A CLINICAL STUDY OF 109 CASES OF SEPTICEMIA*

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Editor's Note: The author of this paper has hardly made it clear that the personal observation of 109 cases of definite blood stream infection constitutes an unusual clinical experience. Dr. Bean has been especially interested in this condition for many years and his observations carry the weight of authority.

PENFOLD and Corkill in the Medical Journal of Australia, March 15, 1928, report a streptococcus hemolyticus septicaemia with recovery. Sanderson, Capon and McWilliam in The Lancet of July, 1927, report two cases of blood stream infection by streptococcus hemolyticus with recovery, giving at the same time a large number of case reports. There have been also numerous case reports in the literature of this country and the continent, illustrating the prevalence of the infection, as well as certain interesting features concerning the different modes of treatment. These reports have stimulated us to a rather detailed study of a series of cases observed since 1918. These cases 109 in all, have been studied mainly from their clinical features, but we will present also such statistics as are available in the usual reports of the standardized hospital. In many instances more than one laboratory checked the findings.

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The use of the term septicemia may be debatable, for, as McCollom has recently stated in his text book, there is much skepticism concerning the existence of a septicemia as such. Certain authorities believe that the presence of bacteria in the circulating blood is a temporary result of their discharge from a focus of infection which is in close or direct communication with the blood stream. That the bacteria grow and multiply in the blood so as to constitute a true bacteremia, seems in most instances extremely unlikely, and occurs, if at all, shortly before death, when we may suppose that the bactericidal powers of the blood are at a low ebb. After death the blood becomes filled with bacteria so that cultures from the heart's blood at autopsy, unless immediately after death, are of very little interest. The above mentioned author also states that while at times it is possible to find streptocci or other organisms circulating in the blood, this seldom continues for any considerable length of time, unless there is a constant source of supply, such as a large vegetation loaded with growing bacteria, hanging upon the valve of the heart, and shedding the bacteria continuously into the blood stream. Notwithstanding the above facts, there is a definite clinical picture which has been called septicemia, and it is this condition which this short review of cases and charts illustrates.

Bacteriology: A large group of bacteria, such as the streptococcus group,

contains many different strains of the organism. Schottmuller (1903 to 1910) reported a great deal of work on the different strains of streptococci. It was through his influence that hemolysis as a basis for classification was introduced. The division was made into two general classes. First, non-hemolytic or streptococcus viridans, and second, hemolytic streptococcus, or the common blood destroying organism. Since Schottmuller's work, many other workers have spent a great deal of time differentiating these various groups. Dochez has found four distinct types of hemolytic streptococci; others have sub-divided the viridans strain, and it is well established that the so-called streptococcus mucosus has now been included in group three of the pneumococcus. Other workers who were concerned with the typing are Holmans, Gordon, Kinsella, Hordes and Swift.

As recently as 1928, Anthony Bassler, noted gastro-enteriologist of New York, made the statement that in isolating the organisms of the stool, in an endeavor to create a therapeutic vaccine, there have been isolated many different strains of streptococci. The streptococcus of erysipelas and the streptococcus of scarletina as well as the streptococcus putridus, have been studied in detail. Further reference will be made later to these groups. In this paper there will be considered the two general classes, the non-hemolytic and the hemolytic, with an additional brief study of the streptococcus putridus, the organism commonly found in puerperal infection.

General Clinical Features: The initial onset is usually with a rigor and fever characterized by remissions and daily exacerbation. The blood is quickly changed and a consequent progressive anemia develops. There is, as a rule, a marked increase in the leucocytes, and in severe cases where resistance fails, the remarkable feature of a rapidly produced leucopenia ensues, with a very serious prognostic import. Hemolysis of the blood corpuscles developes rapidly and extreme pallor follows. In the skin and conjunctivae there are found numerous areas characterized by minute points of yellow necrosis, surrounded by little flakes of hemorrhage. These are due to embolic processes plugging the tiny capillaries and thus giving the characteristic picture. Again, if there is an endocarditis present, small fragments of the heart valves may block the vessels and cause the same features. Thus in the skin, kidneys, brain, spleen and lungs, emboli are most evident. In the skin such emboli produce no hemorrhage but rather a tender nodular swelling, which in sections reveals a focus of inflammatory infiltration around the obstructed vessels (McCollom).

