THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given Alfred Sabato Giordano final oral examination for the degree of Master of Science in Pathology.

We recommend that the degree of Master of Science in Pathology be conferred upon the candidate.

H. E. Robertson
Chairman

Arthur T. Henrici.

J. B. Magath

E. T. Bell.

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H. S. Weibel

E. C. Rosenow.

Date December 1, 1922

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Graduate School, University of Minnesota.

Date: Nov. 13, 1922.

This is to certify that Alfred Sabato Giordano, a candidate for the degree of Master of Science in Pathology, has passed the final written examination for the major in the Department of Pathology.

H E Robertson

For the Major Department.

Graduate School, University of Minnesota.

Date:

This is to certiry that Alfred Sabato Giordano, a candidate for the degree of Master of Science in Pathology, completed the requirements for the minor in the Department of Bacteriology.

E. C. Rosenow

For the Minor Department.

REPORT

of

Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Alfred Sabato Giordano for the degree of Master of Science in Pathology. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science in Pathology.

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10-20 5M

THESIS

STUDIES IN POSTMORTEM BACTERIOLOGY

PART I

Importance, Method and Interpretation of Results

PART II

Specificity of Bacteria and the Relation of

Foci of Infection to the Etiology of Certain Organic Lesions

Alfred Sabato Giordano, B.S., M.D.

Submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Pathology.

October, 1922.

PART I

Importance, Method and Interpretation of Results

It has long been recognized that the greater number of all deaths are the result of primary or secondary invasion of the body by pathogenic bacteria. Fortunately for the clinician and pathologist, most of these organisms leave a fairly characteristic trail, and the reactions between them and the living tissues are so specific that, within certain limits, a careful study makes a presumptive diagnosis moderately certain. However, in at least two circumstances the accuracy of such a clinical diagnosis often becomes questionable: (1) if the reaction of the body is rendered atypical either from unusual variation in immunity, or in the virulence of the invader, the identity of the offending organism is obscured, and (2) if the original focus of the parasite is hidden.

So serious are the results of errors of diagnosis that modern clinical practice demands careful bacteriologic studies as controls in all cases of suspected infection. To mistake the lesions of diphtheria for those of tonsillitis, or the spasms of tetanus for those of strychnine poisoning are indefensible errors unless all the facilities of modern bacteriology have been exhausted.

For the pathologist, bacteriology is equally important, but it is too often neglected or it is used only superficially or incompletely. The two sources of error to which clinicians are exposed are even more prominently emphasized at the postmortem table, where signs are few, symptoms entirely absent, and appearances often deceiving. Moreover, the lesions which have finally caused death are not always sufficiently evident to be recognized even with the aid of the microscope. In such cases the presence or absence of pathogenic bacteria becomes an absolutely decisive factor. Even in lesions in which it becomes clearly apparent that bacteria are largely responsible, the species or type of organism is not demonstrable without appropriate technical procedure.

Two fundamental propositions are established for the clinician and the pathologist: (1) every infection requires the accurate identification of the

offending agent, and (2) in every obscure condition, the presence of pathogenic bacteria must be excluded by systematic routine bacteriologic methods before a definite conclusion may be reached. Carelessness in this respect can too often be charged against the pathologist. The meager reports in the literature and the dissension which exists among the various investigators regarding the value and significance of bacteria recovered postmortem has prompted me to undertake the present study.

Postmortem bacteriologic examinations have been declared unreliable by certain workers.[1] Rosenbach, in 1884, from a study of a number of cases, concluded that postmortem cultures are of little value.[2] Wurtz and Herman, in 1891, found Bacillus coli in the liver, spleen and kidneys in cadavers cultured from twenty-four to thirty-six hours after death.[3] Hauser, in 1897, and later Gradwohl,[4] examined the heart's blood in a series of fifty cases and concluded that dissemination of bacteria from certain foci, especially from the gastro-intestinal tract, takes place soon after death.[5] Similarly, Birch-Hirschfeldt, in 1898, cultured the internal organs, and heart's blood in twenty cadavers ten hours after death, and found Bacillus coli in all of them.

On the other hand, equally careful workers regard postmortem bacteriologic examinations worthy of serious consideration.[6] Fredette believes that cultural results obtained a few hours after death are fairly reliable in demonstrating the presence of organisms existing at the time of death, although he admits the possibility of postmortem invasion.[7] Canavan and Southard, in a series of 200 cases, studied postmortem, concluded that their findings pointed definitely to the intravital occurrence of the bacteria found, although in no instance was the chain of evidence complete.[8] Landsteiner and Austerlitz have shown, both by their experiments on man and animal, that the heart's blood, liver and spleen are seldom the seat of agonal invasion by bacteria of the intestinal tract. Monod and Macaigne,[9] in 1894, and later, Beco,[10] concluded that the bacteria recovered from the internal organs at necropsy were not postmortem invaders, at least during the

first thirty hours after death.[11] Flexner, from similar studies, pointed out the fact that secondary or terminal infections are relatively frequent, especially in cases of chronic disease. This is a very important point as it will be shown later that such an invasion may not be agonal but may represent the actual cause of death.[12] The studies of Löw,[13] Canon and Achard and Phulpin[14] are the most extensive in the literature and these authors all agree that postmortem cultures are important and should be routinely performed, but they believe that cultures from the heart's blood and internal organs are less reliable than those obtained from a peripheral vein. They maintain that bacteria may pass from an infectious focus in the abdomen or from the lungs to the heart's blood.

Simmonds,[15] on the other hand, who has made a careful comparative study of blood cultures made from the median vein and heart's blood in fifty cases, concludes that the cultures from the heart's blood are to be preferred, as he found in three instances, that the culture from the median vein was negative, while that from the heart's blood was positive. He believes that this is owing to the fall in the temperature of the extremities which may injure the few organisms present, while the temperature of the internal organs is maintained at a higher level, sufficient, perhaps, to permit retention of viability. Chvostek[16] and Slawyk[17] concur in this theory, while Canon[13] regarded this as good evidence of postmortem extension of bacteria from the lungs and as a point in favor of the greater reliability of the peripheral vein cultures.

It is obvious that the opinions of the various investigators on postmortem invasion of bacteria are divided. Accordingly it became necessary to determine whether or not postmortem invasion of bacteria occurred, and if so, within what limits.

Technic

After a brief experience I learned that there were many possibilities of error in obtaining uncontaminated material for culture at the necropsy table. These possibilities were eliminated by adopting the following prodecures:

The organ cultured was seared with a hot metal spatula and care exercised to prevent liquids or melted fat from the adjacent tissues from contaminating the seared surface. This was best accomplished by holding the organ in a horizontal position and by applying the hot spatula to the surface of the organ firmly so that the spatula did not move from side to side. After searing for about thirty seconds a sterile pipette with a sharp point, and of approximately 5 c.c. capacity, was thrust through the seared surface and the desired amount of material was aspirated. Solid organs were pierced at such an angle that the point of the pipette would be in the depth of the organ and away from the superadjacent seared surface in order to avoid the possibility of aspirating material which might have been made sterile by the heat applied to the surface. The material thus collected was immediately transferred in part to a long tube of glucose brain broth prepared according to the method of Rosenow.[18] Blood agar plates and other special media were inoculated as conditions demanded. A small amount of the original material was always kept for smears in order to check the bacterial content with the cultures.

There are several reasons for selecting glucose-brain broth as a culture medium.[19] It is inexpensive and easily prepared. Rosenow has pointed out that "The bottom of the tube is rendered anaërobic while the top necessarily remains aërobic and the space between represents a gradient of oxygen pressures intermediate between the two extremes". He has further observed that "The infecting organism may be sensitive to oxygen pressure". In this manner such sensitive bacteria may readily find optimum conditions of growth. I have repeatedly grown strict anaërobes without adding any paraffin to the surface of the liquid.

In order to determine the relation between positive and negative

cultures at successive hours after death, Chart I was constructed from a series of 213 consecutive cases in which cultures were made routinely from the heart's blood, spleen and other organs as conditions demanded. The bodies used for this study were not subjected to refrigeration, but were exposed to the room temperature prevailing in summer or winter.

Chart I

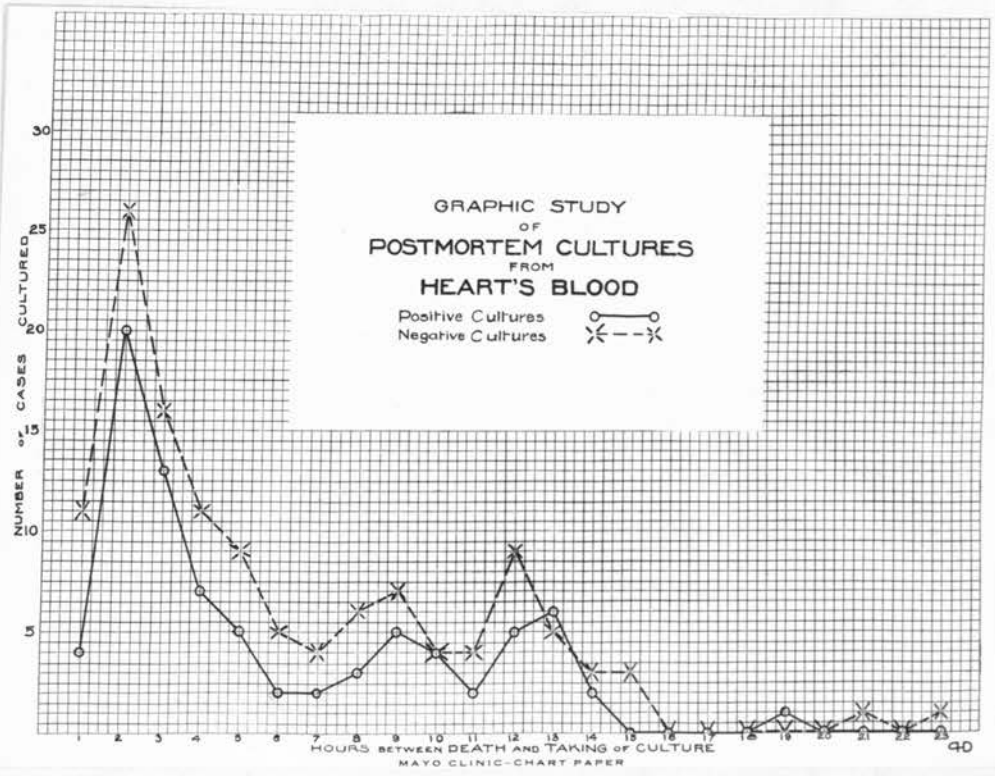

Chart I illustrates the number of positive and negative blood cultures obtained at succeeding hours postmortem. The parallelism of the curves is well preserved. Thus, it is seen that a sustained progressive increase of positive blood cultures at successive hours after death does not occur. Consequently, it is fair to conclude that postmortem invasion of bacteria capable of growing in glucose brain broth or blood agar, does not seem to be of much consequence, at least up to a period of twenty-three hours after death.

