PREVENTION OF HEMORRHAGE IN PULMONARY TUBERCULOSIS BY THE ADMINISTRATION OF AUTOGENOUS VACCINES *

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Discharge of blood from the mouth may be caused by heart disease, carcinoma, hemophilia, arteriosclerosis, vicarious menstruation, hysteria, aneurysm, bleeding gums, or nasal, pharyngeal, or gastric lesion, but the great majority of hemorrhages are from tuberculosis of the lungs.

Stricker¹ found 221 of 480 hemorrhages due to tuberculosis, and in 196 more this was probably the cause. Sée¹ (1884) says, "Aside from infectious diseases, hemophilia, and acute infections of the lungs (pneumonia, abscess, gangrene) we only know of two real causes of hemoptysis—heart disease and pulmonary tuberculosis."

The pathologic conditions preceding hemorrhage vary with the stage of the disease. In early cases it may be due to localized hyperemia in the lung induced by violent or long-continued exercise; or, more likely, due to weakening and erosion of small blood-vessels by the growth of tubercles. Early hemorrhages are always venous; in later stages hemorrhages arise from both the arteries and veins (Minor¹). The connective tissue of the adventitia is more resistant to dissolution than the surrounding pulmonary tissue, and vessels stand out in the walls of cavities unsupported; on these unsupported vessels aneurysms develop and hemorrhage results with a weakening of the wall of the aneurysm and any slight rise in blood-pressure. That hemorrhage is due, in many cases, to rise in blood-pressure is seen in its relation to overexertion. Hemorrhage may also result as an oozing of blood from granulations lining old cavity walls.

The frequency of hemorrhage has been reported as between 30 and 80 per cent. De Renzi¹ says that hemorrhage occurs in one-third to two-thirds of his cases (1894), Fox¹ (1891) in 54 per cent, Aufrecht¹ (1905) in 26.4 per cent, Williams¹ (1887) in 57 per cent, Walsh¹ (1871) in 81 per cent. (Minor). In the 181 cases which I have studied the percentage is much less, 15.46.

The immediate causes of hemorrhage given by various authors are overexertion, straining at stool, blows on the chest wall, and other things that would cause an undue rise in blood-pressure. Excitement, worry, temper, etc., would act in the same way. Hot, damp weather favors hemorrhage. The systemic plethora of the premenstrual period and vicarious menstruation may be rare causes. The overfeeding of tuberculous patients not infrequently predisposes to hemorrhage. The importance of sex is slight. The season of the year has a marked influence on hemorrhage; the worst period of the year, in the vicinity of Chicago, being the summer, and the hot spells are especially dreaded. Epidemics of hemorrhages have occurred, however, at other periods of the year, frequently during the winter and spring. These, I believe, are due to epidemics of "colds," influenza, etc.

Fox¹ (1891) says that heredity is important, patients with a marked family history of tuberculosis showing the greater tendency. Age is also an important factor; hemorrhage is very rare in childhood, more common between the ages of 20 and 30, less common after 45, and rare in old age.

The influence of mixed infection on hemorrhage is not given by any of the authors I have consulted, but Flick concludes from the bacteriologic studies made by Ravenel,² Irwin, and himself that the pneumococcus is an important agent in causing hemorrhage. The influence which mixed infection may exert on the pathologic changes occurring in pulmonary tuberculosis is by no means definitely known. The bacteriologic examination of the sputum reveals but little in the majority of cases because so many of these secondary organisms are found under normal conditions living saprophytically on the mucous membranes in various parts of the respiratory tract. Some authors state that the bronchi in health are free from bacteria (Cornet³). Others assert that a great variety may be present even in health. Post-mortem bacteriologic studies of the lung have revealed but little. Streptococci, notorious as causing terminal septicemia, have been found in a majority of the cases examined. How are we to know whether they were present in the lung early in the disease or invaded as a terminal septicemia? The findings of most investigators in this field show the presence of the *Bacillus coli*, *Proteus vulgaris* and other post-mortem invaders, in addition to the pyogenic cocci and the diphtheria bacillus in the lungs examined. Organisms of secondary infection have been found in the blood-stream in a small number of cases, usually far advanced, and but a short time before death. Panichi,⁴ however, reports that in three of four cases he recovered organisms of mixed infection from the blood-stream at least two months before death.

Prudden⁵ (1894) was unable to produce cavities in guinea-pigs by the inoculation of tubercle bacilli alone. He was able to produce them, however, in tuberculous guinea-pigs by intratracheal injections of streptococci. Marmorek,⁶ on the contrary, was able to produce cavities by injecting tubercle bacilli in conjunction with large quantities of strong tubercle toxins.