In other cases, large purpuric hemorrhages may occur, and the eruption may become confluent, presenting the picture of a purpura hemorrhagica and the hemorrhagic type of measles. Dick and Dick, in their recent work on scarlet fever, have definitely proven that the flush or erythema of scarlet fever is produced by a toxin from the streptococcus of scarletina, thus illustrating one of the effects of this hitherto unknown toxin.

Hematuria may be one of the early signs of streptococcus septicemia, and is due to embolic processes in the kidneys with the resultant release of the blood in the urine. Therefore a careful microscopic examination of urine should be performed early in any questionable febrile case and especially where blood cultures can not be obtained. Often not a single examination but only a protracted detailed search will reveal the characteristic findings.

Splenic and lung infarcts, or embolic processes occur more frequently than is understood, with resultant upper quadrant pain and distress and at times a common splenic friction rub. This symptom is often mistaken for cardiac distress and eroneously diagnosed as coronary disease. Again hemoptysis due to embolic areas in the lungs may take place, and should not be confused with early tuberculosis.

Endocarditis lenta, which has so accurately been described by Libman and others, occurs in many cases, especially in the viridans group. The clinical features of this syndrome are well known.

Sources of Infection or Portals of Entry: Entrance of the organism through the mucous membrane of the mouth and accessory sinuses is well known. This type of transmission is well illustrated by milk borne epidemics carried from the various parts of the United States, in which it has been definitely proven that the streptococcus was transmitted from an infected milker to the udder of the cow, from the udder to the milk, then to the human being. Benson reported in detail an epidemic occurring in Portland, Ore., which was known as the streptococcus sore throat epidemic.

Libman proved conclusively that early ligation of the jugular bulb will often prevent the entrance of the organism into the blood stream after an infection of the lateral sinus following an otitis media.

The universal use of swimming tanks for children during the winter and early summer has been proven to be the source of infection by the hemolytic organism. This, it has been proven, occurs by infection, first, of the cribiform plate, then the ethmoidal cells, and so into the blood stream or meningeal spaces.

A careful study of the literature reveals many cases of septicemia following various other injuries, such as a basal fracture of the skull, post-operative infection, and instrumentation such as a passage of a cystoscope or bronchoscope; but the comparative infrequency of this infection illustrates again the well-known acquired immunity which the human body has against certain organisms.

The Role of Oral Surgery: It is not generally understood how commonly blood stream infection follows oral surgery. Recently, we have had occasion to observe two cases of malignant septicemia following such procedures. One was in a woman aged 54 who had had a wisdom tooth extracted. Three days later she suffered a severe chill and marked rise in temperature, with subsequent development of a firm indurated swelling of the left side of the neck, which included the parotid gland. Three wide incisions over the indurated area were made with resultant evacuation of a large amount of pus. Two days later the patient went into a semi-comatose state and rapidly died. An hemolytic streptococcus was recovered from the blood stream.

The other case was in a young man who had had three teeth extracted because of a suggestive rheumatic history. Two weeks following the extraction the patient developed a marked weakness, chills, fever and a rapidly progressive anemia. There followed the development of petechial spots over the entire body with palpable spleen and embolic phenomenae in the retina. The blood pressure rapidly fell and the patient developed a typical picture of asthenia with marked pigmentation of the mucus membrane of the mouth, the conjunctivae, and the region about the nipples and navel. A diagnosis of adrenal insufficiency was made, and as the blood culture remained negative throughout his illness, the true etiological factor was not discovered until post-mortem. In spite of intensive adrenal therapy, the patient died on the 28th day of the disease. Autopsy revealed both adrenals to be mere sacks filled with a foul smelling pus. Microscopic examination revealed very little normal adrenal tissue and no evidence of tuberculosis. Anatomical diagnosis was metastatic abscesses of the adrenal glands following extraction of teeth.

The Role of Puerperal Infection: Chart one illustrates a detailed study of the portals of entry in the streptococcus cases in our series. Schottmuller brought

CHART I.

Portals of Entry in the Streptococcus Group.

Origin—	Hemolyticus	Viridans
Otitis Media	18	3
Sinusitis	12	1
Tonsillitis	12	0
Erysipelas	3	0
Subacute Endocarditis	18	17
Puerperal Sepsis	6	0
Osteomyelitis	2	0
Post-Operative	9	0
Dental Surgery and General Infection	4	0
	84	21

out the fact that, if streptococci were grown under anaerobic conditions, in many instances the organism characteristic of puerperal septicemia could be isolated. This he named the streptococcus putridus, due to the offensive odor given off as the organism grew. This odor was found to be present in the puerperal cases, especially several days after the termination of labor. Moreover, the organism was isolated from the blood stream as well as from the vaginal secretions. The blood cultures were characteristic, in that, on the tenth day they became black in color, due to the development of hydrogen bi-sulphide. He reported 231 fatal puerperal cases in which the streptococcus putridus was found in 72 cases and in which 31 deaths were due to an extensive generalized peritonitis.

