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Original Articles.

FURTHER STUDIES OF THE INTRACELLULAR BACTERIAL TOXINS.*

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For the past eight years much of my time, so far as it could be given to research work, has been devoted to a study of the intracellular toxins of bacteria, and the purpose of this paper is to briefly state what I have accomplished along this line, and to formulate the theoretical conceptions that have grown out of this investigation. In this work I have been aided by several most competent assistants and students, all of whom have labored without any remuneration worthy of mention, except that which comes to everyone who engages in scientific research intelligently and conscientiously. In 1896 Perkins and I¹ reported the presence in a toxicogenic bacterium found in poisonous ice cream of an active body that proved to be soluble in alcohol, and in this respect, at least, as we shall see later, similar to the toxins which we have recently been studying.

In 1900, with McClymonds,² I was able to demonstrate that the colon germ, so frequently found in cheese, produces no soluble poison, but that the cell substance is markedly toxic. The bacterial cells were steamed and subsequently exposed for several days at 37 degrees to artificial gastric juice without destruction of their toxic properties. In 1901, with the aid of Cooley and Gelston,³ I was able to make substantial advances. The large tanks, so necessary in order to obtain bacterial cell substance in large amount, were devised and put into operation. Without these the work since accomplished could not have been done, because the production of large amounts of bacterial cell substance free from constituents of the culture medium and free from contamination was essential before the chemistry of the cell could be successfully investigated. In a paper before the Association of American Physicians in 1901 I was able to make the following statements concerning the toxin of the colon bacillus:

1. The toxin is contained within the cell, from which it does not, at least under ordinary conditions, diffuse into the culture medium.

2. The toxin is not extracted from the cell by alcohol or ether.

3. Very dilute alkalies do not extract the toxin from the unbroken cells.

4. The unbroken germs may be heated to a high temperature with water without destruction of their toxin.

5. Boiling with a 0.2 per cent. aqueous solution of hydrochloric acid has but little, if any, effect on the germ cell or its contained toxin.

6. Heating the germ substance for an hour at the temperature of the water-bath with water containing from 1 to 5 per cent. hydrochloric acid breaks up the cell and lessens, but does not destroy, the toxicity of the cell content. Prolonged heating may render the toxin inert.

In the paper referred to I spoke several times of the bacterial cell wall, a structure which I am now satisfied has no existence.

In 1902 my students were able to make the following advances:

- (a) Detweiler⁴ showed that the cellular substance of micrococcus prodigiosus, bacillus violaceus, and sarcina aurantiaca and sarcina lutea contains poisonous bodies.

- (b) Wheeler⁵ demonstrated the presence in the cell substance of sarcina lutea of two carbohydrates, a nucleic body yielding xanthin basis (since obtained in crystalline form), and a proteid yielding hexon bases (also since obtained in crystals), thus showing that the cell is made up largely of a glyco-nucleo-proteid molecule.

- (c) Leach⁶ split up the colon bacillus, and proved that it also contains in its molecular structure carbohydrates, nucleic and proteid.

- (d) Marshall and Gelston⁷ determined with great accuracy the toxicity of the colon germ substance, and showed that with this immunity could be obtained, although it was neither marked nor permanent. The germ substance is, moreover, not a favorable agent to employ in inducing immunity on account of its insolubility.

- (e) Gelston⁸ found an intracellular toxin in the bacillus of diphtheria, and showed that commercial antitoxin gives no protection against the intracellular poison.

- (f) J. Walter Vaughan⁹ demonstrated, contrary to the findings of all other investigators along this line, that the anthrax bacillus does produce a poison, and that it is intracellular.

4. The Toxicity of the Dry, Sterile, Cells of Certain Non-pathogenic Bacteria, Trans. Assn. Amer. Phys., 1902.

5. The Chemistry of Sarcina Lutea, Trans. Assn. Amer. Phys., 1902.

6. The Chemistry of Bacillus Coli Communis. Trans. Assn. Amer. Phys., 1902.

7. The Toxicity of the Cellular Substance of the Colon Bacillus, Trans. Assn. Amer. Phys., 1902.

8. The Intracellular Toxin of the Diphtheria Bacillus, Trans. Assn. Amer. Phys., 1902.

9. The Anthrax Toxin, Trans. Assn. Amer. Phys., 1902.

* Read at the Fifty-fifth Annual Session of the American Medical Association, in the Section on Pathology and Physiology, and approved for publication by the Executive Committee.