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Table I

Showing absence of postmortem invasion by bacteria in diseases considered not of bacterial origin.

Number	Diagnosis	Culture of Blood	Culture of Spleen	Hours P.M.
1	Thyrotoxicosis	Negative	Negative	2
2	Addison's disease*	"	"	12
3	Inanition	"	"	5
4	Cancer of thorax - ascites	"	"	2
5	Carcinoma of pancreas	"	"	1.5
6	Brain tumor	"	"	3.5
7	Cystadenoma of ovary	"	"	2
8	Syphilitic aortitis*	"	"	10
9	Hodgkin's disease*	"	"	13
10	Pernicious anemia	"	"	3.5
11	Atelectasis	"	"	7
12	Glioma of the pons	"	"	1
13	Thyrotoxic adenoma	"	"	4
14	Carcinoma of bladder	"	"	23
15	Myelogenous leukemia	"	"	14
16	Acute yellow atrophy	"	"	12
17	Exophthalmic goiter	"	"	3
18	Myelocele	"	"	15
19	Cerebellar tumor	"	"	12
20	Colloid adenoma of thyroid	"	"	7
21	Exophthalmic goiter	"	"	1.5
22	Thyrotoxic adenoma	Hemolytic streptococcus		8
23	Cerebral hemorrhage	Negative	Negative	3
24	Chronic myocarditis	"	"	5
25	Cerebral hemorrhage	"	"	14
26	Tuberculosis of kidney*	"	"	9
27	Coronary sclerosis	"	"	1.5
28	Chronic endocarditis	"	"	1
29	Pulmonary fat embolism	"	"	15
30	Arsenic poisoning	"	"	1.5
31	General abdominal carcinomatosis	"	"	15
32	Chronic endocarditis	"	"	3
33	Tuberculosis of the adrenals*	"	"	21
34	Glioma of pons	"	"	13
35	Multiple adenoma of thyroid	"	"	5.5
36	Exophthalmic goiter	"	"	21
37	Fracture of cervical spine	"	"	1
38	Myelogenous leukemia	"	"	12
39	Cerebral hemorrhage	"	"	9.5
40	Carcinoma of the prostate; multiple metastases	"	"	8.5

* Etiologic agent does not grow in the media employed.

The reliability of these results may be better judged by examining the type of case in which positive or negative cultures are obtained. For instance, if patients dying of diseases ordinarily considered noninfectious, such as neoplasms, cerebral hemorrhage, exophthalmic goiter, and so forth, give uniform negative cultures, it would strengthen the evidence. In this series of 213 cases, forty (Table I, page 6) can be classified as noninfectious in origin or termination, at least the etiologic factor cannot be grown in the media used, and it is significant that in these forty cases the results of cultures of various organs and the blood were negative in all except one in a period of time varying from one to twenty-three hours after death. From this it appears that invasion of the blood stream by the flora of the intact intestinal tract and pulmonary organs rarely occurs within that period of time.

This series of cases afforded the opportunity of studying whether or not the bacteria present in an infectious focus would invade the surrounding organs and blood stream. Fifty-one cases occurred in which there was present a definite focus of infection such as peritonitis, pleuritis, meningitis, and so forth. As shown (Table II, pages 9 and 10), the blood and spleen cultures remained sterile in every instance, although the longest period of time after death was only twelve hours.

In an analysis of the possible factors contributing to positive blood cultures, it is interesting to note that of twenty-six cases in which the gastrointestinal tract was injured either by operation or by disease, the blood cultures were positive (Table III, page 12) in eighteen (69 per cent). This high incidence of positive cultures may possibly be explained by the fact that in all but one case peritonitis was present. Accordingly, the opportunity for absorption of virulent organisms by the peritoneum was afforded; furthermore, operation and disease processes may decrease the individual's power of resistance and thus aid absorption.

Gwyn and Harris have compared ante mortem and postmortem cultures in

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fourteen cases for the purpose of determining the reliability of postmortem cultures. In seven cases the agreement was absolute; two cases showed the presence of an additional organism after death due to a superimposed terminal infection; and five cases showed radical differences in ante mortem and postmortem results.

Richey and Goehring[21] reported twenty-four cases in which both ante mortem and postmortem cultures were made, in twenty of which the agreement was absolute. However, one cannot draw too sharp conclusions from this type of evidence, for ante mortem cultures may be made several days before death, may precede the advent of an overwhelming infection, or may be taken in a period of bacteremia which later disappears, all of which may account for disagreement between ante mortem and postmortem cultures. In order to test this point I tabulated the results in twenty-two cases of my series in which ante mortem cultures had been made, (Table IV, pages 14 and 15) and in fifteen of the twenty-two cases the results were in agreement.

In Case 9, cultures at necropsy yielded a gas-producing anaerobic bacillus, while those made five days previously were negative. The postmortem result is further strengthened by the fact that the clinicians regarded the condition as septicemia.

In Case 4, ante mortem culture antedated the postmortem culture by sixteen days. In the meantime the patient contracted bilateral bronchopneumonia, which may account for the positive culture obtained after death.

In Case 10, the positive culture obtained after death is substantiated by the postmortem findings, which included general and localized peritonitis and serofibrinous pleuro-pericarditis, evidences of a widespread infection. The negative ante mortem culture is not invalidated, for it was taken nine days earlier and may have preceded the advent of the bacteremia.

Table II

Negative cultures in cases showing definite infectious foci.

No.	Aut. No.	Postmortem Diagnosis	Negative Cultures	Positive Cultures	Hrs.P.M.
1	394-20	Peritonitis;broncho-pneumonia	Blood	Spleen and peritoneum - staph.	4
2	416-20	Early peritonitis	Blood and spleen	Peritoneum, B. proteus	4
3	420-20	Infected wound	Blood and spleen	Wound - staph.	2
4	425-20	Pyelo-nephritis	Blood	Kidney - spleen Green prod.strep.	1
5	430-20	Br.pneumonia;pyelo-nephritis;perforated D.U.; peritonitis	Blood and spleen	Peritoneum,lung, kidney - indifferent strep.& B.coli	2
6	431-20	Suppurative meningitis	Blood	Brain-hem.strep.	3
7	436-20	Vegetative endocarditis;acute laryngitis	Blood and spleen	Glottis - green producing strep.	7
8	472-20	Uremia;lobar pneumonia	Blood	Spleen & lung pneumococcus	3
9	480-20	Thrombosis;pelvic vein pulmonary embolism	Blood	Thrombus(vein) & spleen - strep.	1
10	499-20	Multiple lung abscesses	Blood	Spleen & pleura strep. & B.coli	1
11	525-20	Multiple abscesses of kidneys	Blood	Spleen & kidney strep. & B.coli	2.5
12	542-20	Peritonitis - pneumonia	Blood	Peritoneum B.coli & hem.strep. Lung hem.strep.	6
13	547-20	Cerebrospinal meningitis	Blood and spleen	Brain - green strep	2
14	554-20	Pneumonia;gastric ulcers	Blood and spleen	Lung and teeth - green. strep.	3
15	557-20	Brain abscess	Blood and spleen	Brain pus - diplococcus	3
16	599-20	Infected wound	Blood and spleen	Wound - staph.	4
17	640-20	Primary peritonitis	Blood	Spleen & peritoneum hem.strep.	2
18	643-20	Purulent pleuritis	Blood and spleen	Pleural pus - hemolytic strep.	4
19	6-21	Bronchopneumonia	Blood and spleen	Lung - hem.strep.	2.5
20	7-21	Early peritonitis	Blood	Peritoneum - indif. strep. & B. coli	4.5
21	13-21	Peritonitis	Blood	Peritoneum & spleen indif.strep. B.coli.	2
22	33-21	Meningitis	Blood	Meninges hem.strep.	3.5
23	43-21	Pseudo-lobar pneumonia	Blood and spleen	Lung - B.influenza, diplococci, strep.	13
24	44-21	Bronchopneumonia; purulent bronchitis	Blood and spleen	Lung - hemolytic strep.	10
25	48-21	Bronchopneumonia;bilateral purulent bronchitis	Blood	Lung - hemolytic strep. & staph.	12
26	51-21	General peritonitis	Blood	Lung & peritoneum indif.strep. & B. coli	3
27	52-21	Brain abscess; meningitis	Blood and spleen	Meninges and brain indifferent strep.	9