Webb¹ says that an irregular opsonic index to any of the secondary organisms is diagnostic of mixed infection. Wirth⁷ examining twenty-five cases, found abnormal indices in cases showing no temperature and did not find irregular indices in cases showing high and irregular temperatures. He found serums giving a normal result at the time of drawing to show abnormal indices the following day. The normal index he considered as between 0.8 and 1.2. He found no change in the index to *Bacillus capsulatus*, *tetragenus*, *catarrhalis*, *Bacillus pneumoniae*, *Bacillus coli*, or *subtilis*, but he found a variation to staphylococcus, streptococcus, pneumococcus, and influenza bacillus. The following were his results: influenza, 2 out of 17 examined; staphylococcus, 2 out of 17 examined; pneumococcus, 18 out of 24 examined; streptococcus, 6 out of 19 examined. I have taken the opsonic index to the pneumococcus, strepto-

* Work done under the Max Pam Research Fund. The article was awarded the Freer medal by the prize essay committee of the Alumni Association of Rush Medical College.

Klebs: Tuberculosis, ed. 1, New York, 1909, Appleton & Co., p. 212

2. Ravenel and Irwin: Phipps Inst., Rep., 1906 III, 229; IV, 392.

3. Cornet: Nothnagel, Encyclopedia of Practical Medicine, Am. ed., Philadelphia, 1904, Saunders & Co., p. 488.

4. Panichi: Der Pneumococcus im Blut bei Lungentuberculose, Berl. klin. Wchnschr., 1908, No. 41, p. 1840.

5. Prudden: Concurrent Infection and Formation of Cavities in Acute Pulmonary Tuberculosis, New York Med. Jour., July 7, 1894.

6. Marmorek: Production expérimentale de cavernes pulmonaires chez le cobaye et le lapin. Soc. de biol. Séance du 26 Janvier, 1904.

7. Wirth: Beitr. z. Klin. d. Tuberk. (Brauer's), xii, 159.

coccus and staphylococcus in 40 cases representing all stages of the disease, both active and inactive, and found an abnormal index in only one case. The index in this case was 0.75 and this was to the staphylococcus. This patient had an anal fistula in which the staphylococcus was present in large numbers. The normal index in both Wirth's report and my own was considered as between 0.8 and 1.2. Therefore I do not consider the opsonic index of value in the diagnosis of mixed infection in tuberculosis.

It is difficult to estimate the importance of mixed infection in tuberculosis at the present time. The experimental results are contradictory and the conclusions of investigators are at variance. Because of the atypical course of the disease, the rapid variations in temperature at irregular intervals, the fact that extensive infiltration may occur in a few days and disappear leaving areas of caseation or softening, I am convinced that organisms other than the slow-growing, persistent, slightly toxic, tubercle bacillus are concerned. Some authors have contended that practically all the damage to lung tissue is done by organisms other than the tubercle bacillus.

Weaver⁸ has shown that injections of killed streptococci protects rabbits against subsequent injections of large numbers of living virulent streptococci. The work of Wright⁹ and others has shown that injections of killed and attenuated bacteria have a protective effect against subsequent infection. This production of active immunity has been known for a long time and its importance in preventive medicine has been proved conclusively by Jennerian vaccination against small-pox, and Pasteur's vaccination against chicken cholera, anthrax and hydrophobia. It has been successfully employed against typhoid. Wright has collected statistics dealing in all with 49,600 individuals, of whom 8,600 were inoculated and showed a case incidence of 2.25 per cent. with a mortality of 12 per cent. In the remaining 41,000 uninoculated the case incidence was 5.75 per cent. with a case mortality of 21 per cent.

The data on protective inoculations against pyogenic infections are very meager, but the results that have been obtained in therapeutic inoculations against the gonococcus, streptococcus, staphylococcus, pneumococcus, etc., especially in chronic, subacute and localized infections, seem to show that injections of killed organisms hasten recovery and protect against relapse.

Webb¹ has used killed organisms against mixed infection in tuberculosis and has observed a protection in inoculated cases against influenza. Five patients inoculated against influenza with their own organisms, and eight inoculated against influenza with stock vaccines, all giving histories of repeated former attacks, escaped the epidemic. Preventive inoculations were not given in thirty-two cases, the patients denying that they ever had influenza, and fifteen succumbed to an influenza epidemic.