Clinical Data: It has long been known that there are many cases of early septicemia, which can only be recognized by thorough laboratory study. By this we mean that in certain cases, embolic or diagnostic phenomena have not developed, but the organism may be caught and grown from the blood stream. Often the chills are insignificant and afternoon rise in temperature slight. The history of gradually increasing weaknesses, especially in the viridans or non-hemolytic type, may lead one to correct diagnosis. The proper time for taking blood cultures seems to be a debatable one. Many authorities believe that they should be taken before or during the chill. Others assert that daily blood cultures should be taken at the same recorded hours. We have found it best to take the blood when the temperature is on the rise. A goodly amount of blood should be removed. This can be done without any harmful psychic effect on the patient. The details of this technic will not be taken up in this paper. Suffice it to say that the chart illustrates the practical import of waiting for the

CHART II.

Sex and Age Incidence

	Hemolyticus	Viridans	Percentage
Male	52	11	17
Female	38	8	23

Age Incidence in Years

	Youngest	Oldest	Average
Hemolyticus	2	79	40.05
Viridans	8	64	36

CHART III.

Blood Culture Study

	Positive	Negative	Deaths	P. C.
Hemolyticus	68	16	70	83%
Viridans	17	0	16	94%
Staphylococcus	8	0	7	87%

results of the blood culture. We have felt for some time that a sufficient number of days should be given for the organism to grow in the blood. Recently it has been brought to our attention, in a case of streptococcus viridans, that it was 15 days before the characteristic growth appeared on the agar. The non-hemolytic organism is much more sluggish in its growth than the hemolytic. It is quite common in the latter class to obtain a positive blood culture within twenty-four hours after the blood is taken.

Staphylococcus Septicemia: This is a blood stream infection in which there is rapid multiplication of the staphylococcus, usually the albus. It is characterized by the development of multiple focal areas, suppurative in character. A culture of the predominant organism may be obtained whenever the metastasis takes place.

CHART IV.

Duration of Disease and Causes of Death

Duration

	Culture Studies	From History
Hemolyticus	44 days	68
Viridans	148 days	218

Cause of Death

	Hemolyticus	Viridans
Menengitis	22	0
Myocardial	58	16
Uraemia	13	0

There were nine cases of staphylococcus septicemia in this series, with one recovery. This case was reported in detail by Dr. Ivan Wooley and is included here due to his kindness. Complications in this group, such as osteomyelitis, furunculosis, metastatic abscesses, etc., are well known. Often, as McCollom brings out, the original site of infection may be lost by the time the patient comes to post-mortem examination, when large collections of pus will be revealed without any apparent portal of entry. The latter may have been only a simple abrasion or a small papule. Recently a case was seen in a woman who, three days before being admitted to the hospital, had a small papule on the upper lip. This had been opened with a needle. The second day following, the patient had a severe chill, elevation of temperature, marked nausea and vomiting and prostration. She was taken to the hospital and was seen in consultation on the fifth day of the disease, thirty-six hours before death. At this time there were large areas of fluctuation over the upper lip and right facial region. The patient was dull and practically comatose. Blood culture showed a pure culture of staphylococcus albus. Gentian violet was given in large doses, intravenously, without any appreciable effect. Autopsy revealed numerous necrotic areas in the spleen, kidneys, adrenals, and an area at the apex of the heart as large as an English walnut which had become necrotic and was on the point of rupture.

Immunilogical Studies: Much detailed bacteriological work in the past has failed to establish any definite facts concerning immunity to the staphylococcus or streptococcus, with the possible exception of the work of Dick and Dick on the streptococcus of scarletina. Many theories have been advanced. While one individual may acquire an infection, become violently ill, and recover without any ill effects, another individual with a slight abrasion of the skin rapidly succumbs.

Meersholm advanced the theory that the reticulo-endothelial cells are to be considered as a site of production of anti-bodies and a defense mechanism. He states that the removal of the spleen in mice, infected with the organism, increased the death rate 20 to 40 per cent.