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Table II Continued

No.	Aut. No.	Postmortem Diagnosis	Negative Cultures	Positive Cultures	Hrs.P.M.
28	73-21	Acute peritonitis	Blood	Spleen & peritoneum strep.staph. & B.coli	7
29	75-21	General peritonitis	Blood	Spleen & peritoneum hemolytic strep.	5
30	87-21	Early Bronchopneumonia	Blood and spleen	Lung;indif.strep.	12
31	88-21	Purulent meningitis	Blood and spleen	Meninges - strep. and B. coli	8
32	100-21	Bilateral bronchopneumonia	Blood	Spleen B. coli lung - strep.	3
33	101-21	Peritonitis	Blood and spleen	Peritoneum - B.coli & strep.	1
34	105-21	Bronchopneumonia	Blood and spleen	Influenza(B) and hemolytic strep.lung	11
35	107-21	Encephalitis	Blood and spleen	Brain - green strep.	1
36	111-21	Purulent meningitis	Blood and spleen	Brain - staph.&strep.	8
37	113-21	Pelvic peritonitis	Blood	Blood & spleen-B.coli	1
38	114-21	Pericardial & pleural effusion	Blood and spleen	Lung - strep.& staph.	10
39	121-21	Brain abscess	Blood and spleen	Brain & abscess-staph	11
40	127-21	Peritonitis	Blood and spleen	Peritoneum & bile B.coli	2
41	131-21	General peritonitis	Blood and spleen	Peritoneum-hem.strep.	3
42	142-21	Bronchopneumonia	Blood and spleen	Lung - pneumococcus	2
43	148-21	Bronchopneumonia	Blood and spleen	Lung - streptococcus	4
44	149-21	Choledochostomy - hemorrhage	Blood and spleen	Lung - staph. & strep.	5.5
45	158-21	Perforated Gastric ulcer	Blood and spleen	Peritoneum Colon B. and strep.	12
46	164-21	Peritonitis; gangrenous appendix	Blood and spleen	Peritoneum Colon B. and strep.	1.5
47	169-21	Pneumonia	Blood and spleen	Lung - pneumococcus	3.5
48	180-21	Bilateral bronchopneumonia	Blood and spleen	Lung - pneumococcus	11
49	188-21	Peritonitis(perforated duodenum)	Blood and spleen	Peritoneum - Colon B. & staph.	5
50	203-21	Brain abscess	Blood and spleen	Abscess - pneumococcus	1.5
51	286-21	Puerperal sepsis	Blood	Spleen and uterus - hemolytic strep.	9

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In Case 1, five days elapsed between the cultures. Postmortem findings undoubtedly supported the positive bacteriologic findings. Necropsy revealed bilateral suppurative otitis media and mastoiditis, thrombosis of the right lateral and sigmoid sinuses, multiple pulmonary abscesses, bilateral suppurative mastitis, and empyema in the left side.

In Case 7, an interval of fourteen days separated the cultures made before and after death. The presence, at necropsy, of bilateral empyema, bilateral perirenal abscesses, bilateral pyelonephritis, and an abscess in the psoas muscles is indicative of a widespread infection and corroborates the cultural results obtained after death.

Case 14 presented a typical picture of generalized sepsis before death, but two ante mortem cultures made thirty-eight and thirteen days before death were negative. Necropsy revealed multiple pyemic abscesses of the extremities, vegetative endocarditis, thrombosis of both femoral veins, a large psoas abscess, and bilateral multiple focal abscesses of the kidneys, all of which attest the validity of the postmortem cultures.

The last of five negative cultures obtained ante mortem in Case 3 was made eighteen days before death. In support of the positive cultures after death are the necropsy findings of acute general peritonitis following perforation of the colon; acute bilateral pyelitis; acute bilateral bronchopneumonia with pleuritis, and disseminated petechial subcutaneous purpuric spots.

In my experience it has not been necessary to attribute discrepancies between ante mortem and postmortem cultures to agonal or postmortem invasion. I do not deny the possibility of terminal bacterial infection, but when it occurs it cannot be discarded for it may be the most important contributory factor to the cause of death. This is well illustrated in a patient who came to the Clinic for treatment of abdominal lymphosarcoma (Case 349328). While enroute he became acutely ill and soon after reaching the hospital, he died. Necropsy revealed, besides general abdominal lymphosarcomatosis, general fibrinous peritonitis and

Table III

Results of cultures in cases in which the gastro-intestinal tract was injured either by disease or operation.

Number	Aut.Number	Hrs. P.M.	Postmortem Diagnosis	Blood	Spleen	Peritoneum
1	402-20	1.5	Peritonitis following enterostomy	Strep.B.Coli	Strep.B.Coli	Strep.B.Coli
2	427-20	4	Gastrectomy, peritonitis	Strep.B.Coli	Strep.B.Coli	Strep.B.Coli
3	437-20	2	Perforated duodenal ulcer, peritonitis, pyelonephritis	Strep.B.Coli	Strep.B.Coli	Strep.B.Coli
4	529-20	4	Enterostomy,peritonitis,pneumonia	Strep.B.Coli	Strep.B.Coli	Strep.B.Coli
5	551-20	2	Gastrectomy,peritonitis,pneumonia	Strep.B.Coli	Strep.B.Coli	Strep.B.Coli
6	692-21	1	Colectomy,pelvic abscess	Strep.B.Coli	Strep.B.Coli	
7	57-21	8	Duodenal fistula,peritonitis	Strep.B.Coli	Strep.B.Coli	Strep.B.Coli
8	542-20	6	Appendectomy,peritonitis,pneumonia	No growth	No growth	Strep.B.Coli
9	13-21	2	Colectomy,peritonitis	No growth	Strep.B.Coli	Strep.B.Coli
10	65-21	6	Colostomy,peritonitis	B.Coli	B.Coli	Hem.strep.;Coli
11	97-21	14	Gastrectomy,peritonitis,pneumonia	B.Coli	Strep.B.Coli	
12	106-21	13	Kraske operation;peritonitis	Hem.strep.	No growth	Strep.B.Coli
13	110-21	1	Appendectomy;peritonitis	Strep.	Strep.	Strep.
14	158-21	12	Perforated gastric ulcer,peritonitis;pneumonia	No growth	No growth	Strep.B.Coli
15	434-20	12	Enterostomy;peritonitis	Strep.Hem.	Strep.Hem.	Strep.Hem.
16	657-20	6	Ruptured appendix;peritonitis	Hem.strep.	No growth	Hem.strep;colon
17	42-21	1.5	Enterostomy;peritonitis	Hem.strep.	Hem.strep.	Hem.strep.
18	56-21	10	Excision of gastric ulcer; peritonitis	Hem.strep.	Hem.strep.	Hem.strep.
19	3-21	2.5	Excision of gastric ulcer; peritonitis	No growth	No growth	
20	430-20	2	Perforated duodenal ulcer; peritonitis;pyelonephritis	No growth	No growth	Strep.B.Coli
21	416-20	4	Ulcerative colitis;peritonitis	No growth	No growth	B.Proteus
22	650-20	3.5	Colectomy;peritonitis	No growth	No growth	
23	2-21	2	Gastric and duodenal ulcers; cysto-pyelonephritis	No growth	No growth	
24	92-21	2	Colectomy;peritonitis;pneumonia	B.Coli	No growth	
25	135-21	2.5	Perforated gastric ulcer;peritonitis;pneumonia	Pneumococcus		Pneumococcus
26	112-21	2	Amoebic dysentery	B.Coli	B.Coli	No growth

pleuritis; from the peritoneum and pleura as well as from the blood stream a pure culture of Streptococcus hemolyticus was isolated. The infection, although terminal, was certainly the immediate cause of death.

The heart's blood and the spleen were cultured in a series of 189 cases and were found simultaneously positive in sixty-one (36 per cent). The blood alone was positive in eight (4 per cent) and the spleen alone was positive in fourteen (7 per cent). This suggests that the spleen may serve as well as, if not better than, the blood for determining bacteremia, as it is more easily manipulated and cultured.

Bacteriologic study at postmortem may illuminate, modify, or completely change the clinical and autopsy diagnosis. For example, in two apparently unrelated deaths not readily explainable on clinical or pathologic grounds, careful routine bacteriologic studies revealed that the deaths were due to Bacillus tetanus. The importance of these findings is obvious, and in all probability the organism would not have been recovered if the routine media employed had not been suitable for the growth of anaerobic bacteria.

In another group of cases the pathologic changes which might be considered a cause of death may be exceedingly meager. In two cases in the series, the sole gross pathologic findings pertaining to the cause of death consisted of a very questionable peritonitis. Culture of the peritoneal fluid and heart's blood yielded Streptococcus hemolyticus in pure culture. In the light of such findings the pathologist may explain the cause of death more satisfactorily, especially if death has occurred before frank gross anatomic manifestations appear.

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Table IV

Comparison of Antemortem and Postmortem Cultures

Case	Necropsy Number	Postmortem Diagnosis	Date of Antemortem Culture	Result of Culture	Date of Postmortem Culture	Length of time After Death, Hours	Result of Culture
1	409-20	Sinus thrombosis, bilateral otitis media	7-19-20	Negative	7-22-20	3	Streptococcus hemolyticus in the blood, spleen, and lung abscess
2	425-20	Pyelonephritis, endocarditis	7-29-20	Negative	7-30-20	1	Negative
3	427-20	Ulcerative colitis, peritonitis	7-13-20	Negative	8- 1-20	4	Bacillus Coli in the blood, spleen, lung, and kidneys
4	455-20	Pneumonia, ulcerative stomatitis	7-31-20	Negative	8-16-20	4	Streptococcus hemolyticus in the blood, spleen and lungs
5	460-20	Thrombophlebitis	8-11-20	Streptococcus in blood	8-17-20	4	Streptococcus hemolyticus in the blood and spleen
6	485-20	Malignant endocarditis	8-28-20	Streptococcus viridans in blood	9- 1-20	3	Streptococcus viridans in the blood, spleen, and vegetations of the endocardium and pleural fluid
7	559-20	Bilateral empyema, pyelonephritis	9-23-20	Negative	10- 7-20	2	Bacillus coli and streptococci in blood and kidneys
8	656-20	Acute yellow atrophy of liver	11-22-20	Negative	11-24-20	12	Negative
9	683-20	Septic pneumonia, acute nephritis	12- 4-20	Negative	12- 9-20	9	Gas-producing anaerobic bacillus in the blood and kidneys
10	691-20	Septicemia	12- 4-20	Negative	12-13-20	3	Streptococcus in the blood, spleen, peritoneum and pleura
11	710-20	Radical mastoidectomy	12-18-20	Negative	12-27-20	12	Negative