1. Ein in Elsereme und Käse gefundener giftproduzierender Bacillus, Archiv. f. Hygiene, 1896, xxxiii, 308.

2. Bacteriologic Poisons in Milk, Jacobi Festschrift, p. 108.

3. The Bacterial Toxins, Trans. Assn. Amer. Phys., 1901; The Toxin of the Colon Bacillus, THE JOURNAL A. M. A., Feb. 23, 1901; Amer. Med., May, 1901.

In 1903, Wheeler¹⁰ made some investigations which, in my opinion, have thrown much light on the problem, inasmuch as they lead to the suggestion that the bacterial cell is essentially a chemical compound of definite and constant composition. It was found that when the cellular substance is extracted with dilute acids, the portion split off is practically the same whether 0.1 or 1 per cent. acid be employed. Furthermore, it was demonstrated that the amido-nitrogen split off with acid is the same, whether 1 per cent., 5 per cent., or 33 1/3 per cent. sulphuric acid be used.

Leach¹¹ obtained additional information along the same line by the action of mineral acids on the colon bacillus.

McIntyre¹² applied my methods to bacillus pyocyaneus, and demonstrated the existence of an intracellular poison in this organism.

Munson and Spencer¹³ showed that the hepatic cells of vertebrates may be split up with the production of a poisonous group.

During the present year, Wheeler and I have been able, by acting on the germ substance with sodium alcoholate, to split off and obtain in soluble form highly poisonous groups. This has been accomplished with the colon, typhoid and anthrax bacilli, and with all of these we have produced antibodies which neutralize the toxin, but so far we can not speak with certainty concerning their antibacterial action. The colon toxin immunizes guinea-pigs against both itself and the living germ, but with the other organisms experiments have not been carried far enough to justify a statement one way or the other. The colon toxin split off from the germ substance is still a complex body, and gives the biuret and Millon reaction. It is freely soluble in water and absolute alcohol and insoluble in ether, petroleum ether, and chloroform. The alcoholic solution as obtained from the germ substance by the action of sodium alcoholate contains two bodies, or rather two groups of bodies, one of which is poisonous, while the other is not actively so, at least. The toxin is precipitated from alcoholic solution by platinum chlorid, while the non-toxic body is left in solution. Of the mixture of the two obtained by evaporation of the alcohol in vacuo, 8 mg. is the minimum lethal dose for guinea-pigs weighing from 300 to 400 grams, but only 15 per cent. of this mixture is toxic. This makes the minimum lethal dose of the toxin between 1 and 2 mg., or one part to from 300,000 to 400,000 parts of body weight of guinea-pig. By administering gradually increased doses of this toxin, guinea-pigs are immunized, and when such immunized pigs receive 2 c.c. of a twenty-four-hour culture of a virulent colon bacillus, they are but slightly affected, while controls invariably die within from ten to twenty-four hours.

That this is the specific toxin of the colon bacillus, it seems to me there can be no doubt, because it gives immunity in the guinea-pig at least, to both dead and living cultures of the germ. This toxin is, I believe, composed of a haptophore and a toxophore group. Concerning the nature of the former, I am not prepared as yet to express an opinion. There are certain reasons for suspecting that the toxophore group is a neurin. These reasons are both chemical and physiological. Neu-

rin is a highly poisonous body that is not decomposed on being boiled with sodium alcoholate; so is the colon toxin. Neurin acts on the respiratory center and arrests the respiratory movements, while the heart continues to beat normally. This is especially marked with our toxins, those obtained from the colon, typhoid and anthrax bacilli; most marked with the last mentioned. When this poison is injected intravenously in doses of a fraction of a milligram, the respiratory movements cease immediately, while the heart continues to beat for five minutes or even longer. It will be understood that these are only suggestions that the toxophore group is a neurin body. They are by no means proofs, and I hold the right to change my opinion on this point after further investigation. As Behring has suggested, the toxophore group may be the same in a number of different pathogenic bacteria.