Since June 15, 1909, I have administered autogenous vaccine in thirty-one cases of pulmonary tuberculosis at the Ottawa Tent Colony. Of these thirty-one cases twenty-one were under observation two months or longer. Patients not under observation at least two months are not included in this report.

Vaccines were not administered as a protective measure, but therapeutically. It has been observed that during the fall and winter of 1909-10 hemorrhages have

been less frequent than before. The class of patients, diet, exercise, sleeping conditions, and supervision were practically the same as in preceding years; the only new factor introduced into the treatment was the autogenous vaccines. It occurred to me that possibly the injection of vaccines against the organisms of secondary infection had a protective action against tissue dissolution and hence against hemorrhage.

The vaccines administered in all cases were autogenous. They were prepared by taking carefully selected particles of sputum and washing by whipping vigorously in several changes of sterile water with sterile forceps. The washed sputum was then introduced into about 10 to 15 c.c. of either plain bouillon or a medium made up of 1 part of sterile beef serum and 3 parts of bouillon. This was incubated at 37° C. for twenty-four or forty-eight hours, at which time a moderately thick growth had developed. The beef serum mixture appeared to have no advantage over the plain bouillon. The growth was then examined for bacteria, and the relative number of cocci, in pairs, tetrads, clumps and chains were noted. Allen¹⁰ says the proportion of the various organisms thus grown is approximately the same as when introduced. More recently I have been using large blood-agar slants for the cultivation of bacteria from the sputum. The emulsion of bacteria was shaken vigorously for ten or fifteen minutes, centrifuged at high speed for from forty-five seconds to one and one-half minutes, depending on the density, and the supernatant homogeneous emulsion decanted into another tube.

The number of organisms was then estimated by Wright's method. This is done by taking up one volume of 1.5 per cent. solution of sodium citrate in a capillary pipette, then equal volumes of blood and bacterial suspension, mixing thoroughly on a slide, drawing up into the pipette and then making four slides by placing a small drop on each and drawing out in a thin smear by dragging the edge of another slide over it. These were stained with methylene blue and the erythrocytes and bacteria present in fifteen fields in each of the four slides were counted. An estimation of the number of organisms present in a cubic millimeter of the emulsion was then calculated. The number of erythrocytes in 1 cubic millimeter was considered as 5,000,000; the number of erythrocytes in the number of fields counted is to the number of bacteria as 5,000,000 is to x . By multiplying by 1,000 the approximate number of organisms in 1 c.c. was obtained. This is a long and laborious procedure, so I tried counting the bacteria in a blood-counting chamber in the same way the blood-count is made. To do this it was necessary that the organisms be stained. I used a fresh, carefully filtered solution of gentian violet or Unna's methylene blue. I drew some of this stain into the pipette, a volume of the bacterial suspension, to be estimated, then more stain, and finished my dilution with either distilled water or salt solution. The pipette was shaken vigorously, several drops blown out and a small drop placed in the Thoma or Turk counting-chamber and covered with an ordinary thin coverslip. The coverslip used in blood-counting is too thick to use with the oil immersion lens. The chamber was then set aside until the organisms had settled: it usually takes about one to six hours, depending on the diluent used and the size and number of the organisms present. Whether the organisms have all settled out or not is easily determined by focusing on the

8. Weaver: Jour. Infect. Dis., 1908, v. 589.

9. Wright: Studies on Immunization, Ed. 1, London, 1909, Constable & Co., Ltd.

10. Allen: Vaccine Therapy and Opsonic Treatment, Ed. 2, Philadelphia, 1908, Blakiston's Son & Co.

lines of the chamber and then raising the lens through several planes and looking for organisms in suspension. The bacteria are well stained and easily distinguished. If there are confusing particles of dirt present, a weak alcoholic solution can be used as a diluent; this gives a very clean slide and the bacteria are easily picked out. The method is very simple and rapid, and, I believe, more accurate than Wright's method. In the preparation of vaccines during the past four months, November, 1909, to March, 1910, I have used this method exclusively.

The organisms were killed by heating to 60 C. for forty-five minutes, either before or after counting, and sterility was insured by inoculating a tube of broth or blood-agar from the heated suspension. The suspension was then placed in a sterile bottle of brown glass and a drop of strong phenol or compound solution of cresol added.

