. Within a few hours after contamination, in warm weather, the milk becomes practically a pure culture, swarming with disease-producing bacteria. It is quite obvious, therefore, that should the source of supply be beyond our control, we should render the milk safe by heating it to a temperature sufficient to destroy the bacteria against which we desire to protect those who are in our charge. If the milk does not contain more than 50,000 bacteria to the cubic centimeter at the time of delivery it can be regarded as of fairly good quality. The approximate number of bacteria contained in the milk is determined by diluting a small portion and then adding it in definite minute quantities to a melted gelatine; in this, after it has congealed, each individual organism present multiplies to form a colony, and by counting the number of colonies after their development, we can determine the number of bacteria originally present in the minute portion of the diluted milk added to the culture medium. The predominant species present can be ascertained by simple methods of isolation and cultivation. By means of the centrifuge and the microscope tubercle bacilli in milk can be detected, and through the presence in excess of a certain type of cells knowledge is obtained of some diseased conditions of the udder. The great value of the microscope in protecting the public from bad milk supplies, from bad water, and from the extension of certain unrecognized infectious diseases is so manifest that in many of our larger cities the boards of health have established well-equipped laboratories for the purpose of making the necessary examinations. The diminished death rate following these measures for the prevention of disease has fully justified the undertaking.

We have learned, through the microscope, that the germs of typhoid fever may be present in the saliva of a patient, upon his body, and in his dejecta. It has been shown absolutely in unpublished experiments that swallowing a few of the living organisms will produce the disease. We know further that if some of these organisms in the saliva of the patient, upon his hands, garments, etc., are transferred by himself, or others, to articles of food, such as milk, cooked potatoes, meat, etc., that they will multiply with great rapidity and render the environment of the patient exceedingly dangerous to others. Investigations have shown conclusively that typhoid fever clings to houses and families; it is incumbent upon you as physicians, therefore, to see to it that the handkerchiefs, napkins, towels, garments, and dishes used by patients suffering with typhoid fever shall be subjected to the action of boiling water or some other germicide before they leave the sick room, that the patient's person be thoroughly cleansed, and that disinfectants be used with thoroughness in order to protect those who come in contact with him. Recent German statistics tell us that nurses who had attended patients suffering with typhoid fever become themselves very heavy sufferers from that disease. No one questions that typhoid fever is conveyed primarily through the water or milk supply, but it is established beyond doubt that the infectious agent of the disease passes also directly from the patient to his surroundings, through failure on the part of the attending physician to take the proper precautions. The knowledge that we have gained in this respect is the outcome of work in the laboratory, and it is well that this fact should be made known to the public as well as the profession in order that they also may fully appreciate the value to them as well as the profession of a thorough laboratory training of the physician, for they are sometimes in a position to afford moral and material aid to those upon whom the responsibility for the teaching rests, but who have not the facilities for carrying out their desires. I implore you gentlemen who have graduated to-night to keep abreast of the times and maintain your touch with laboratory work. Let your first toy be a microscope and make that microscope an instrument of daily use.

Leaving the subject of bacteria after little more than a passing mention of it, notwithstanding its vast importance, I will ask your attention for a moment to another class of parasites, namely, those that belong to the animal kingdom. These are of greater significance in the Tropics than in the Temperate Zone; nevertheless, in no latitudes are human beings entirely free from them, and our intercourse with tropical countries daily increases their importance to us. Fortunately this study is one of great biologic interest, and the field is one that is still open to exploration. The value of the microscope in the recognition of certain intestinal infections is too well known to require more than a mere mention. The chronic form of tropical dysentery can be diagnosed only with this instrument, which renders visible the animal parasites or amoebae that cause it. Many mistakes are made by those who are not sufficiently well trained or who have not had the necessary experience. Within the past year or so I have seen a case given up to die as one of pernicious malaria and pernicious anemia, when a microscopic examination of about one minute disclosed a hookworm infection which was curable and from which the patient recovered. In the case I mention, the microscopic examination had been reported negative by a young physician who was either careless or improperly trained. I mention this, not in a spirit of criticism, but to illustrate the great necessity for a better and more thorough laboratory training of the young physician, who is often eager for knowledge that he is unable to obtain, because the necessary facilities and assistance are lacking. I may be pardoned if in this connection I refer to the great work recently accomplished by Dr. Bailey K. Ashford, who on the island of Porto Rico demonstrated by means of the microscope that thousands of cases of anemia, affecting practically the whole population with the destruction of some lives, was due to infection with an animal parasite, the hookworm, an infection that is curable and easily prevented. Another animal parasite of considerable interest and which we should be prepared to recognize is the *Trichina spiralis*. It can always be found in the rats of our slaughter-houses where hogs are killed, and it is transferred to man through the eating of pork that is insufficiently cooked. Americans are comparatively free from this infection because they will only consume pork that is well cooked. A large portion of our foreign population, however, consists of persons who are accustomed to eating raw pork or smoked sausage; such persons are frequently infected and pass for cases of typhoid fever. As the disease is often fatal, and the minute animal which causes it can be recognized only with some form of microscope, its recognition becomes a matter of great importance. Still another and important form of animal parasite whose presence can be determined only with the microscope is the parasite of malaria, of which there are several forms. The recognition of this parasite is comparatively easy to one who has a little practice, while one to whom it has never been shown will fail completely to recognize it in the fresh blood. Fortunately our perfected staining procedures are now so simple that the method for its recognition may be taught with ease. This parasite is found in the blood, and the infection is contracted only through the bites of mosquitoes of a certain genus. These mosquitoes fly only at night; the mode of prevention, therefore, is quite simple, namely, to protect oneself from the bites of mosquitoes after sundown. Another mosquito-borne disease is filariasis, an infection in which a diagnosis may be made by detection of minute embryos in the blood when examined with the microscope. Please remember that the nature of these parasites and the manner in which the diseases are contracted could have been determined only by microscopical examination of blood and of mosquitoes in the laboratory.