When the dried colon germ substance is heated with sodium alcoholate, about one-third of the cellular substance goes into solution in the alcohol, while the rest of it remains out of solution. All the toxin is dissolved in the alcohol, provided the extraction be repeated three or four times, but, as has been stated, of the one-third of the germ substance that goes into solution in the alcohol, only about 15 per cent. is toxin.

The part of the cell substance insoluble in alcohol is soluble in water, wholly on addition of traces of acid, and while non-poisonous, it is scarcely less interesting than the toxic part. The aqueous solution contains a hemolysin and a group that splits up the hemoglobin into hematin and a globulin. The hemolysin is precipitated from the aqueous solution by the addition of acid and the application of heat. It is thermo-stable, and can be heated to 110 degrees without appreciable loss of its hemolytic properties. This promises to give us a rare opportunity of finding out something more definite than is known up to the present time concerning the nature of hemolysins. I may say that traces of hemolysin have been previously found in colon cultures, and have been studied by Kayser,¹⁴ who also found it to be thermo-stable. This hemolysin is not active at low temperatures, and requires an incubation period before it manifests its effects. So far as I know, this is the first time that it has been demonstrated that a hemolysin can be obtained by splitting up the bacterial cell with chemical agents. It will probably be found that bacterial hemolysins are chemical groups in the bacterial molecule, and that those found in solution in culture media result from the normal disintegration of the bacterial molecule, which is always taking place with more or less rapidity. I know of no previous observation of the group that splits up the hemoglobin molecule with the formation of hematin. This body is now being investigated by Cooley in my laboratory, and a report of the work will be made later.

Uniformly the bacterial toxins, so far as we have studied them, lower the temperature of guinea-pigs. This is true of both fatal and non-fatal doses. If the cellular substance of the colon bacillus be thrown into the abdominal cavity of a guinea-pig, the temperature begins to fall within two hours, and continues to do so as long as the animal lives, provided the dose is a fatal one. If at any time the temperature ceases to fall and begins to rise, even after it has fallen below 95 F., the recovery of the animal can be safely predicted. When the split-off toxin is injected the fall

10. The Action of Mineral Acid on the Cellular Substance of Bacillus Typhosus, *THE JOURNAL A. M. A.*, 1904, xlii, 1000.

11. The Chemistry of Bacillus Coli Communis, *Ibid.*, p. 1003.

12. The Intracellular Toxin of Bacillus Pyocyaneus, *THE JOURNAL A. M. A.*, 1904, xlii, 1073.

13. The Extraction of a Toxin from Liver Cells, *THE JOURNAL A. M. A.*, 1904, xlii, 1075.

14. Ueber Bakterienhämolsine, in Besonderen das Collinsin, *Zeitschrift f. Hygiene*, 1903, xl, 118.

begins in a few minutes and continues to do so if the animal dies. In case of recovery, the moment of change for the better is indicated by the beginning of a rise of temperature. This matter also, as well as the destruction of the bacillus in the peritoneal cavity of immunized animals, is being studied in detail by V. C. Vaughan, Jr., and we hope to give more accurate information concerning the relation of the infectious diseases to temperature.

When the sterile germ substance of the colon bacillus is thrown into the abdominal cavity of a guinea-pig, a hemorrhagic peritonitis results. When the split-off toxin is used in the same way death results, provided the dose be large enough, in a few minutes, and there is no evidence of irritation of the peritoneum. When the dose is not fatal, recovery from the split-off toxin is apparently complete within two or three hours. When the soluble toxin is injected intravenously, death occurs within from five to twenty minutes, or with very minute doses there is no apparent effect.

CONCLUSIONS.

The investigations which I have hastily outlined have led me to the following conclusions:

1. The colon bacillus in its essential part is a chemical compound as truly as sodium sulphate or phenylhydrazin.

I have been convinced of this by the following facts, ascertained in our investigations:

(a) When treated with dilute mineral acids, the body split off from the germ substance is uniform, both qualitatively and quantitatively, whether the acid employed be 0.1 per cent. or 1 per cent.