Another interesting theory has been advanced recently by Ramsay, in the British Medical Journal, April 24, 1928. He states that in his opinion successful resistence to any bacterial infection, depends largely on the ordinary response of our endocrine glands. That is, the thyroid, superenal and pituitary form one group, in opposition to the pancreas and parathyroid in the others. And the balance of the various functions may establish the resultant resistence. Vinces has stressed the important role of the parathyroids in infection. He has proven that the calcium content of the blood is lowered in the presence of infection, and by using parathyroid extract, together with calcium, the resistence of the patient is often improved.

Ramsay also brings out the fact that in the seriously ill pneumonia or septicemic patients, the use of pituitary and thyroid extract seems to be of benefit and often tides the patient over the crisis, thus establishing the possible truth of his endocrine principle.

Treatment: The main value of this study has been in the development of various methods of treatment. During the past eleven years the medical profession has passed through various styles or modes in treatment. Trans-

fusions of citrated and whole blood were in great vogue during the early part of this study, and many of the cases reported received large quantities. The results were not startling except in those cases of hemolytic septicemia, or possibly those due to the streptococcus putridus, which followed childbirth. These patients, as is well known, develope an extraordinary immunity to the streptococcus and often recover without any special therapy. Transfusions of blood were used in viridans and other forms of streptococcus infection. The chart will show that beneficial results obtained therefrom, are rather problematical. It is safe to say that it is not a treatment which justifies the enthusiasm evinced at its inauguration, but should be considered only in those cases which respond to no other accepted form of therapy.

The Aniline Dyes: As was reported in an early communication by the author, the various aniline dyes were tried in many of the cases. Due to the brilliant work of Young and Hill of Baltimore, and Pemberton of Philadelphia, the bactericidal powers of the various aniline dyes are established. There have been many reports containing adverse criticism, and in some cases serious damage to the patient following the use of mercurochrome has been reported. An open mind should be kept as to its value for sufficient data exist in the literature to prove that it is a method not without danger. One should be very conservative in its use. Although Hill has stated that he has never seen a case of renal damage, others have reported cases of tubular necrosis; and in our small series there have been two cases of hemorrhagic nephritis with salivation following the use of mercurochrome intravenously.

Martin and Hill in the American Journal of Medical Sciences, May, 1929, have introduced mercurochrome as a possible biliary antiseptic. Having carried out experiments revealing the fact that the dye is retained in the gall bladder for some time after it has been given intravenously, they state that intravenous medication with mercurochrome causes the dye to remain in the gall bladder for at least eighteen hours, whereas its oral administration in keratin covered capsules, has no such beneficial effect. This work led them to the conclusion that mercurochrome has a definite antiseptic action in the liver and gall bladder. If this is the case, perhaps its use is justified, but by some other method than that at present in use.

In our series, gentian violet was given intravenously in three of the staphylococcus infections without any apparent inhibition of the growth of the organism. Large quantities of whole blood were given also, and the results are not startling, although others in the literature have reported favorable results.

CHART V.

Various Modes of Therapy and Results

	No. of Cases	Transfusions	Murcurchrome	Gentian Violet	Sodium Cacodylate	Serum	Salitylates	Recovery	Deaths	Percentage
Streptococcus Hemolyticus	84	26	13	0	9	4	16	14	70	83
Viridans	17	2	0	0	3	0	12	1	16	94
Staphylococcus	8	1	0	8	0	0	0	1	7	87

Penfold and Corkill, as mentioned above, report a case of streptococcus hemolyticus septicemia in which the patient recovered following the use of an antistreptococcus serum or rather a post-influenzual serum, prepared by the Australian commonwealth. They brought out the very important observation that the titre of the particular serum should be tested out by the mouse injection method. They conclude with this statement, "in the event of isolation of streptococcus, the powers of each of the antistreptococcic sera to protect mice against the particular strain should be ascertained and compared. That which is most effective should be employed."

Sanderson, Capon and McMillan report two cases of recovery with the intramuscular injection of 10 cc. doses of the scarletina anti-streptococcus serum. We have found that the serum ordinarily obtained does not seem to be specific for the organism under question, for in one case the organism in the blood stream rapidly increased in numbers, in spite of the fact that 100 cc. of the serum was given daily.