To make clear to you the importance of the microscope to students of medicine, let us consider the extent to which these gentlemen must have used the instrument in order to qualify themselves for their degree. The man who as a physician under-takes the responsibility of the care and treatment of the human body must have some knowledge of the component parts of the body, their arrangement and distribution, and the functions they perform. Naturally the student must at first devote a considerable part of his time to the study of anatomy, and with the anatomy the microscopic structure of the various tissues and organs. This implies a great deal.

In the second place, he must become familiar with the cellular elements of the blood, because this is a tissue that can be easily removed from the body and studied during life, and by a microscopical examination of this tissue we are frequently able to throw a flood of light upon the nature of a disease or illness. For example, in the blood we find two great groups of cells, the red corpuscles and the white. Among the latter there are several different forms, and in addition to the cells named there exist also in the blood a considerable number of smaller bodies known as plaques or platelets, which have frequently been mistaken by beginners for animal parasites. With the aid of the microscope we can count the red blood corpuscles, the iron-containing elements of the blood, and determine whether they are deficient in number or in quality. This will often enable us to recognize conditions of severe anemia or intoxication. In regard to the white corpuscles of the blood, or leucocytes, we can ascertain whether they are present in large excess or whether they are markedly deficient, both of which conditions indicate an impairment of health. Further, if there is a marked increase in these corpuscles, we may be able to ascertain, by counting them, the particular forms that are in excess, and this may enable us to determine, first, whether the condition is one in which the body is infested by animal parasites; second, whether there is some concealed abscess or focus of inflammation in the body; third, whether the condition is one of leukemia, and if so, whether it belongs to the acute form that brings about death within a few months or a year, or whether it is the more chronic form in which the condition is much less dangerous. Since the physician may make these and other determinations by means of a microscopical examination of the blood, the subject is one of very great importance to him and to the patient, and in order to be safe in his deductions he must possess a complete and accurate knowledge of the variable conditions and appearances found in the blood of healthy persons. Could anything demonstrate more conclusively than this the value to the student and to the public of a thorough and complete training in the use of the microscope?

So much for the study of the blood, which is only a single tissue of the body. Since the physician may be called upon to treat an injury or local diseased condition of any part or tissue, it is necessary for him to know the structure of all the tissues and the changes brought about in them by disease or injury, in order that he may select the best and safest means to aid in effecting a cure. It is necessary, therefore, to take up the study of the various tissues seriatim. For example, he must learn the minute structure of bone, and of the bone marrow. He must become familiar with the cellular elements of cartilage in order that he may be able to determine, when cartilage is present in a tissue, whether it is normal in character or of the type that belongs to tumor formation. He must learn the structure of the various types of muscle tissue, the voluntary, involuntary, and the cardiac muscle, in order that he may appreciate the changes that take place in hypertrophies, degenerations, and infiltrations. He must also be familiar with the cellular elements and their arrangement in the brain, spinal cord, and nerves, the degenerations to which they are subject, the causes of these and the effects produced by them. He must study thoroughly the microscopical structure of the kidney and the various changes that occur in the different forms of Bright's disease and other abnormal conditions. These are of special importance because most poisons are eliminated by the kidneys. To him the microscopical structure of the liver is one of vast interest, in connection with the degenerations to which the organ is subject, and the effect of these upon its functions and upon the functioning power of the kidneys. In order to appreciate what is meant by pneumonia he must know the structure of the normal lung and the interrelation of the lobes, lobules, blood-vessels, air tubes and spaces, and the lymphatics. He must be familiar with the structure of the organ in order to understand the mode of lodgment there of the bacilli of tuberculosis and the channels along which they pass in carrying the disease from one part of the organ to another. The same familiarity must be acquired with the lymph glands in order to understand why in certain conditions swellings appear at the elbow, in the arm-pit, in the neck and elsewhere; and to fully appreciate the changes in the glands in conditions of disease, he must be familiar with the normal structures as they are seen under the microscope. Further than this every one of the tissues of the body is liable at some time in life to take on the aspect of malignancy and become what is known as a carcinoma or cancer, or a sarcoma. His knowledge of the nature of these tumors and of the proper mode of treatment would be very deficient if he did not know that they are made up of cells normal for the body at some period in life, or in some location, and that the differences between perfectly normal cells and those of a malignant cancer may lie solely in their location and distribution. These are all facts which the student must know, and which he will only be prepared to appreciate when his first training with the microscope in the study of tissues has been laborious and painstaking.