(b) The amount of amido-nitrogen split off is the same, whether 1 per cent., 5 per cent., or 33 1/3 per cent. sulphuric acid be used. These findings indicate that the germ substance has a definite chemical composition, and that cleavage occurs along a definite line under the influence of the acid. That the toxic, hemolytic, hemoglobin splitting, carbohydrate, and other groups are chemically combined in the cell, is indicated by the fact that they are not extracted by agents acting physically as solvents, but are separated only by those agents that split up molecules.

2. The colon bacillus is a chemical compound, in whose molecule we have demonstrated the existence of the following groups: Nuclein, amido, diamido, mono-amido, carbohydrate, toxic, hemolytic, and hemoglobin splitting. Graphically, we may represent the colon molecule as in Figure 1.

There may be, and probably are, many other groups; then, each of these may, and probably does, contain sub-groups. Besides, these groups are attached to one another to form a highly complex molecule, and the lines along which the molecule splits up depend on the kind and the amount of the energy applied. The force with which these groups are held in the molecular whole varies in strength, consequently some groups are easily split off, while others are separated only under the influence of relatively powerful agents. The toxic group in the molecule of some pathogenic bacteria drops off in the presence of moisture and at a temperature of 37° C. This is true of those germs, such as the bacilli of tetanus and diphtheria, that are said to form soluble toxins. Many germs also have hemolytic groups, which become detached from the molecule under similar conditions. Some of the groups in the bacterial molecule are essential to the vitality of the cell. Such I suppose to be the case with the nuclein group, while

others are not essential. The latter is probably true of the toxic group in certain bacteria, and this explains the fact that most pathogenic bacteria can be attenuated by growth in certain media, or under certain unusual conditions of temperature.

3. Every cell in the animal body contains complex molecules similar to those of the bacillus. As has been stated, my students, Munson and Spencer, have shown that a poison can be split off from the liver cell by the action of dilute mineral acids, and next year I hope to study the action of sodium alcoholate on these and other cells of the animal body.

4. The reaction of the colon molecule and a body molecule or cell is chemical, just as much so as that between sulphuric acid and calcium carbonate. When these two molecules are brought within the range of chemical attraction, if the chemism between a group in the one and a group in the other is greater than that which holds these groups in their respective molecules, a reaction takes place. Each group is split off from its molecular combination, and the two combine to form a new molecule; and the injury done the bacillus or the cell depends on the group that has been abstracted. No bacillus molecule can do the body cell harm unless such a reaction takes place. It also follows that a toxin split off from a bacterial molecule and injected in the free state into an animal does harm, or breaks down the body molecules more promptly than when the unbroken bacillus is introduced, as sodium chlorid is not a poison.

Fig. 1.

a = Nuclein group.
b = Amido group.
c = Diamido group.
d = Monoamido group.
e = Toxic group.
f = Hemolytic group.
g = Hemoglobin splitting group.
h = Carbohydrate group.

Fig. 2.—Body cell.

but if it be broken up into its constituent base and acid, either of these, when introduced into the body, destroys the first cells with which it comes in contact. This is, I think, nicely illustrated with our colon toxin. The living culture or the dead germ substance, when placed in the abdominal cavity of a guinea-pig, requires from ten to twenty-four hours to kill, because the colon molecule must be split up before the toxic group becomes active, but when the free toxic group is employed, it may kill within as many minutes, because it is ready to combine with groups in the cell instantly on coming within range of their chemism. Moreover, when the free toxin or toxic group is thrown into the abdominal cavity, it requires a longer time to kill than when injected intravenously because, in either case, it reacts with the cells with which it first comes in contact, and with which it is capable of combining. When injected intravenously, some part of the free toxic group comes in contact with the cells of the respiratory center, and death, or at least arrest of the respiratory movements, is almost instantaneous.

5. If this conception of the reaction between bacillus and cell be true, the formation of antitoxins is capable of an explanation, which seems to me simpler than any yet proposed. This may be illustrated by the accompanying figures.