Table IV Continued

Case	Necropsy Number	Postmortem Diagnosis	Date of Antemortem Culture	Result of Culture	Date of Postmortem Culture	Length of Time After Death, Hours	Result of Culture
12	39-21	Empyema, pyemia	1-24-21	Streptococcus in blood	1-28-21	1	Indifferent streptococcus in the blood, spleen, and lungs
13	86-21	Pyelonephritis	2-24-21	Negative	2-28-21	13	Bacillus coli in blood and spleen
14	90-21	Vegetative endocarditis, multiple abscesses	2-15-21	Negative	2-28-21	13	Streptococcus hemolyticus in the blood, spleen and abscess
15	105-21	Hyperthyroidism	3-14-21	Negative	3-16-21	11	Negative
16	111-21	Meningitis	3-17-21	Negative	3-22-21	8	Negative
17	114-21	Nephritis, pulmonary edema	3-23-21	Negative	3-23-21	10	Negative
18	157-21	Hyperthyroidism	3-26-21	Negative	4-20-21	5.5	Negative
19	187-21	Meningitis	5- 7-21	Streptococcus hemolyticus in the spinal fluid	5- 7-21	19	Streptococcus hemolyticus in the blood, spleen, brain, kidneys, and lungs
20	216-21	Septicemia, panophthalmitis	5-22-21	Streptococcus hemolyticus in the blood	5-27-21	3	Streptococcus hemolyticus in the blood, spleen, and lungs
21	286-21	Septicemia (abortion)	6-30-21	Streptococcus hemolyticus in the blood	7- 4-21	9	Blood negative; Streptococcus hemolyticus in the uterus
22	342-21	Meningitis, otitis media	8- 4-21	Pneumococcus in spinal fluid	8- 4-21	2	Pneumococcus Type II in the brain, spinal fluid, ears, and sphenoid

Summary

1. Bacteriologic cultures were made postmortem in 213 cases.
2. The blood was cultured in 206 cases and it was positive in eighty (38.8 per cent).
3. The spleen and heart's blood were cultured in 189 cases and were found positive in sixty-one (31 per cent).
4. The spleen serves as well as, if not better than, the heart's blood for determining a terminal bacteremia.
5. A sustained, progressive increase in the number of positive cultures obtained at successive hours after death has not been observed in the period covered by my cases.
6. Uniformly negative results occurred in the cases of this series, which are ordinarily regarded as noninfectious in type. This strengthens the belief in the reliability of cultures made postmortem.
7. A failure to obtain positive blood cultures in fifty-one cases, in which an abundant focus of infection was demonstrated at necropsy, is a strong evidence that invasion of the blood stream after death rarely occurs within a twenty-three hour period.
8. If discrepancies occurred in the results obtained by ante mortem and postmortem cultures, they were generally explained by the evidence of a superimposed process revealed at necropsy, or by the length of time intervening between the two cultures.
9. Postmortem bacteriology may strengthen, illuminate, or sharply modify the cause of death, as revealed by clinical and necropsy diagnosis.
10. It is possible that terminal invasion may occur, and if it does occur it must not be dismissed, as it may be the most important contributory factor to the cause of death.
11. With strict adherence to a reliable technic, postmortem bacteriologic findings are extremely valuable, and we are not making the most of our opportunity at

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necropsy table unless routine cultures are made.

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Specificity of Bacteria and the Relation of Foci of Infection to the Etiology of Certain Organic Lesions.

Since the evidence presented in Part I was sufficient to conclude that the bacteria recovered after death possessed a definite intravital significance, it became of interest then to determine whether organisms recovered from foci of infection and specific lesions possessed a selective localizing power similar to that exhibited by certain bacteria recovered from similar locations during life.

The recognition of the part played by bacterial infections in the causation of chronic diseases has gained in importance with the multiplication of observations upon the occurrence of such infections in human beings, as ulcers of the gastro-intestinal tract and analogous lesions of other organs associated with chronic foci of infection. The data for a proper appreciation of the relation existing between foci of infection and chronic infectious diseases can be more accurately obtained by a systematic bacteriologic study at autopsy than by clinical investigation during life. This is obvious when we consider that at necropsy certain regions are accessible in a way seldom offered during life. This is particularly true of the accessory nasal sinuses, internal ear and the central nervous system. These foci are available for direct examination and for cultural studies, and it is possible to rule out at once other regions as foci of infection, and still further, lesions whose etiology is sought can be accurately studied and the pathologic changes other than those in question may be established or eliminated. In Part I it was proved that routine systematic bacteriologic examination at the necropsy not infrequently reveals the presence of pathogenic microörganisms that were not suspected during life. It is often these incomplete cases that offer the key to the prevention of an epidemic of certain infectious diseases. Indeed, such examinations have been regarded by Robertson[22] of the Mayo Clinic as belonging to the technic of postmortem section, and just as important as the study of the pathologic anatomy of the lesion.

Many men have contributed to our knowledge of focal infection and the

doctrine is now so firmly rooted as to become a tenet of the medical profession. Conspicuous among these contributions is the work of Rosenow[23] who has gone a step further by enunciating the principle that certain bacteria have a selective localizing power. While studying the transmutations within the streptococcus-pneumococcus groups, he noted that as avirulent strains were passed through animals they acquired increasing virulence, and as this occurred the strains exhibited a selective affinity for certain tissues. Thus it occurred to him that a similar mechanism might take place in diseases focal in origin. How well founded this hypothesis has been, is evident when one considers the results obtained by Rosenow[23] and others working along similar lines.

Focal infection as it occurs in man has been recently reproduced in experimental animals by Rosenow and Meisser.[24] These investigators have established a focus of infection in dogs by devitalizing several teeth and filling the root canal with bacteria recovered from patients suffering from nephritis and nephrolithiasis respectively; after a period of from two to four months, similar lesions were found in dogs.

As to what determines the specificity of organisms is not clear. However, we do know that certain organisms, when introduced into a suitable host produce specific reactions in certain organs such as the tuberculosis and typhoid bacillus. Also we do know that certain organisms have variable invasive powers for tissues. As Evans[25] points out, the Treponema pallidum may invade the unimpaired mucous membrane of the lip and the gonnococcus invades the conjunctiva while both of these two structures are quite resistant to invasion by other organisms.

The technic used in culturing solid organs at postmortem has already been described in detail in Part I. I shall here describe the procedure used in obtaining the material from foci of infection and from lesions experimentally produced.

When infected teeth were removed the gums and teeth were washed with

80 per cent alcohol, allowed to dry, and painted with tincture of iodin. The gums were then reflected and external alveolectomy was done with a mallet and chisel. The tooth was then lifted from its socket, and if any granuloma were present, they were curetted out and immediately placed in glucose brain broth media. The apex of each tooth removed was snipped off with pincers, or the entire tooth was wrapped in sterile gauze crushed by a vise, and the root canal cultured. Sterile instruments were used throughout. If free pus was encountered in the socket of the tooth, it was taken up with a capillary pipette; some of this was cultured in glucose brain broth and on blood agar plates. The balance was suspended in normal sterile saline solution for inoculation purposes. Direct smears were routinely made of the cultured material in order to rule out contamination.

When dealing with organs having relatively thin walls such as the gastro-intestinal tract, the desired area, such as a gastric ulcer, was excised with sterile scissors from the mucosa to the serosa and placed in sterile salt solution in which it was vigorously washed in several changes. If any area of the tissue was in any way contaminated it was placed in a 1:1000 solution of mercuric chloride for six hours and then the excess of mercuric chloride was washed off in a series of washings in salt solution or the tissue was placed upon sterile wire gauze and sterile salt solution was allowed to run over the tissue for an hour, changing the surfaces exposed to the running solution at intervals. Then it was placed in a sterile mortar and ground up with sterile sand. An emulsion was made of the macerated substance with normal sterile saline and cultures were then made.

Experimental animals were inoculated either with glucose brain broth cultures grown from twelve to eighteen hours, or with a suspension of the infected material in sterile saline solution. Subcultures were rarely used for inoculation purposes.

The reason for choosing young cultures that were not subjected to prolonged growth on artificial media is obvious when one considers the fundamental principles that govern the pathogenicity of bacteria as laid down by Pasteur.

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He demonstrated that old cultures lose their pathogenicity and also that virulent organisms are attenuated when subjected to growth on artificial media and at a minimal temperature. Rosenow[19] has gone a step further and shown that certain organisms, especially those in the pneumo-streptococcus group, are very sensitive to differences in oxygen tension and to changes in the hydrogen ion concentration. These difficulties he has overcome by the use of tall tubes of glucose brain broth containing a buffer salt. I have strictly followed these general fundamental principles in my technic under the supposition that changes in the pathogenicity of the organisms would also affect their specificity. Tissues were removed from the heart, liver, kidney, and spleen, and all evident lesions found in the animals. These were fixed in 10 per cent formalin, imbedded in paraffin, and the sections cut were stained by hematoxylin eosin and by the Gram-Weigert method. The material used for this study comprises cases of gastric ulcers, biliary cirrhosis, focal nephritis, primary peritonitis, and ulcerative endocarditis.

Gastric ulcers

Three cases of gastric ulcer were studied, one of which was complicated by renal lesions. The source of material in these three cases was from the teeth which were condemned as foci of infection during the life of the patient by the attending physician and the dentist.

Case 1 (Aut. 2-21). Mr. V. S., aged sixty-eight years, came to the Clinic complaining of involuntary and frequent urination. Initial urinary symptoms occurred five years before, and symptoms of duodenal ulcer had been present intermittently for twenty years. The anatomic diagnosis at necropsy included multiple gastric ulcers, duodenal ulcer, marked dental caries and sepsis, suppurative cysto-ureteropyelonephritis, with focal abscesses in both kidneys.

Of the six teeth removed aseptically, around two there was found periapical infection, and in two others infected granuloma. From the apices of the teeth staphylococci and short chain streptococci were cultured. These organisms

were also found in the smears and cultures from the granulomatous material. Culture from the kidney yielded chiefly colon bacilli and staphylococci. Rabbits were injected with glucose brain broth culture of an infected tooth apex; others with a normal saline suspension of the periapical pus; and still others with a glucose brain broth culture of the patient's kidneys. The brief protocols appended below are typical of the results obtained in these cases. The lesions and their distribution in the other animals of the series are summarized in Table V, pages 38 and 39.