Having completed this study of the minute elements of the tissues he is carried to the bacteriological laboratory, where the microscope is again brought into requisition to give him the necessary familiarity with the minute causes of disease, the means by which they are recognized, identified, and, in certain cases, cultivated artificially. He is first made familiar with certain harmless forms that are found on the body and in nature, in order that he may be on his guard against error. He is then permitted to study the commoner ones that bring about the condition known as suppuration, or the formation of pus, then probably the organisms of erysipelas, pneumonia, typhoid fever, diphtheria, tuberculosis, and various other infections. At this time he is probably working in the chemical laboratory and making use of the microscope in the identification of various crystalline bodies. In the next stage he proceeds to the laboratory of pathology, where he comes into contact chiefly with the various changes brought about in the cellular elements of the body by the bacteria that he has already studied and by the poisons which they elaborate. Here also he learns to distinguish the different forms of tumor growths, is made acquainted with the origin of these tumors and the manner in which they invade adjacent structures if they are malignant. He learns that in typhoid fever the bacteria select a certain form of tissue called lymphoid, producing ulcers in the intestine and enlargement of the spleen with certain microscopic changes. He studies in the frog's tongue, the web of its foot or in its mesentery, the various changes in the blood vessels that occur in a simple inflammation. He learns here that in certain inflammatory conditions some of the cells in the blood pass through the walls of the vessels by virtue of their own power of independent movement. He learns that many of these cells engulf and destroy bacteria, and that the so-called pus of an abscess is composed largely of cells that emigrate from the blood vessels. This fact is of great importance to him, and having seen the phenomenon of emigration take place it is firmly impressed upon his mind and he never forgets it. It is also necessary for him to learn the method pursued by nature in the healing of open wounds and in the replacement of lost tissue. By means of the microscope he sees for himself that this regeneration takes place chiefly through proliferation of certain types of tissue cells; that other types of cell elements possess only a limited power of multiplication in the human body, and that where a loss of tissue on the surface is replaced, the gap is filled by a newly formed exceedingly vascular structure, called granulation tissue. He is taught that as the granulation tissue becomes older it contracts and shuts off its own blood supply, becoming changed eventually into cicatricial or scar tissue, which is always of low vitality because of its poor supply of blood. This teaches him to avoid the location of scars in making wounds for operation. As a part of this laboratory course, he must acquire a knowledge of the cellular changes brought about in the tissues by the presence of the tubercle bacillus, and the characteristic form of degeneration produced by it, so that in the future he will know just what the condition is that he is called upon to treat, he will know how cavities are formed in the lungs in tuberculosis, and he will also be able to recognize a tuberculous focus in any tissue he may be required to examine with his microscope. In his study of certain tissues he learns the results of the presence in the circulating blood of certain poisonous substances; he sees the effects of other poisons upon the iron-containing pigment of the blood, through which it is deposited in masses in certain spaces or in certain cells; he sees in malaria the masses of brownish material contained in certain cells and which he learns has come from the blood, but not directly. He is shown the animal parasites of malaria which consume the iron of the blood and change it into the insoluble form shown to him in the tissues. It forever remains clear to him afterwards that malarial anemia results from the appropriation by the parasite of the iron of the blood. In thin sections through the lungs of persons who had been employed in mines, in stone quarries, or as metal workers, he sees masses of coal dust, stone dust, or metallic dust deposited in the tissues of the organs, and he is fully prepared to appreciate the significance of the changes that accompany the presence of this foreign material and the manner in which they are brought about. It is not necessary to say that a young physician who has received such training as this can readily form an intelligent conception of any ordinary disease process in a patient and decide upon the most suitable means to be used in overcoming it or in ameliorating the patient's condition, and he knows when medicine should not be given.

Along with this training, or perhaps immediately afterward, the advanced student is again brought into contact with the microscope in his course in clinical microscopy, which, although the last, is not the least important part of his training, and which teaches him the value of the microscope in his daily routine work. Here he learns in detail the most improved methods for the examination of blood. He learns to examine sputum for tubercle bacilli in cases suspected of being tuberculous; he learns to recognize the bacillus of influenza, the micrococcus of pneumonia, or the cells which indicate a condition of asthma, or, possibly, those belonging to a heart lesion; perhaps he learns to make a diagnosis in a case of diphtheria from a microscopical examination of a culture from the patient's throat. While this is usually done by the department of health, the student should be given every opportunity to make his own diagnosis in order that when he is thrown upon his own resources he will not be at a loss from lack of experience. Here he learns to recognize cases of Bright's disease and other morbid conditions of the kidney by the use of the microscope; he learns the practical application of the instrument in the identification of intestinal parasites; he learns to diagnose cases of septicemia or pyemia by means of a cultural examination of the blood; he learns to make the agglutination test to give him a positive diagnosis in typhoid fever, or, better still, he learns to draw a 20 c.c. syringe-full of blood from a vein in the arm during the first two or three days of the fever without discomfort to the patient, and then by means of cultures to make a positive diagnosis of typhoid fever within a couple of days. This is one of the great achievements of the past year or two, and every physician should know that by means of a cultural examination of the blood a positive diagnosis can be readily made with the microscope long before agglutination can be obtained. This is true of over 90 per cent of the cases.

Such, in brief, is the experience of the average medical student with the microscope in his every-day work, and the fact can not be too strongly impressed upon the younger men that he who uses the microscope most often and most seriously in his earlier days will prove the most accurate diagnostician and the best and most successful surgeon or practitioner of medicine.

It has been possible, in the time at my disposal, only to skim lightly over the subject of the uses of the microscope in medicine, but I hope I have made clear to you the inestimable practical value of the instrument and its indispensability to both the student and practitioner.