The size and frequency of the dose administered depended on the condition of the patient. In afebrile patients in fairly good physical condition comparatively large doses, 200 to 500 million, were given, at intervals of seven to ten days. In febrile cases with the patients in poor physical condition, doses of 25 million were administered every second or third day for several doses and then increased to 50 and 100 million. When doses of 100 million or more were given the interval was lengthened to from five to ten days. In all cases considered in this report, at least three doses were administered. The number of hemorrhages occurring in all classes of patients under observation for at least two months, from June 15, 1908, to March 1, 1909, are compared with the number of hemorrhages occurring in all classes of patients under observation for at least two months, from June 15, 1909, to March 1, 1910. The number of hemorrhages occurring in all classes of patients receiving vaccines during the latter period is compared with the number of hemorrhages occurring in cases not receiving vaccines during the same period.

TABLE 1.—HEMORRHAGES BETWEEN JUNE 15, 1908, AND MARCH 1, 1909, NO PATIENTS RECEIVING VACCINES

Class.	Cases, No.	Hemorrhages, No.	Hemorrhage, Per Cent.
Incipient	42	0	14.28
Moderately advanced..	44	11	25
Advanced	13	1	7.7
Far advanced.....	1	0	
Total	100	18	18

TABLE 2.—HEMORRHAGES BETWEEN JUNE 15, 1909, AND MARCH 4, 1910, ALL PATIENTS, THOSE RECEIVING VACCINES AND THOSE NOT RECEIVING VACCINES

Class.	Cases, No.	Vaccin- ated, No.	Hemor- rhages, No.	Hemor- rhage, Per Cent.
Incipient	16	3	0	0
Moderately advanced..	30	4	5	16.6
Advanced	24	11	4	16.66
Far advanced.....	11	3	1	9.1
Total	81	21	10	12.34

TABLE 3.—HEMORRHAGES BETWEEN JUNE 15, 1909, AND MARCH 1, 1910, PATIENTS RECEIVING VACCINES

Class.	Cases, No.	Hemorrhages, No.	Hemorrhage, Per Cent.
Incipient	3	..	
Moderately advanced..	4	..	
Advanced	11	1	9
Far advanced.....	3	..	
Total	21	1	4.7

TABLE 4.—HEMORRHAGES BETWEEN JUNE 15, 1909, AND MARCH 1, 1910, PATIENTS NOT RECEIVING VACCINES

Class.	Cases, No.	Hemorrhages, No.	Hemorrhage, Per Cent.
Incipient	13	..	
Moderately advanced..	26	5	19.2
Advanced	13	3	23.1
Far advanced.....	8	1	12.5
Total	60	9	15

It is seen from the tables that the total number of hemorrhages during the same period of time and during the same seasons of 1909-1910 is about 50 per cent. less than the total number of hemorrhages occurring during a corresponding period in 1908-1909.

From June 15, 1909, to March 1, 1910, in patients receiving vaccines the percentage of hemorrhage is only one-third of the percentage in patients not receiving vaccines. All patients were under exactly the same conditions of housing, feeding, and medical supervision. While it is not admissible to draw definite conclusions from such a small number of cases, the results seem to be indicative and will justify the administration of autogenous vaccines in a larger number of cases as a protective measure. A report will be made next year.

I wish to thank Miss Elizabeth Peck and Miss Elizabeth Byrne for assistance in the preparation of vaccines and the determination of opsonic indices.

In addition to the articles previously cited, the following references will be found of interest:

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TINCTURE OF IODIN FOR THE UMBILICAL CORD

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The increasing use of iodine suggested to me its application to the freshly severed umbilical cord. The tincture, as is well known, tends to form a dry iodine-impregnated scale or scab over any moist surface not giving off a purulent discharge, such as a clean varicose ulcer or a freshly sutured wound. The treatment to be described was tried on several infants with satisfactory results. In one case the cord was found mummified and separated on the fourth day, the granulated surface healed to a small dry scab within the same week. Others averaged ten days to two weeks for the entire process. Iodism was not observed. The technic used is as follows:

As soon as the cord is cut and tied, blood and vernix caseosa are wiped off with a sterile pledget. The stump is then painted with the official tincture until deeply stained; especially the cut end, the ligature, and the line of attachment. Due care should be taken to avoid the epidermis beyond the line of union with the cord. After the bath, dry sterile gauze or cotton is packed about the stump and held with the usual binder. In case the dressing becomes soiled or moist it is changed at once. After the cord falls off the granulating or denuded surface remaining is painted as before, and the dressing is reapplied. The advantages of the method consist in simplicity, increased rapidity of drying, and the penetrating bactericidal property of the drug.

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