Large doses of this drug were tried out in many of the cases. The drug was given up to the point of tolerance of the individual, preferably by mouth, but in several instances intravenously. Tinnitus and temporary deafness usually ensued. The improvement has been most marked with this form of therapy, and there are four cases that are symptomatically well at the present time in whom the main form of therapy was the salicylate. One important factor is the continuation of the drug after the temperature returns to normal, for in two cases a definite remission occurred only to be checked by subsequent large doses of salicylates. Needless to say, in a streptococcus viridans infection the use of salicylates does not seem to exert any beneficial effect. The general treatment should consist of high caloric feedings and general hygenic care with special reference to cheerful surroundings.

Differential Diagnosis: The recurring chills and high fever with daily remission or intermission, early delirium, mental apathy and the appearance of marked prostration, indicates a possible septicemia of the streptococcus type. The absence of acute gastro-intestinal symptoms and a cutaneous eruption, which are quite characteristic of pyocyaneus septicemia, and of severe pains in the shoulders, arms and larger joints, commonly found with the staphylococcus septicemia, aid in the differential diagnosis.

According to Osler, the streptococcus infection is further differentiated from the absence in the latter of delirium or marked mental acuteness, and by a more marked anemia. Blood culture should be repeated until a positive result is obtained. A great mistake is made in accepting as definite a laboratory report from a blood culture as early as twenty-four hours or even seventy-two hours after the blood is taken. This practice has proven to be unreliable in many cases.

CHART VI.

Embolic Phenomena and Their Incidence

	Hemolytic	Viridans	Total	P. C.
Petechiae	65	12	77	87%
Painful Modes	24	2	26	29%
Retinal Hemorrhage	39	0	39	44%
Splenic Infarct	18	1	19	21%
Hematuria	68	0	68	77%
Hemiplegia	6	1	7	7.9%
Multiple Abscesses	1	0	1	1.1%

Further aids in differential diagnosis are as follows:

Staphylococcus septicemia is usually complicated by the development of numerous abscesses, meningitis and pericarditis. Practically all cases of acute osteomyelitis are due to the staphylococcus entering the bone marrow by the way of the blood stream. This may occur during the septicemia, or without a demonstrable septicemia being present. These latter cases of septicemia are often confused with acute articular rheumatism, in which the characteristic rheumatic swelling may be absent. The presence of petechial or articular eruption is of great diagnostic value. Perhaps the most suggestive of all physical findings in staphylococcus septicemia is the development of subcutaneous and intramuscular abscesses. In fact this infection is characterized by the extreme frequency of secondary foci. Chills followed by profuse sweating are rarely absent, according to Tice.

In this class of septicemia, cultures should be taken from various areas of the body, as well as from the urine, stools, and blood. Positive cultures from any of the foci are sufficient to warrant the diagnosis.

Differential diagnosis from early tuberculosis is often difficult. The afternoon temperature, the gradual loss of strength and occasional signs of a failing heart, may cause many rales in the lung fields. Corkill states that embolic phenomena, enlarged spleen and the signs of progressive heart failure often clarify the diagnosis. Pernicious anemia, typhoid, malaria, Malta fever, must be eliminated. Finally, the only accurate and positive means of diagnosis is the use of frequent blood cultures.

Prognosis: This is discouraging at the best. Libman reported that out of one hundred and fifty cases, four recovered. Billings states that in one hundred cases, ninety-seven per cent died. Behrens, describing sub-acute endocarditis, reported seventeen cases, stating that death occurred in one hundred per cent. And in regard to treatment the same author concludes with the statement that he has tried all of the arsenicals, salicylates, mercurials, vaccine, serum and blood transfusion, with the same result. In conclusion he asserts that where a valvular lesion of the heart is accompanied by anemia, and streptococcus viridans is obtained, the prognosis is practically always fatal.

Barker states in regard to staphylococcus septicemia, that the prognosis is very poor and the treatment should be symptomatic. Libman also brings out the fact that there are a small number of spontaneous recoveries and that the disease may exist in a recurrent form.

SUMMARY

(1) Septicemia is a term used to describe a definite clinical picture. (2) The three most common causative organisms are the two groups of the streptococcus, the hemolytic and non-hemolytic (or viridans) and staphylococcus. (3) Early diagnosis is important, and can be substantiated only by careful and detailed blood culture study. (4) Early report of negative cultures should be discouraged. (5) No well established specific treatment has been discovered. The question of the advisability of the use of various aniline dyes is debatable. Salicylate of soda has a well established place. Serum and vaccine therapy is of doubtful value. (6) The prognosis generally is poor, but varies, depending upon the organisms isolated.

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