Let me caution you against accepting the idea that the microscope will tell all that you need to know. While it is one of the most valuable aids to diagnosis, it is only an aid, and the information it gives must, therefore, be properly interpreted. Let not your object in taking up its use be for the purpose of making original investigations. If you are destined for such work the opportunities will present later; your primary aim should be to properly equip yourselves for the practice of medicine and surgery, and thus enormously lessen the burden of your responsibility and increase to the same extent the amount of good you can confer upon your fellow man.

A Study of Filtration in the Lung of the Frog

BY A. E. GUENTHER AND R. A. LYMAN

INTRODUCTION

The passage of water and of solids or gases in solution through more or less clearly defined membranes of the animal body must be an event of frequent occurrence. The absorption of food material by the epithelial cells lining the alimentary tract, the taking in of oxygen and the excretion of carbon dioxide by the delicate cells lining the alveoli of the lungs, the continual formation of lymph are processes involving a transfer of material from one side of an apparently continuous membrane to the other. It has been a matter of long-standing controversy whether the passage of substances through membranes in the living body is the result of purely physical and chemical forces or whether there is involved a special activity which by way of distinction is designated as vital. As a prominent example of vital activity may be mentioned the result of Heidenhain's work, who showed that serum is absorbed from the intestine under conditions which exclude all known purely physical forces. This fact has been corroborated by Reid by more complete experiments. His results show that water, inorganic and organic solids, are actively absorbed, after ligation of all the lacteals and when the pressure in the gut was far below that of the mesenteric vein. Our incomplete knowledge of the structure of protoplasm makes it impossible to conceive any mechanism by which material may be transported from one side to the other of a living membrane after apparent total exclusion of the physical processes of filtration, diffusion, and osmosis. Nevertheless, it is the almost universal belief of physiologists that vital activity will in time, as regards the passage of materials through animal membranes, be explained on a relatively simple physical and chemical basis.

The three physical forces are, however, with great probability involved in every vital manifestation of the kind in question. The conception of filtration is the simplest. It is the passage of a fluid through a membrane as the result of differences in hydrostatic pressure on the two sides of the membrane. The amount of fluid forced through increases with the pressure, but in a lower ratio. Difference in hydrostatic pressure, then, is the first of a series of factors influencing the extent to which filtration takes place. When filtration takes place from a solution of electrolytes into a pure solvent through a membrane impermeable to the electrolytes in solution, then the hydrostatic pressure must just exceed the osmotic power of the solution. With permeable or semipermeable membranes, the hydrostatic pressure necessary becomes lessened in proportion to the extent of diffusion of the electrolytes. When the positions of the solution and pure solvent are reversed the forces resulting from osmosis and hydrostatic pressure act in the same direction. Obviously, the osmotic relations of liquid to filtrate form a second group of factors modifying the extent to which filtration takes place.

Thirdly, the rapidity of filtration rises also with the temperature. According to Schmidt the temperature coefficient is approximately that for the flow of fluids through capillary tubes.

Fourthly, the character of the liquid to be filtered, it would seem, must affect both the rapidity of filtration and the quantitative composition of the filtrate. The relation of concentration of the filtrate to that of the original solution is of the utmost importance to the physiologist. There is a general agreement that in the filtration of colloids the concentration of the filtrate is lessened, while no such change occurs in the filtration of crystalloids. In the latter case the concentration remains the same at various filtration pressures, but in the former case a marked uncertainty exists as to the results obtained with varying pressures. According to Runeberg the concentration is higher at low pressures than at high pressures, but exactly opposite results have been affirmed.

Finally it may be said that filtration depends upon the porosity of the membrane, and any action of the liquid on the membrane by modifying the character of the membrane may alter the extent of filtration. Much of the divergence of opinion is possibly due to the varying conditions of the membranes used. Previous drying, state of imbibition of the fibers, and the amount of deformation by stretching must influence the passage of fluid through animal membranes if such a passage is brought about by virtue of narrow paths. This explanation of variability is the more plausible when it is considered that most of the work done was carried out on thick membranes, such as the intestine, bladder, pericardium, skin, and ureter.

Most observers agree that with a constant pressure the amount of filtrate falls off in time. Tigerstedt and Santesson state that this diminution is much more rapid during the earlier hours of the experiment than later on. A period of rest between two successive filtration tests often causes an increase in the permeability of the membrane above that possessed at the close of the first test. Such results are not obtained when filtration is effected through unglazed porcelain. The hypothesis that animal membranes possess tortuous channels which can be distorted by pressure, thus increasing the resistance to filtration, and which through their elasticity manifest a certain amount of recovery, helps in an understanding of these peculiarities.

Our knowledge of the phenomena of filtration through animal membranes is, however, very limited and in most of the experimental work done no effort was made to test methodically whether the membrane was alive or not. Experiments on living membranes, it would seem, must yield information of greater value to physiology. Tigerstedt and Santesson have very clearly pointed out the difference between dead and living filters. "A fresh frog's lung, filled with 0.6 per cent sodic chloride solution, will stand a pressure of some 13 to 14 mm. of mercury without filtering for many hours; heating in water at 54° C., or treatment with weak acetic acid, frog's bile, weak sodic hydrate, or distilled water, at once, however, (presumably by killing the cells) allows filtration." A modification of this experiment was made use of in the present investigation as an indication of the vitality of the membrane employed. In a number of preliminary experiments in which physiological saline was being passed through the lung of a frog it was found that a momentary exposure of the lung tissue to the vapor of chloroform resulted in an immediate and plainly visible acceleration of the rate of flow. Dead lung tissue does not exhibit this phenomenon. Obviously, we had here, at command, a convenient and efficient test of the vitality of the lung. All the experiments reported in this paper are restricted to lungs showing this reaction.