Suppose that the chemical attraction between group "e" in the bacillus molecule, and group "m" in the cell molecule, is greater than that which holds these groups in their respective molecules, then these groups will be

broken away from their molecules and unite to form a new molecule, which, being saturated and stable, is not harmful. The injury done to the cell will depend on the importance that group "m" bears to the functioning power of the cell, and the injury done to the animal depends on the number of cells whose physiologic function is thus interrupted. I take it that a true toxin—understanding this term to apply only to those agents which are capable of producing antibodies in the animal organism—does not completely destroy cells. It injures animal cells, but leaves them in such a condition that they can repair themselves. Indeed, it seems to me that no other explanation is, at present, at least possible, because the formation of the anti-body is dependent on this process of repair, and an agent that destroys the body cells of the animal is a poison, but not a toxin. It is not only possible, but probable, at the present time, that at least one pathogenic organism, the tubercle bacillus, produces a poison which is not a toxin. In the case of the toxins which I have been studying, I would explain their lethal effects on the animal as follows: The toxic group of the cell has a special chemical affinity for a certain group of the body cells that control respiration. It does not destroy these cells, but throws a certain number of them out of commission, so to speak, and if this number be great enough, respiration ceases and the animal dies. However, careful tracing of the respiratory movements, before one commits himself positively to this theory, will be necessary. I can not resist the temptation of suggesting the possibility that a cell toxin leaves the nuclein group of the cell intact, while the cell poison breaks up this group, and consequently permanently destroys the cell and renders the formation of an antibody impossible.

When the toxin is introduced into the body the injured cell, by virtue of its chemical attraction, repairs its loss by splitting off from the nutritive substances within the range of its chemism groups of "m," and in doing this it splits off more "m's" than it can use, and the excess becomes the antitoxin of the blood serum. With this exception it is easily understood why the number of antitoxins that may be formed is practically unlimited in number and why each is specific. As group "e" in no two kinds of bacterial cells is identical, the group split off from the body cell will not be identical.

In concluding, I wish to express my high appreciation of Ehrlich's theory. In my opinion it is the most valuable theory ever presented to scientific medicine, and deserves to be ranked with the theory of gravitation and with that of ether, and I think that it is not too much to say that its author has done more to stimulate scientific research than any other man in the profession, and it is with much hesitation that I have suggested the modification of Ehrlich's theory set forth in this paper. The ideas which I have expressed have grown out of a study of Ehrlich's theory, and if there be in these ideas anything of a permanent value, I hope that they may be considered a tribute to his genius. While, on the other hand, if my suggestions prove to be without value, they can not, in any way, detract from the honor due him whom all workers in this line regard as the master.

The details of experimental work done in my laboratory along the lines of this paper will appear in later papers in THE JOURNAL.

DISCUSSION.

DR. JAMES J. TERRILL, Galveston, Tex.—If the cell were rotated and the "m" band as represented in Dr. Vaughan's

diagram—if that cell is capable of replacing that "m" with, say, one, two or a hundred times, why is it not possible that the body which contains "e" (the colon bacillus, for instance, which still retains, according to this theory, its nucleus separate and intact)—why does not that have the power of replacing this "e" one, two, three and a hundred times, and therefore nothing be gained in this matter? I would like to put that question to Dr. Vaughan and hear his explanation of his theory.

DR. JOSEPH CLEMENTS, Nutley, N. J.—We have before us a great problem—that of infection and immunity. We have the facts, by the interpretation of which we are to solve this great problem, and these facts are of two kinds—first, the protoplasmic activities of the organism in which the infection or immunity is to obtain, then the other factors (which I may term the external factors), which are the so-called germs and toxins. Are we not looking too much at one end of this question? Are we not dealing too much with the external parts of the factors, to the exclusion, somewhat, of the other—the more important—part, which is the protoplasmic activities, so that we can not really and absolutely and correctly interpret the phenomena on this principle and this basis? We shall have to turn our attention a little more to the other side of it—to the protoplasmic activities of the organism in which this great problem is being worked out.

DR. HENRY SEWALL, Denver—If I have rightly understood my studies in immunity, the treatment of bacterial substances with hydrochloric acid is one of the means by which toxins are turned into toxoids. I would like to know if Dr. Vaughan's researches have not thrown some light on the essential difference between the toxin and the toxoid. It would seem as if the difference between poisonous activity and the production of immunity might be cleared up by such work as this.