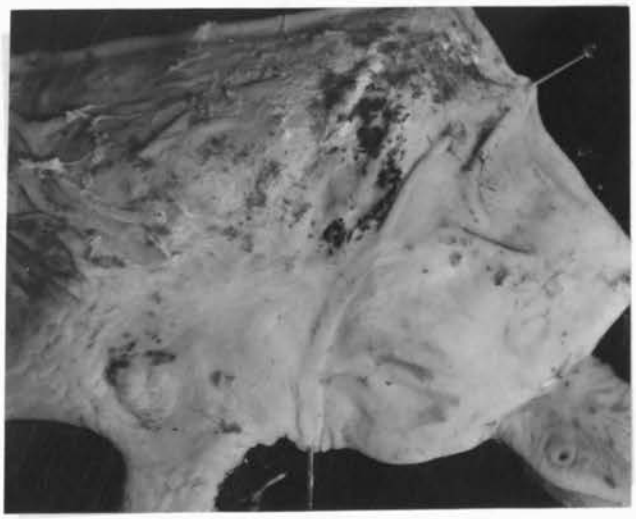
Rabbits 52 and 53, weighing 1,000 gm. each, were injected intravenously with 5 c.c. of glucose brain broth culture of an infected tooth apex containing almost a pure culture of green producing streptococci and a few colonies of staphylococci.

Rabbit 52 was found dead at the end of thirty-six hours. Rabbit 53 was killed by chloroform forty-eight hours after injection. A careful complete autopsy revealed areas of submucous hemorrhages and a clearly defined area of ulceration on the posterior surface of the greater curvature of the stomach extending through the muscular wall. (Figure 11). Viewed from the serous surface this lesion has a grayish pink color and is sharply defined by a circle of punctate areas of hemorrhage (Figure 2). Cultures from the blood, spleen and bile were sterile while those from the kidney yielded only green producing streptococci.

Rabbits 54 and 55 were injected intravenously with the pus suspended in normal sterile saline solution. This pus was obtained from the abscess cavities found after the removal of two teeth. Direct smears stained by Gram's method revealed pus cells, staphylococci and streptococci. Rabbits 58 and 59 were injected intravenously with 5 c.c. each, of a twelve hour old glucose brain broth culture made from the pus.

Rabbits 54 and 55 died thirty hours later while Rabbits 58 and 59 were killed by chloroform forty-eight hours after injection. Necropsy revealed gastric lesions in all of the four animals while in Rabbits 55,58, and 59 in addition were

Figure 1

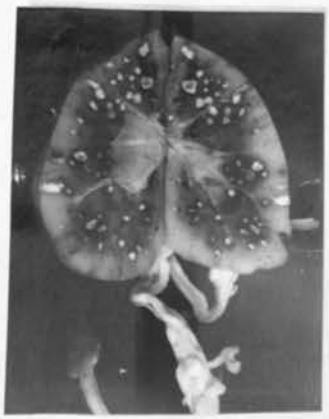


R53. Showing hemorrhagic necrosis in the mucosa. Natural size.

Figure 2

R75. Natural size.

Figure 3



R59. Focal renal abscesses.

found multiple focal abscesses in the cortex and medulla of both kidneys (Figure 3). Cultures from the blood and spleen were sterile, while those from the kidney and stomach ulcer yielded chiefly staphylococcus, with a few colonies of green producing streptococci. The two organisms were plated on blood agar and a pure culture of each was injected in five rabbits. It is interesting to note that the animals injected with the subculture of staphylococcus were only affected with renal abscesses and of the three animals injected with subcultures of streptococci there were found focal hemorrhagic areas in the gastric mucosa. On the other hand only in Rabbit 60 which was injected with a pure culture of streptococci obtained from the gastric ulcer of Rabbit 58, and not subjected to subculture, there was found a definite gastric ulcer.

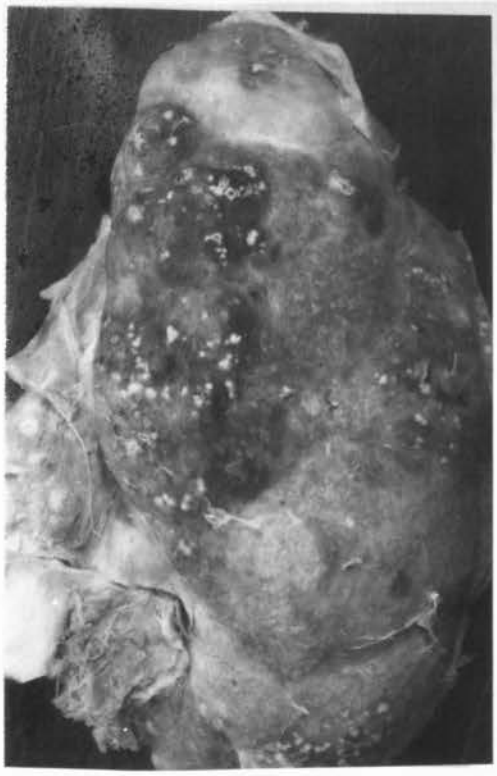
As previously stated the culture from the patient's kidney yielded chiefly colon bacilli and staphylococci. The colon bacilli were separated and the culture was injected intravenously into Rabbits 56 and 57. Both animals were found dead twenty-four hours later. Necropsy revealed no gross or microscopic lesions, and cultures from the blood, spleen and kidney yielded colon bacilli.

Pathologic anatomy of gastric and renal lesions of the patient as compared with the lesions produced in the experimental animals:

In the kidneys of the patient there were found many focal and conglomerate abscesses. Many of these abscesses were relatively recent; others were in the process of repair and still others apparently entirely organized as one might conclude from the numerous scarred depressions (Figures 4 and 5). The rabbit's kidneys in which focal abscesses were found, correspond to those of the patient in distribution and acute reaction (Figures 6 and 7).

The gastric lesions of the patient were multiple and histologically the base of the ulcers was made up of scar tissue infiltrated with polymorphonuclears and lymphocytes. This infiltration extended deep into the muscularis (Figure 8). Sections stained by Gram's method revealed gram-positive cocci in the lesions (Figure 9). The ulcers produced in the rabbits are identical in distribution but cannot be compared to those found in the patient because they are recent and of

Figure 4



Aut. 2-21. Focal renal abscesses.

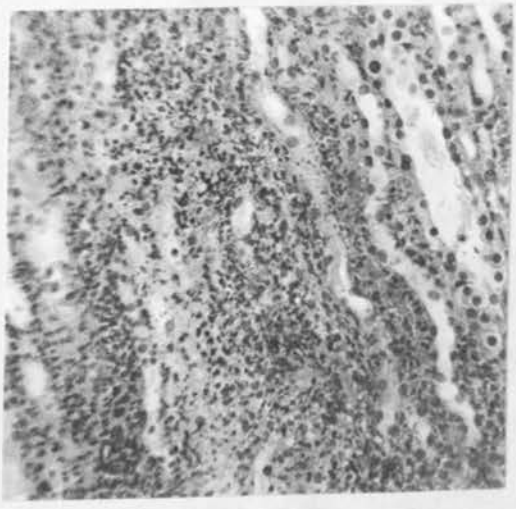
Figure 5

Aut. 2-21. Corical surface of Figure 4.

Figure 6

R59. Focal renal abscesses. X40.

Figure 7



R59. Focal renal abscess. X200.

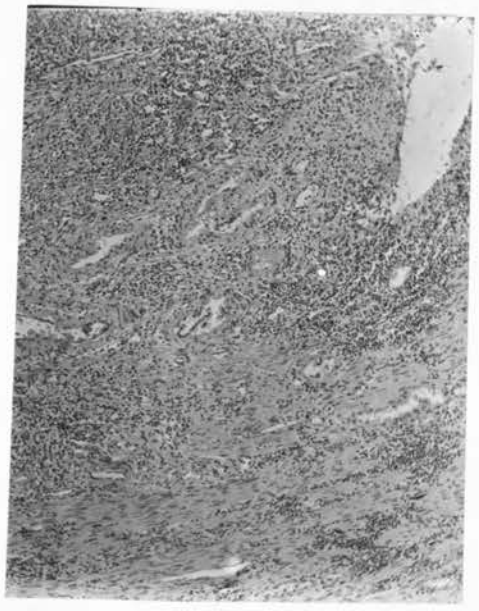
relatively short duration. However, it is interesting to note that two types of lesions were produced. In Rabbits 52 and 53 which were injected with cultures of streptococci, the lesions produced were apparently slight, consisting of areas of hemorrhages, desquamation of the mucosa (Figure 1), and infiltration of the surrounding tissue with polymorphonuclear leukocytes and streptococci (Figure 10). On the other hand, in Rabbits 54, 55, 58 and 59 which were injected with the suspended pus, containing both streptococci and staphylococci, the gastric lesions were different. Grossly the base and surrounding tissues of the ulcer were so markedly thickened as to attract attention to the presence of the lesion before even opening the stomach, while microscopically the lesion was found to be circumscribed or focal in character (Figures 11, 12, 13 and 14).

Case 2. (Aut. 43-21). Mr. F.S., aged sixty-nine years, came to the Clinic with symptoms of gastric ulcer. Three weeks before, he had had an attack of hematemesis. A diagnosis of perforating gastric ulcer was made, and operation consisting of excision of the ulcer by cautery and posterior gastroenterostomy was performed after appropriate preliminary medical treatment. At necropsy the chief pathologic lesions were bilateral bronchopneumonia, purulent bronchitis, and chronic diffuse nephritis. Several teeth pronounced diseased by ante mortem dental examination were extracted at necropsy and granulomata were removed under strict aseptic precautions.

Rabbits 72 and 73 were injected intravenously with 5 c.c. glucose brain broth culture made from the granulomata. Rabbit 73 was found dead the following morning and was discarded on account of postmortem decomposition. Rabbit 72 was killed by chloroform forty-eight hours after inoculation and necropsy revealed a grayish area 8 by 4 mm. on the greater curvature of the stomach, surrounded by petechial hemorrhages and edema. On opening the stomach the corresponding mucosa of this area was intact. The remaining organs were without evident lesion.