In order to insure constancy of results, it is necessary to select lungs with considerable care. The great majority of the frogs used in the laboratory this year were infected with the parasite *Distomum variegatum* Rud., which lived inside of the lung. When present in small number they produced no detectable change in the lung tissue. When present in considerable numbers they produce most decided pathological changes. A glary fluid having the appearance of mucus appears in the lungs. As this condition might permit of error such lungs were rigorously excluded. Another source of error was detected in the method used in preliminary experiments of fastening the lungs to the tubes which held them. The ligatures used were extremely liable to so injure the delicate tissue as to kill it and permit of a more rapid filtration of fluid than allowed by the intact lung. This difficulty, it is believed, is entirely overcome by the procedure ultimately adopted.

It has been demonstrated in recent years that sodium, calcium, and potassium salts are essential requirements to the normal maintenance of many kinds of living tissue. In order that they may be most efficient they must exist in definite proportions in the medium surrounding the tissue. These salts act by virtue of the ions into which they are dissociated. Investigators have generally laid stress upon the importance of the kation, yielding a minor and more indirect influence to the anion. Whether the ions form ion-proteid compounds or simply act in a physical manner by keeping the colloid material of protoplasm in a proper state of solution has not been definitely determined. In either case it seemed a matter of interest to determine whether the ion content of the fluid filtering through a frog's lung produced any changes in its condition so as to affect the rate of filtration.

METHOD

The method used consisted essentially of slipping the apex of a frog's lung over the end of a glass tube and tying it tightly in place. The end of the tube, together with the lung, was then immersed into a beaker containing the solution to be filtered. The other end of the tube was brought into connection with a mercury manometer and with a pressure bulb by means of which a negative pressure could be established within the tube. The amount of pressure could be adjusted from time to time and kept constant by referring to the mercury manometer. The details of the apparatus can readily be gained from fig. 1.

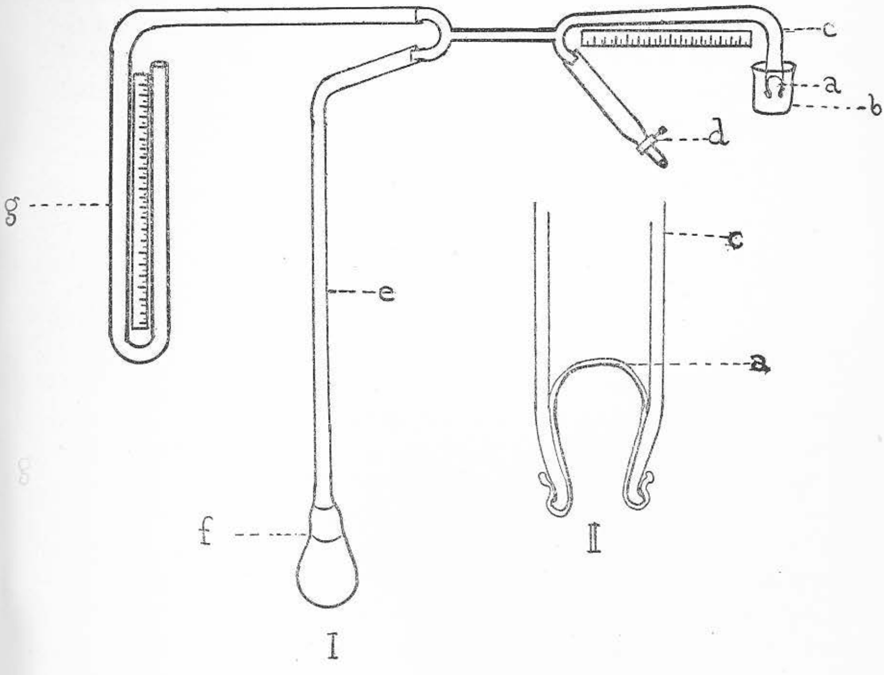

Fig. 1. Diagram of apparatus.—I. The letter *a* represents the frog's lung tied in place; *b*, beaker containing the solution to be filtered; *c*, graduated tube to read the amount of filtration; *d*, outlet with clamp to make adjustments; *e*, tube leading to pressure bulb; *f*, pressure bulb; *g*, manometer with scale. II. End of tube *c*, on larger scale; *c*, glass tube; *a*, lung bulging up into tube.

The letter *a* indicates the lung everted into the graduated tube *c* as the result of the negative pressure within the tube. One hundred cubic centimeters of the liquid to be filtered are placed in the beaker *b*. The atmospheric pressure on the surface of the liquid in *b* tends to force the liquid up into the tube *c*, the graduations of which enable an observer to determine the amount filtered per unit of time. The direction in which water passes through the lung is, therefore, from the pleuro-peritoneal membrane towards the epithelium lining the alveoli of the lung, and thus into the interior of the lung. For the sake of brevity this has been called exit filtration since in an intact frog the passage of fluid in this direction would be from the body cavity out through the lungs. By a very simple procedure the lung can be tied onto the tube, inside out, so that the direction of the flow of fluid is just reversed. This has been designated as entrance filtration.