DR. S. J. MELTZER, New York City—One of the constituent chemical groups of the colon bacillus was designated by Dr. Vaughan as hemolytic. These groups were obtained after the bacterial bodies were exposed to the chemical action of sulphuric acid. Hemolysis can be produced by many different methods. For instance, by osmosis, as in the hemolysis caused by water or any hypotonic solution; or by chemical actions, as in the effects of bile acids, etc.; or by biologic methods, as in the effects of alien serum. In the last case the hemolytic effect is not due to osmosis nor to any known chemical action; it is, so to say, a vital phenomenon. I wish to call attention to the difference between the hemolysis of the colon bacillus spoken of by Dr. Vaughan and the bacterial hemolysis spoken of by other bacteriologists. The hemolytic effect of the tetanus bacillus is a purely biologic phenomenon and is equal in its effect to that of alien serum, while the hemolytic effect of the profoundly disintegrated colon bacillus is apparently only of a chemical nature. Dr. Vaughan tells us that a colon bacillus is nothing but a chemical mechanism. It consists of six definite chemical groups, perhaps more, but the bacillus is nothing but a combination of these groups. We know that all living organisms contain a good many chemical groups. Does Dr. Vaughan mean to convey the view that the colon bacillus consists of nothing else but these chemical groups? Perhaps I misunderstood him. But if this is, indeed, his view, then I for one would not be converted to it until Dr. Vaughan, or someone else, succeeds in creating a colon bacillus by putting together all the constituent chemical groups without the aid of a living bacillus—were the creation only a very modest colonculus. Until then I will be grateful to Dr. Vaughan and other eminent chemists for establishing many more definite chemical groups as constituents of living organisms, but will stick to the belief that these organisms possess, beside the chemical groups, some other factor which for a great many years to come we will have to designate as vital.

DR. VICTOR C. VAUGHAN—I shall answer as best I may these questions. The one about the possibility of the colon bacillus rebuilding itself is an interesting and proper question. This is exactly what does happen when the bacillus grows in the body. In the animal that is not immune, the colon bacillus builds itself and continues to elaborate poison until it kills.

In regard to Dr. Meltzer's question, I may say that I am not trying to solve the problem of life. I am studying the material of which the colon bacillus is composed. The question of the origin of life is too big for me to undertake to discuss. I imagine that life is something more than matter, and, as stated before, I am simply discussing the material out of which the cell is built. I have used the term hemolysis, not in a biologic but in a chemical sense, and exactly as I understand it has been largely used by Ehrlich and all others working on this subject. I can precipitate the hemolysin, wash it free from other substances, put it into the blood and study its action. I have certain reasons for believing that there is a toxoid group in the colon cell. This point I have not gone into in the paper but hope to do so in a later communication. I have formulated the theory which I have offered because some theory is necessary in order to do systematic and scientific work.

DR. WINFIELD S. HALL, Chicago—I have been very deeply impressed with the character of this work which Dr. Vaughan and his associates in his department have been doing for a number of years, and I feel that this Section is very highly favored in receiving from Dr. Vaughan so clear a statement of the work that he has done and of the hypothesis on which he is working for future results. I can not help feeling that in this work he is really laying the foundation of a broad, scientific basis for the whole subject of toxins and of immunity and immunization. I believe that the discovery of diphtheria antitoxin was a chance discovery. Several of these discoveries have been made, but the relation of these individual toxins and antitoxins, the one to the other, has been purely hypothetical. I believe that the work of Professor Vaughan and his associates will result in clearing up this whole subject, now only hypothetical, and in giving to the world a science of immunization. I wish to offer a resolution, not of thanks, but of appreciation. Dr. Vaughan is not working for thanks; but appreciation helps along a little occasionally, and I move a vote of appreciation to Dr. Vaughan and his department for this epoch-making work that he is doing.

[The resolution was adopted by a unanimous vote.]

PRIMARY MALIGNANT ENDOTRACHEAL TUMOR.

PRELIMINARY REPORT.*

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This case is of interest from not less than three standpoints: First, that of the physician, because of the importance and extreme difficulty of diagnosis; second, that of the surgeon, because the treatment is purely operative, and third, that of the pathologist, not only because of the rarity of malignant growths in this situation, but because of the histologic structure of this tumor. This paper is directed especially to the pathology.