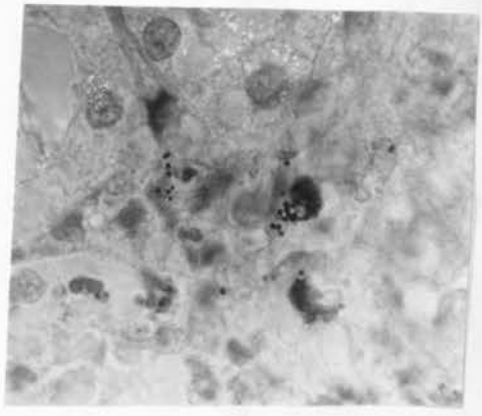
The gastric lesion above described was excised and ground up with sterile sand. This material yielded a pure culture of indifferent streptococci.

Figure 8



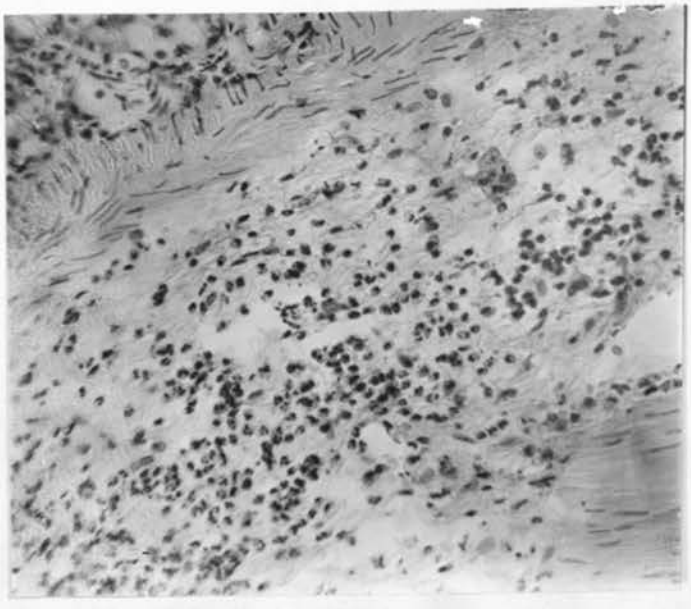
Aut. 2-21. Base of ulcer in patient's stomach showing marked leukocytic infiltration of submucosa and muscularis. X50.

Figure 9



Aut. 2-21. Gram's stain. Showing diplococci in base of ulcer. X1000.

Figure 10



R53. Section from gastric lesion showing polymorphonuclear infiltration of submucosa and muscularis. X200.

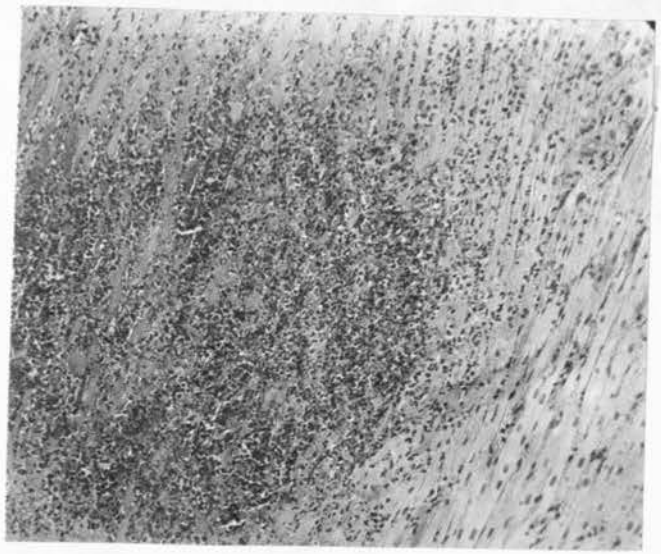
Rabbits 74 and 75 were injected intravenously with the culture of the gastric ulcer of Rabbit 72. Both animals were killed by chloroform three days later and necropsy revealed lesions similar to those described in Rabbit 72 except that in Rabbit 75 the lesions were multiple (Figure 2). Microscopically these lesions were characterized by diffuse polymorphonuclear infiltration of the muscular and serous coats while the mucosa was intact (Figures 13 and 14).

Case 3. (Aut. 56-21). Mr. J. P. D., aged forty-eight years, came to the Clinic with a history of symptoms characteristic of gastric ulcer. A large perforating gastric ulcer was excised. The patient died of bronchopneumonia. Culture of the blood, spleen and peritoneum at autopsy yielded a pure growth of hemolytic streptococci.

The roentgen-ray and clinical dental reports had advised the extraction of the remaining upper teeth. Accordingly an infected tooth was extracted at necropsy under aseptic conditions and cultures from the apex as well as the pyorrhea pockets yielded pure cultures of green producing streptococci.

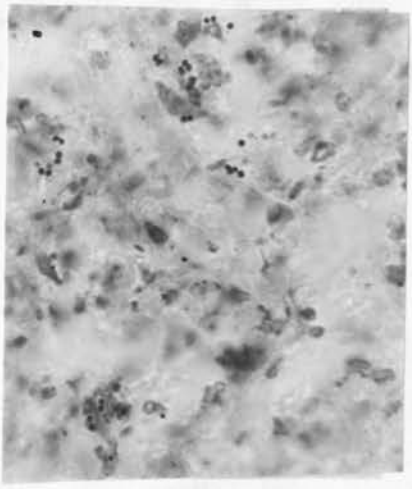
Rabbits 2255 and 2256, weighing 2000 gm. each, were injected intravenously with 5 c.c. of glucose brain broth culture of pus from the socket of one of the teeth. Three days later the animals were chloroformed and autopsy revealed punctate hemorrhages with an area of ulceration in the cardiac end of the stomach of both animals, while the remaining organs presented no gross lesions.

Figure 11



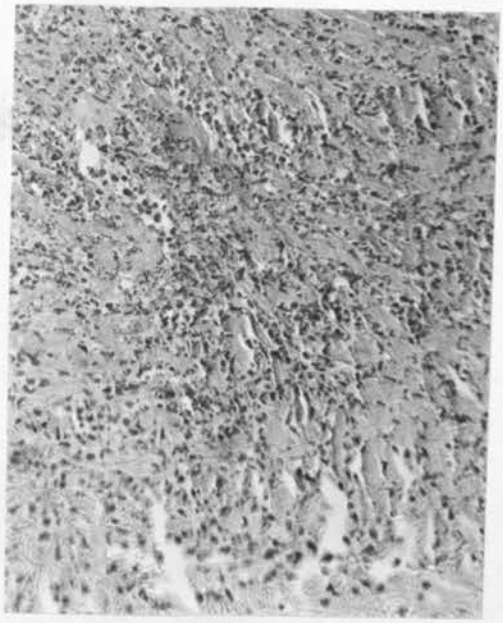
R58. Focal necrosis in muscular wall of stomach. X100.

Figure 12



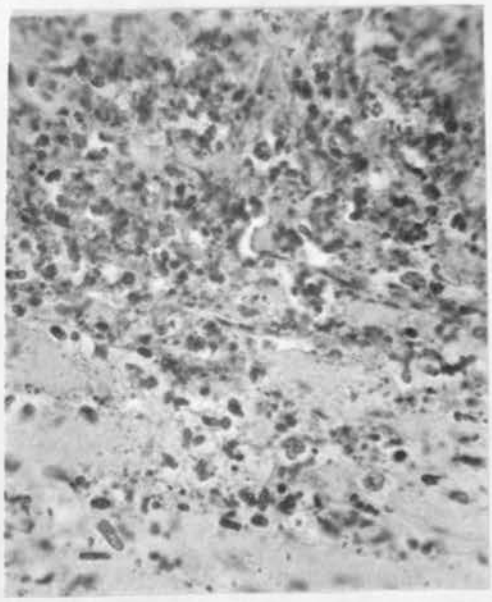
R5C. Gram's stain. Diplostreptococci in base of gastric ulcer. X1000.

Figure 13



R59. Base of gastric ulcer, showing polymorphonuclear infiltration. X200

Figure 14



R59. Higher power of Figure 13. X500.

Discussion

In summary I wish to direct attention to several interesting features in these experiments. In the first animal passage when the streptococcus was injected alone, only lesions in the stomach were produced. On second animal passage, when the organism was not subjected to subculture it retained its specificity, while when it was subcultured the lesions were not as frequent and were less marked. When the streptococcus was injected with the staphylococcus, lesions of more marked and extensive character were produced while when the staphylococcus was injected alone it localized almost exclusively in the kidneys, and sometimes in the myocardium.

These cases illustrate the value of knowing all the lesions present which could be of focal origin in a given case. Had only the gastric lesions been known in Case I it would have been difficult to interpret the renal abscesses obtained in the animals. Thus it is possible that in the ante mortem study of lesions focal in origin, which at times appear irrelevant, they may actually have their counterpart in an unsuspected lesion. Further, I wish to call attention to the fact that so far in the study of focal infection the streptococcus group has been given great prominence as an etiologic factor while the staphylococcus has usually been regarded of relatively little consequence.

That the staphylococcus may enter the circulation from foci of infection in the naso-pharynx was suggested by Billings[27] and experimentally demonstrated by Rosenow and Ashby,[28] while Israel,[29] Brewer,[30] Jordan,[31] McKenzie[32] and Phemister[33] have reported various lesions such as osteomyelitis, renal abscesses and myositis, as being secondary to focal lesions in the skin. In reviewing my records of 1000 necropsies I have encountered two cases of diffuse myelitis and one of septicemia secondary to staphylococcus infection of the skin.[34] Recently Meisser and Rosenow have shown experimentally in dogs that when teeth are infected with pathogenic staphylococci from the tonsils of a case of advanced nephritis, extensive lesions of the kidneys were produced. In view of the fact that staphylococci, when in-

jected intravenously, produce lesions of the kidneys and other organs, and that when chronic foci of infection are established with these organisms, they actually get into the circulation, it is obvious that in the future we should give more serious consideration to focal staphylococcus infections.

Biliary cirrhosis

Cirrhosis of the liver has, for many years, attracted the attention of the experimental pathologist, but up to the present time, the etiology of this not uncommon disease is as yet obscure. I shall here limit my brief discussion to the relation of bacteria to biliary cirrhosis of the liver.