It has already been stated that the application of a ligature to the delicate lung tissue is very liable to so injure it as to vitiate the experiment. Numerous trials, however, have led us to believe that with the method employed this source of error is to a large extent, if not entirely, overcome. The atmospheric pressure, exerted through the fluid to be filtered, presses the lung tissue against the inner side of the wall of tube *c* for a considerable distance and prevents the liquid from coming in through any possible leak near the ligature.

In performing an experiment the lungs are carefully exposed in the body of the frog. The lung is cut across with a single snip of a pair of scissors. After seizing the cut edge of the lung with forceps it is drawn over the end of the tube and tied in place. Great care is taken not to touch the apex of the lung in any way. The beaker containing the test liquid is quickly brought up over the lung and several cubic centimeters placed in the tube *c* which flow down and fill the lung. There exists, therefore, no possibility of the lungs suffering from drying.

EXPERIMENTS

Filtration of pure sodium chloride.—In considering the passage of water through the wall of a frog's lung it must be borne in mind that the lung is not a simple membrane, but consists of a multitude of different histological elements which are enclosed, within and without, by a layer of epithelial cells. There is thus formed a distensible pouch the wall of which is produced inwards so as to give rise to a network of septa. The septa, whose thickened edges extend free into the central cavity of the lung, may be divided into three classes which differ mainly in size. The larger septa form numerous chambers which are subdivided into smaller chambers by the septa of the other two classes. These chambers are the alveoli of the lungs.

The wall of the lung consists principally of smooth muscle fibers, fibrous connective tissue, numerous blood and lymph vessels and nerves. The smooth muscle is a prominent constituent, forming thick muscle columns in the free edges of the septa. The connective tissue fills the spaces between the other structures enumerated and forms the principal mass of the outer wall of the lung. In this location it is densest exteriorly. Medially there follows then a thin layer of muscle, and this in turn is underlaid by a subepithelial connective tissue layer which is rich in capillary blood vessels.

The inner surface of the lung is lined by a continuous, single layer of epithelial cells. The latter are of two kinds. On the ridges formed by the septa are to be found low, cylindrical, ciliated cells among which are interspersed many goblet cells. On the other hand, the sides of the septa and the depths of the alveoli are lined by the respiratory epithelium, a uniformly flat, squamous variety lying directly on the capillaries. Exteriorly, the lungs are covered by the serous pleuro-peritoneal membrane made up of a single layer of epithelial cells resting on a layer of connective tissue. Of all these histological structures it is probably the two layers of epithelial cells which are most concerned in the phenomena of filtration. Do they or do they not permit filtration?

As stated in the introduction, Tigerstedt and Santesson were able to show that frog's lung will withstand filtration for many hours when subjected to physiological saline under thirteen or fourteen millimeters mercury pressure. Our experiments fully corroborate this statement. Table I shows a typical experiment.

TABLE I

PREPARATION OF FROG'S LUNG. NO PARASITES. EXIT FILTRATION
Both interior and exterior of lung bathed by 0.7% sodium chloride solution
1 mm. of scale = 0.0324 gram distilled water

TIME	READING ON SCALE	FILTRATE IN MMS.	PRESSURE MMS. HG.	TEMPERATURE
11 A. M.	14.9	....	0	27.5 C.
11 A. M.	14.8	....	-40	27.5 C.
4 P. M.....	14.7	2	0	27.5 C.
4 P. M.....	13.5	....	-40	27.5 C.
8 P. M.....	13.6	13	0	27.5 C.
8 P. M.....	12.8	....	-40	27.5 C.

During the first 5 hours the amount of fluid forced through the lung equaled only 2 scale units or 64 mg.; during the next 4 hours the rate was much greater, so that at the expiration of the ninth hour after the beginning of the experiment 421 mg. had passed through. A glance at Table I will show that a discrepancy exists between the readings taken at 40 mm. pressure and those taken at zero pressure. This is due to the fact that the tissue yields to the pressure to which it is subjected and bulges up into the tube, making the filtrate appear greater than it really is. The amount of bulging varies considerably, and readings must, therefore, always be made at zero pressure so as to correct for the relaxation of the tissue. This has been done in reporting the remaining experiments without further mention. It may be concluded from experiments like that of Table I that, in spite of the very high pressure, filtration through frog's lung is very slight during the early hours. It is usually somewhat more than in the case given. In experiments taken at random the amounts during the first hour were 0, 5, 0, 0, 1, 1, 1, 0, 0, and 1 scale units.

The amount of filtrate increases with the time if the observations are confined to living tissues. This is also shown in Table I. It may be said that the gradual deterioration of the lung allows a more and more rapid passage of fluid. This statement seems justified by a consideration of the influence of substances known to be deleterious to living matter. Thus, in one instance, a frog's lung subjected to 0.7 per cent sodium chloride solution permitted the filtration of 1 mm. of fluid in an hour. The sodium chloride was then replaced by distilled water. During the succeeding hour 58 mm. of fluid passed through. In another case the acceleration in filtration was from 0 mms. during the first hour to 4 mms. during the second hour. These figures show the wide range of the variations.