Primary tumor of the trachea is exceedingly rare, and, according to Scheuer,¹ but 22 per cent. of these are primary malignant growths.

Sir Morell Mackenzie,² after sixteen years of experience, saw but four cases of tracheal tumor, and it is probable that but one or two of these were primary and malignant.

Only twenty-eight cases of this disease are reported, most of which were discovered at autopsy in Germany or Austria.

In 1882 Delafield³ reported a case of primary carcinoma of the bronchi, which invaded the trachea to a very slight extent. A number of cases of secondary invasion of the trachea by laryngeal carcinoma have been reported. A careful search through American medical literature failed to disclose a case of primary malignant endotracheal tumor.

History.—The patient, a woman, aged 34, married, living in a malarial district, had always enjoyed good health until the present trouble began, although her husband, a physician, observed that she had been rather pale during the past year or two.

In the summer of 1903 a slight cough began, uninfluenced by treatment, and in August dyspnea and expectoration were superadded. The sputum was thick, tenacious, blood-stained and mucopurulent, reaction neutral, and showed, microscopically, squamous epithelium, blood, diplococci, staphylococci, streptococci, but no pneumococci, tubercle bacilli nor yellow elastic tissue. A second examination gave similar results and the quantity for twenty-four hours was 400 c.c. There was no fever and these symptoms gradually increased in severity until Nov. 27, 1903, when she was seen for the first time.

General Examination.—The dyspnea was extreme, of the inspiratory type like that observed in laryngeal obstruction. Each inspiration was prolonged, labored and accompanied by insinking of the supraclavicular and infraclavicular fossæ and retraction of the base of the thorax. The rate of respiration and pulse was usually about normal.

The constant struggle for breath, interrupted by frequent paroxysms of coughing, caused sleeplessness and exhaustion. A few bronchitic râles were heard over both lungs, otherwise the examination of thoracic and abdominal contents and urine was negative.

Laryngoscopic Examination.—This examination, which was rendered extremely difficult by the dyspnea and paralysis of the right vocal cord, showed a swelling in the lower portion of the trachea, the surface of which was the same color as the tracheal mucous membrane. This swelling was erroneously interpreted as indicating external pressure on the walls of the windpipe. Two fluoroscopic and skiagraphic examinations gave negative results. As an absolute diagnosis was impossible, a probable diagnosis was made of a tumor, possibly aneurismal, pressing on the trachea in the region of the innominate artery. An exploratory operation was advised, but was declined by the patient. (The autopsy demonstrated that this probable diagnosis was erroneous.) The prognosis was absolutely unfavorable.

Death.—A few weeks later aspiration bronchopneumonia occurred, accompanied by a fever ranging from 101.2 to 103.8 degrees F., which disappeared on the ninth day. Suffocation and exhaustion, preceded by deep cyanosis, caused death on Jan. 1, 1904, seven months after the onset of the first symptoms.

Autopsy.—The autopsy was performed ten hours after death. The brain and spinal cord were not examined, and there was no thoracic aneurism nor tumor. With the exception of a tracheal bronchitis, the examination of the thoracic and abdominal contents revealed nothing of importance.

At or about the lower third of the anterior wall of the trachea was a papillomatous tumor about the size of the distal phalanx of an adult finger, which extended almost to the bifurcation of the trachea and measuring 5x3½ cm. This tumor caused extreme stenosis and occupied more than three-fourths of the lumen of the tube.

Immediately beneath this growth were a few moderately enlarged glands about the size of a marrowfat pea, which were firmly adherent to the outer wall of the windpipe. This region corresponds to the place where the innominate artery

* Read at the Fifty-fifth Annual Session of the American Medical Association, in the Section on Pathology and Physiology, and approved for publication by the Executive Committee: Drs. V. C. Vaughan, Frank B. Wynn and Joseph McFarland.

1. Ueber tracheal Tumoren. Inaug. Diss., Muchen, 1893.

2. H. Crutchley: London Lancet, 1884, vol. II, p. 822.

3. New York Med. Jour. and Obst. Rev., 1882, p. 406.