Adami[35] was the first to demonstrate that certain bacteria may be the etiologic factor of cirrhosis. He found associated in the cirrhotic liver of cattle affected with enzoötic disease known as Picton, a bacillus which he isolated in pure culture and demonstrated the same organism in the liver. However, when experimental animals were inoculated with it, they would die before any changes occurred in the liver. Weaver,[36] in 1889, isolated a gram negative bacillus from an incidental case of infectious cirrhosis of the liver in a guinea pig. This organism, when injected in large doses, would kill the animals, but when injected in small doses, would produce a condition closely resembling cirrhosis of the liver. Hektoen,[37] in 1901, isolated a bacillus belonging to the pseudodiphtheritic group from the lesion of a blastomycetic dermatitis. This bacillus injected subcutaneously produced cirrhotic changes in the liver. Unfortunately, as often is the case, both of these organisms soon lost their specificity and no complete studies could be made. Nevertheless, in both cases there is sufficient evidence which tends to demonstrate that these organisms had a tendency to localize in the liver and produce a rather characteristic lesion. It also brings out the fact that the specificity of some organisms is very transient, perhaps owing to the unsuitable environment to which they are subjected during their growth on artificial media.

Case 4. (Aut. 473-21). Mrs. J. R., aged fifty years, came to the Clinic

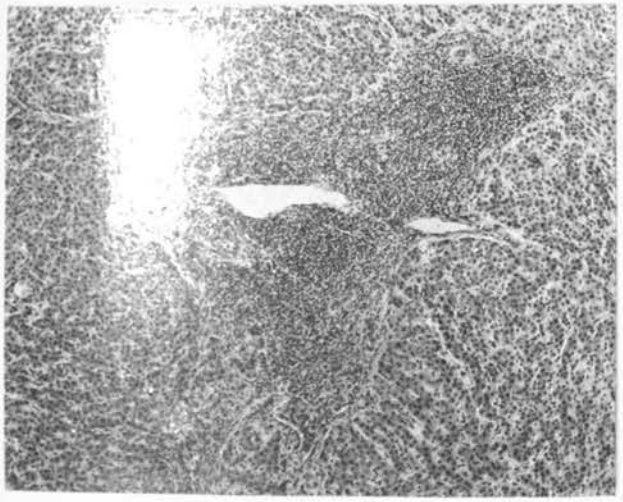
having had intermittent attacks of chills and fever with general abdominal pain for two years. For the past six months previous to her admission to the Clinic, these attacks were accompanied by slight jaundice and clay colored stools while her temperature varied from 94 to 104 degrees Fahrenheit. Examination revealed moderate icterus and a soft but slightly tender abdomen. The liver was four fingers' breadth below the costal margin in the mid-clavicular line. At operation the gallbladder was found shrunken around a mass of calculi which were also present in the cystic and common ducts. In spite of removing the calculi from the common and major hepatic ducts jaundice persisted and the patient gradually failed.

Necropsy performed three hours after death revealed no other abnormal findings of interest except a large, firm, deeply bile-stained liver weighing 2200 gm. The common bile duct was dilated and the hepatic ducts, from the porta hepatis to the periphery of the liver as far as they could be followed, were found to contain soft greenish concretions. Cultures from the heart's blood and spleen were sterile. Cultures from the liver and biliary concretions yielded a pure culture of green-producing diplo-streptococcus.

Dog 1 was injected intravenously with 5 c.c. of a fourteen hour old culture obtained from the concretions found in the hepatic ducts. Rabbits A7, A8, A9 and A10 were injected intravenously with 3 c.c. each of similar culture as Dog 1. Blood agar plates of the injected culture yielded a pure growth of very fine green-producing colonies. Three days later animals were killed by means of ether, and autopsy was performed.

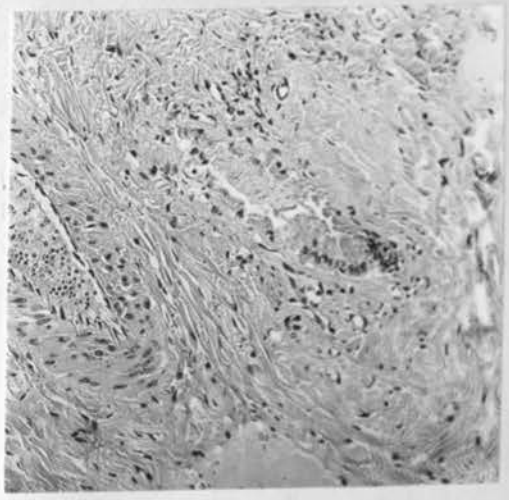
Dog 1. Pleural cavities, lungs and abdominal organs were without gross abnormalities except the liver which was markedly congested, and scattered throughout the surface were present discrete areas of hemorrhage. On section the central veins stood out prominently. In the gallbladder was found about 5 c.c. of greenish bile containing minute soft, greenish particles, the largest two being 4 by 8 by 3 mm., and 3 by 5 by 2 mm. respectively (Figure 19). The gallbladder wall was markedly edematous. The common bile duct contained many very minute sand like

Figure 15



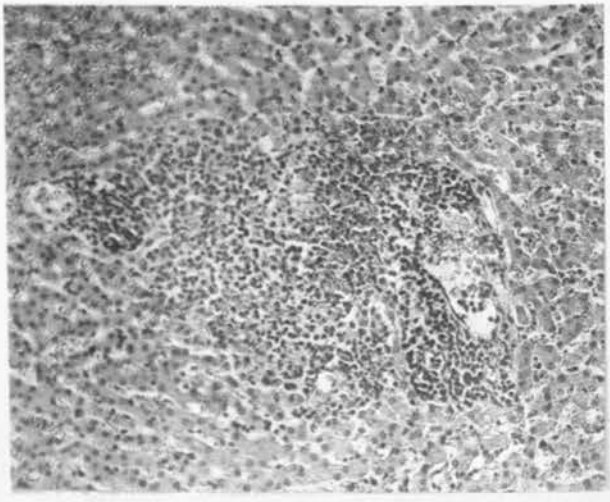
Aut. 473-21. Liver, showing marked periportal infiltration with obliteration of some of the bile ducts. X120

Figure 16



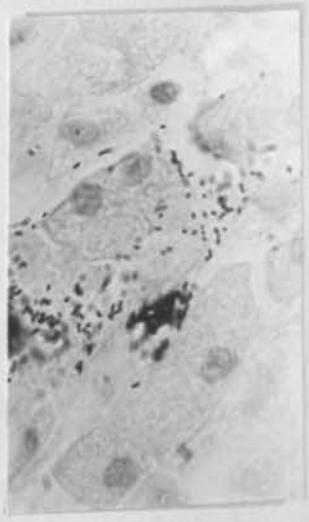
Dog 2. (a) Bile duct with desquamated epithelium. X120.

Figure 17



Dog 2. Showing periportal leucocytic infiltration and necrosis. X120.

Figure 18



Dog 2. Gram stain of liver, showing diplo-streptococci. X1000.

bodies.

Cultures were made from the liver, bile, spleen and kidney, all of which yielded a green producing diplo-streptococcus. The blood culture was sterile.

Rabbit A7 revealed coccydiosis of the liver and was discarded.

Rabbit A8. All organs appeared to be without any evident lesions. The gallbladder contained a dirty greenish bile in which were suspended many fine greenish particles and scattered throughout the mucous membrane were seen discrete yellow pin point areas of hemorrhage.

Cultures from the liver, spleen and kidney yielded similar green producing streptococcus. The blood and bile were sterile.

Rabbit A9 was macroscopically similar to Rabbit A8 except that the gallbladder wall was thick and edematous. Cultures yielded similar results as in Rabbit A8.

Microscopic study of sections.--In the patient's liver the bile ducts are markedly infiltrated with polymorphonuclear leukocytes and lymphocytes. The liver cells near the periportal region show various stages of disintegration. Some of the bile ducts are completely sclerosed while others are filled with epithelial debris(Figure 15). Sections from the heart, kidney and spleen of Dog 1 presented no noteworthy changes, while in the liver the epithelium of the bile ducts is desquamated (Figure 16) while in some, the lumen is filled with polymorphonuclears and cellular debris. Scattered throughout the section are present focal areas of necrosis which are most numerous around the periportal spaces (Figures 17 and 20), and contain large foci of gram-positive diplo-streptococci (Figure 18). The gallbladder wall is markedly edematous. The submucosa and muscularis are infiltrated with polymorphonuclear leukocytes, eosinophils and lymphocytes (Figures 21 and 22). Sections from Rabbits A8 and A9 are in general, similar to those of Dog 1, except that the leukocytic infiltration is made up chiefly of eosinophils and lymphocytes.

The above experiments, though they conclusively prove that the organisms exhibited a marked tendency to produce lesions in the biliary tract, still allow

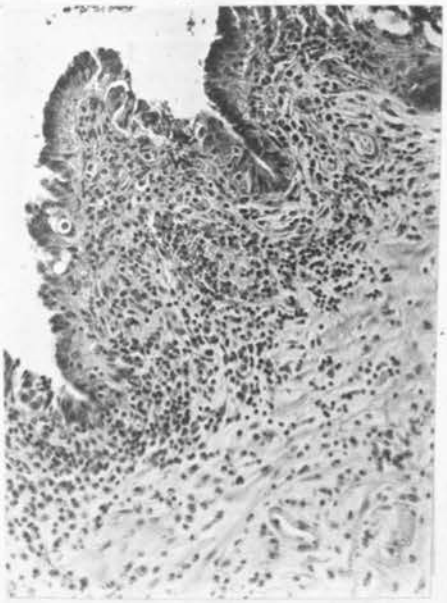
Figure 19

Dog 1. Soft concretions in gallbladder. X2

Figure 20

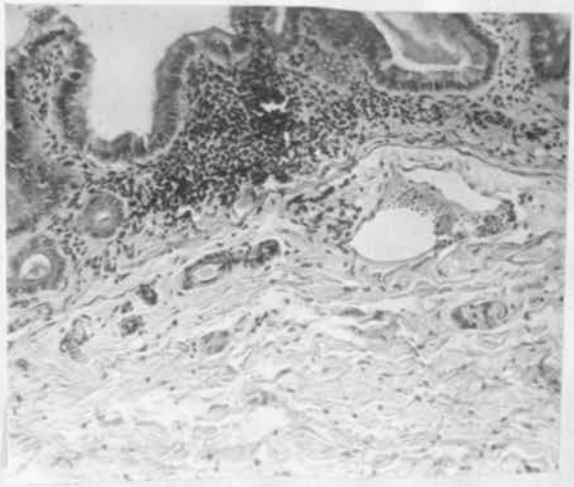
R A10. Periportal leucocytic infiltration. X120.