The chloroform test.—Equally striking is the effect of chloroform. A frog's lung subjected to 0.7 per cent sodium chloride solution under a pressure of 40 mm. Hg. allowed but 4 mm. of filtration during the first 5½ hours. An exposure to the vapor of chloroform for 5 minutes produced such changes, presumably in the epithelial cells lining the lung, that 48 mm. passed through during the next hour. Very many similar examples might be given, since every experiment terminated by exposing the lungs to chloroform vapor in order to determine whether an acceleration of flow take place or not. Lungs removed from the frog's body some time previously do not exhibit this reaction.

For example, a lung after twenty hours immersion into physiological saline had assumed a pale, yellowish white color, all the hemoglobin, plainly visible in the blood vessels of an intact lung having diffused into the surrounding medium. This lung permitted in successive periods of 5 minutes each, 4, 2, and 3 mm. filtration respectively; treatment with chloroform vapor for 1 minute gave during subsequent periods of 5 minutes each, 3.5, 2.5, 3, and 2 mm. respectively. Such an experiment seems to justify the chloroform test as evidence of the vitality of lung tissue.

Filtration of pure calcium chloride solutions.—It has been the aim of this series of experiments to determine the effect, if any, of the ions of sodium, calcium, and potassium on filtration through frog's lung. In every case the salts employed were the chlorides. The calcium and potassium chloride were made up in 1 per cent solutions, which are approximately isotonic with 0.7 per cent sodium chloride. In this way osmotic changes are avoided and the passage of fluid results, very likely, solely from differences in hydrostatic pressure. This would be true, strictly, if the diffusion of ions in both directions occurred at equal rates.

Naturally, in an investigation of this kind, the first tests would deal with pure solutions. It has already been stated that with physiological saline a very slight, if any, filtration takes place during the first few hours, even at pressures as high as 40 mm. Hg. Higher pressures were found impracticable since they were liable to tear the tissue, causing gross leakage. Pure 1 per cent solutions of calcium chloride filtered to a considerable extent. In one case the amount of liquid passing through the lung when both sides were exposed to the calcium solution and when the difference in hydrostatic pressure equaled 40 mm. Hg. was 10 mm. during the first hour. In another case under similar conditions the amount of filtration was also 10 mm., but in this case there preceded an hour's exposure to sodium chloride under pressure, during which the filtration was but 1 mm. in amount. Subjection to the fumes of chloroform for one minute resulted during the next hour in a filtration of 63 mm. These experiments are sufficient to show that 1 per cent solutions of calcium chloride will not maintain the lung tissue in normal condition as long as an isotonic solution of sodium chloride. A calcium solution is, however, not as injurious as pure water and not nearly as deleterious as the vapor of chloroform.

Filtration of pure potassium chloride solutions.—Tests with 1 per cent solutions of potassium chloride approximately isotonic with 0.7 per cent saline gave equally positive results. In one experiment 18 mm. of the solution filtered through in one hour. At the expiration of this time the chloroform test was positive, giving after one minute's exposure a filtration of 87 mm. for the succeeding hour. In some of the cases, as in the experiments with calcium chloride, there was given a preliminary bath in saline for one hour to insure absence of leakage. The maximum amount of filtration during this time was only one millimeter. A substitution of potassium chloride for the sodium chloride gave during the succeeding hour a filtrate of four millimeters. The figures vary considerably in different tests, but on the whole potassium seems to be more injurious than calcium, exhibiting, therefore, in this respect a relation to lung tissue similar to that shown towards cardiac and skeletal muscle.

Exit and entrance filtration.—With physiological saline under 40 mm. Hg. pressure filtration took place in one direction through the wall of the lung as readily as in the other. Thus, in a series of tests on exit filtration, the amounts filtered through during the first hour were 0, 5, 0, 1, 1, 0, and 1 mm. In a corresponding series, of entrance filtration the figures were 0.5, 0, 1, 1, and 0. These results give no indication of any differences in filtration due to direction of flow. Had the tests been carried out over longer periods of time such differences might have revealed themselves. It is an old observation of Meckel that the membrane lining the inner surface of the egg-shell permits filtration far more easily from within outwards than in the reverse direction. A similar phenomenon has been reported in filtration through the frog's skin. We were able to convince ourselves of the latter fact. Filtration through the frog's skin, however, is a slow process, so that it does not lend itself as readily to experiments of this nature as does the frog's lung.

TABLE II

EXIT FILTRATION DURING ONE HOUR	ENTRANCE FILTRATION DURING ONE HOUR	CONDITIONS
87 mm. KCl	3 mm. KCl	After exposure to chloroform vapor for one minute
83 mm. KCl	0 mm. KCl	
63 mm. CaCl	4 mm. KCl	
48 mm. NaCl	5 mm. NaCl	
48 mm. NaCl	5 mm. NaCl	
58 mm. H O	4 mm. H O	After saline 1 hour
17 mm. H O	1 mm. H O	
4 mm. KCl	4 mm. KCl	KCl on both sides
21 mm. KCl	6.5 mm. KCl	
2 mm. KCl	2 mm. KCl	
0.5 mm. KCl	4 mm. KCl	
18 mm. KCl	0.5 mm. KCl	
10 mm. CaCl	5 mm. CaCl	CaCl on both sides
10 mm. CaCl	3 mm. CaCl	
10 mm. KCl	0 mm. KCl	KCl in beaker and CaCl in tube
13 mm. KCl	1.5 mm. KCl	
7 mm. CaCl	1 mm. CaCl	CaCl in beaker; NaCl in tube
1 mm. CaCl	1 mm. CaCl	
6 mm. KCl	0 mm. KCl	KCl in beaker; NaCl in tube
1 mm. KCl	0 mm. KCl	

An examination of Table II, in which entrance and exit filtrations through frog's lung under a variety of conditions are contrasted, indicates clearly that it does make a difference in which direction the pressure forces the liquid. The figures, as is usual in filtration experiments, show great variations, but the contrast between those representing entrance filtration and those representing exit filtration is so obvious that a conclusion can be drawn with certainty. Entrance filtration is much less pronounced than exit filtration. With distilled water the average ratio was about 1:15. After exposure of lungs to chloroform vapor for one minute the average ratio for all the solutions was also about 1:15.

That structures so widely different as frog's skin, egg membrane, and frog's lung should exhibit the same phenomenon is striking and of interest. Various hypotheses might be formulated to account for the fact. It might be assumed that the structure of the membrane is such that one side is made up of more yielding material than the other side. Paths more or less tortuous in character passing through such a membrane will be deformed or obliterated to a certain extent and therefore offer more resistance to the passage of fluid, providing the pressure is applied to the more yielding side. Theoretically, the lung is admirably constructed to suit the requirements of this hypothesis. The septa standing out from the inner surface of the lung form between them the deep alveolar recesses, the depths of which, lined by pavement epithelium, represent the thinnest portion of the filtration surface. It is easy to imagine that pressure applied to this side of the wall of the lung might cause the outstanding septa to fold over and protect the more delicate epithelium from the action of the filtering fluid. Since filtration becomes marked only when the tissue has undergone deterioration, and since, moreover, folding over of the septa would delay deterioration, it would seem that this hypothesis offers a sufficient explanation of the differences in question. To test this supposition lungs were stretched, as in actual experiments, under 40 mm. Hg. pressure, and then plunged into the hardening reagents, mercuric chloride and absolute alcohol. Sections of the lungs did not support the view that under pressure the septa are folded down over the respiratory epithelium. When the lungs are inflated by the action of pressure in the interior the septa stand erect, and the alveoli are freely open to the central lumen of the lung. But when the lungs are everted, which in the method of experiment employed is the case in exit filtration, then the septa are folded and pressed down, protecting to some extent the respiratory epithelium. Practically the membrane becomes denser and should hinder filtration, but the experimental results show a reverse effect. Filtration is more rapid. On this account the hypothesis must be abandoned.

After close consideration of the details of the experiments in which the two sides, i. e. the interior and exterior surfaces of the lungs were exposed to solutions of varying injurious action, it became clear that the acceleration of filtration varied with the injurious effect of the substances to which the lung was exposed. Furthermore, that the differences produced by reversing the positions of the solutions without a change in the direction of pressure are so small as to be negligible. It is important also to bear in mind that in exit filtration the direction of flow of fluid is from the pleuro-peritoneal membrane to the alveolar side of the lung, and in entrance filtration it is from the alveolar side towards the pleuro-peritoneal epithelium.

At this point it is necessary to lay stress upon an observation made early in the course of this study. Lungs affected with parasites are characterized by the presence in their interior of varying amounts of a thick, glary, viscid secretion resembling mucus in appearance. This secretion may well be formed by the numerous goblet cells situated in the epithelial layer on the ridges or free edges of the septa. It is not miscible with water and is gradually converted into a whitish mass by immersion into absolute alcohol. It is formed in considerable quantities after chloroform or on subjection of the lung to water and always on the alveolar side of the wall of the lung. It is the formation of this substance which in all probability causes the difference in exit and entrance filtration. Impenetrable by the liquid, in response to which it was thrown out by the secretory cells, it protects those portions of the membrane which otherwise would allow filtration readily. But this protection is adequate only if the direction of flow of the fluid presses the "mucus" against the membrane.

This is the case in entrance filtration. In exit filtration the direction of flow of the filtering fluid tends to carry the "mucus" away from the membrane. On this hypothesis the tests in Table II find a plausible explanation.

CONCLUSIONS

In dealing with membranes so easily alterable as are those composed of living epithelial cells, it is to be expected that the experimental results will show variations more or less wide. These are the more so to be expected when it is considered that the surface through which filtration is to take place is one variable in extent and continues to vary during the experiment, owing to the fact that the tissue yields gradually to the pressure applied. In spite of these variations the figures obtained after different experimental procedures are so clearly in the same direction and in general differ so greatly in magnitude that the following conclusions may be drawn:

1. The lung of a frog will permit little, if any, filtration in either direction under pressures as high as 40 mm. Hg. so long as the tissue remains normal. If, however, the lung has suffered deterioration filtration takes place more or less readily.

2. Pure solutions of potassium or calcium chloride are much less efficient in maintaining the lung in normal condition than isotonic solutions of physiological saline.

3. When filtration does take place, exit filtration is much more pronounced than entrance filtration. The assumption is made that this difference depends upon the presence of a secretion formed upon the alveolar surface of the lung in response to the stimulus furnished by the injurious action of the filtering solution.

4. In a living lung filtration increases in the course of time as the vitality of the tissue decreases, while in a dead lung filtration is most rapid at the beginning and decreases slightly with the time.

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