Figure 21



R A8. Gallbladder showing leucocytic infiltration and desquamation of epithelium. X120.

Figure 22



Dog 2. Gallbladder showing leucocytic infiltration. X120

one to rightfully argue that the lesions may have preexisted in the animals. In order to conclusively test this assumption, another set of experiments was made, using the organisms recovered from the liver of Dog 1, and the same technic, except that the inoculations were made after performing a laparotomy under ether anesthesia. The gallbladder was explored by removing all of its bile with a syringe, and the walls were palpated for calculi. The physical properties of the bile were noted and cultures were made of it. Then a small piece of liver was removed for microscopic examination.

Two dogs and two rabbits were used. The gallbladders of all of these animals were free from calculi as far as could be determined by palpation at operation. The bile was clear and no floating particles were present. The bile was found sterile in all of the animals used while the microscopic sections of the liver removed for control were free from lesions. The animals were killed with ether on the third day after inoculation and necropsy was immediately performed. Dogs 2 and 3, and Rabbits A10 and A11 presented in general, similar macroscopic and microscopic findings as described in Dog 2, with only slight variations in extension of the lesions while the remaining organs were free from any gross or microscopic lesions.

Discussion

From the above experiments it would seem, then, that the organism recovered from the liver and calculi in the bile ducts of the patient had a distinctive affinity for the tissues in the biliary tract, particularly the biliary ducts and gallbladder. The lesions produced in the experimental animals closely simulate those found in the patient except that in the experiments we are dealing with an acute process. The liver lesions were easy to control, but the interpretation of the concretions found in the gallbladder is difficult because even by performing a laparotomy it is almost impossible to palpate the presence of small calculi, especially when they are soft, as were those found in the animals. It would seem, then, that these organisms were the etiologic factor in producing lesions in the

liver which may represent the early stage of biliary cirrhosis.

The results of the above experiments were unexpected, and consequently it was then too late to study the original focus, if any existed outside of the biliary system. Further, an attempt to repeat the experiments with the stock cultures was a complete failure; apparently the organisms had lost their specific property. As we have seen, Weaver and Hektoen had a similar experience.

Nephritis

The following two cases of nephritis occurred in this series:

Case 5. (Aut. 615-20). Mr. C. F. K. came to the Clinic with a history of difficulty in urination of about fifteen years' duration. At examination marked prostatic hypertrophy was found. Kidney function was good, and primary prostatectomy was done. Death occurred suddenly on the seventeenth day after operation. At necropsy the anatomic diagnosis was: pulmonary embolism, multiple renal abscesses with acute pyelonephritis (Figure 23). Cultures of the blood, spleen and kidney yielded hemolytic streptococci.

Rabbits 44 and 45 were injected intravenously with 4 c.c. of glucose brain broth culture of the patient's kidney. The animals were catheterized before injection and the urine was found to be normal. Four days after injection both animals were chloroformed and necropsy revealed multiple diffuse abscesses in the medulla and cortex of both kidneys. No other lesions were found in the remaining organs. Urine obtained at postmortem contained considerable albumin, few pus cells and granular casts. Cultures of the blood, spleen, kidney and urine yielded pure cultures of hemolytic streptococci.

Histologic examination of the kidneys revealed focal necrosis. The epithelium of the tubules was desquamated and in areas the tubules were filled with pus casts containing gram-positive streptococci (Figures 24 and 25).

Table V

Results of Animal Experiments

Case number	Animal number	Organisms injected	Source	Vehicle	Route	Animal passage	Effect on animals	Lesions in						
								Heart	Lungs	Stomach	Kidney	Joints	Miscellaneous	
1	R52	Streptococci	Tooth apex	G.B.B.	I	First	D	-	+	+	-	+	-	
1	R53	Streptococci	Tooth apex	G.B.B.	I	First	Cl	-	-	+	-	-	-	
1	R54	Strep. & staph.	Tooth apex	Saline	I	First	D	-	-	+	-	-	-	
1	R55	Strep. & staph.	Tooth pus	Saline	I	First	D	+	-	+	+	-	-	
1	R56	B. coli	Kidney	G.B.B.	I	First	D	-	-	-	-	-	-	
1	R57	B. coli	Kidney	G.B.B.	I	First	Cl	-	-	-	-	-	-	
1	R58	Staph. & strep.	Tooth pus	G.B.B.	I	First	Cl	+	-	+	+	-	-	
1	R59	Staph. & strep.	Tooth pus	G.B.B.	I	Second	Cl	+	-	+	+	-	-	
1	R60	Streptococci	Stomach of R58	G.B.B.	I	Second	D	-	+	+	-	-	-	
1	R61	Streptococci	Stomach of R54	G.B.B.	I	First	D	-	-	-	-	-	-	
1	R62	Staphylococci	Kidney of R58	G.B.B.	I	Second	Cl	+	-	+	+	-	-	
1	R63	Staphylococci	Kidney of R58	G.B.B.	I	First	D	-	-	-	-	-	-	
1	R64	Staphylococci	Stomach of R54	G.B.B.	I	Second	Cl	+	-	-	+	-	-	
1	R65	Staphylococci	Stomach of R54	G.B.B.	I	Second	Cl	-	-	-	+	-	-	
1	R66	Streptococci	Stomach of R54	G.B.B.	I	Second	Cl	-	+	+	-	-	-	
1	R67	Streptococci	Stomach of R54	G.B.B.	I	Second	Cl	-	-	-	-	-	-	
2	R72	Streptococci	Tooth	G.B.B.	I	First	Cl	-	-	+	-	-	-	
2	R73	Streptococci	Tooth	G.B.B.	I	First	D	-	-	-	-	-	-	
2	R74	Streptococci	Stomach of R72	G.B.B.	I	Second	Cl	-	-	+	-	-	-	
2	R75	Streptococci	Stomach of R72	G.B.B.	I	Second	D	-	-	+	-	-	-	
3	R2255	Streptococci	Tooth	G.B.B.	I	First	Cl	-	-	+	-	-	-	
3	R2256	Streptococci	Tooth	G.B.B.	I	First	Cl	-	-	+	-	-	-	
5	R44	Streptococci	Kidney	G.B.B.	I	First	Cl	-	-	-	+	-	-	
5	R45	Streptococci	Kidney	G.B.B.	I	First	Cl	-	-	-	+	-	-	
6	R46	Anaerobic bacillus	Kidney	G.B.B.	I	First	D	+	+	-	+	-	-	

Note:

G.B.B.=Glucose brain broth media
I =Intravenous injection
D =Animal died
Cl=Killed by chloroform

Table V (continued)

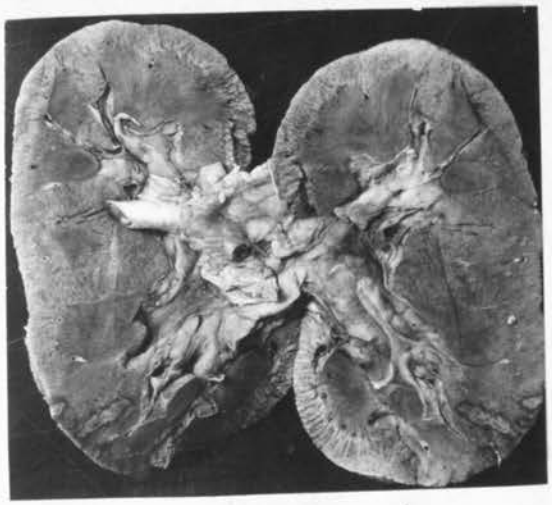
Results of Animal Experiments

Case number	Animal number	Organisms injected	Source	Vehicle	Route	Animal passage	Effect on animals	Lesions in						
								Heart	Lungs	Stomach	Kidney	Joints	Subcutaneous	
6	R47	Anaerobic bacillus	Kidney	G.B.B.	I	First	D	+	+	-	+	-	-	
6	R48	Anaerobic bacillus	Kidney	G.B.B.	I	Second	D	+	+	-	+	-	-	
6	R49	Anaerobic bacillus	Kidney	G.B.B.	I	Second	D	+	+	-	+	-	-	
6	R50	Anaerobic bacillus	Kidney	G.B.B.	I	Third	Cl	-	-	-	+	-	-	
7	R23	Hemolytic strep.	Tooth	G.B.B.	I	First	Cl	+	-	-	-	+	-	
7	R24	Hemolytic strep.	Tooth	G.B.B.	I	First	Cl	+	-	-	-	+	-	
7	R25	Hemolytic strep.	Tooth	G.B.B.	I	First	Cl	+	-	-	-	-	-	
7	R26	Hemolytic strep.	Tooth	G.B.B.	I	First	Cl	+	-	-	-	+	-	
7	R27	Hemolytic strep.	Tooth	G.B.B.	I	First	Cl	+	-	-	-	+	-	
7	R28	Hemolytic strep.	Tooth	G.B.B.	I	Second	Cl	+	-	-	-	+	-	
7	R29	Hemolytic strep.	Tooth	G.B.B.	I	Second	Cl	+	-	-	-	-	-	
8	R31	Strep. viridans	Tooth	G.B.B.	I	First	Cl	+	-	-	-	-	-	
8	R32	Strep. viridans	Tooth	G.B.B.	I	First	Cl	+	-	-	+	+	-	
8	R33	Strep. viridans	Tooth	G.B.B.	I	First	Cl	+	-	-	-	-	-	
8	R34	Strep. viridans	Tooth	G.B.B.	I	First	Cl	+	-	-	-	+	-	
8	R35	Strep. viridans	Tooth	G.B.B.	I	First	Cl	+	-	-	-	-	-	
8	R36	Strep. viridans	Tooth	G.B.B.	I	First	Cl	+	-	-	-	-	-	

Note:

G.B.B.=Glucose brain broth media
I =Intravenous injection
D =Animal died
Cl=Killed by chloroform

Figure 23

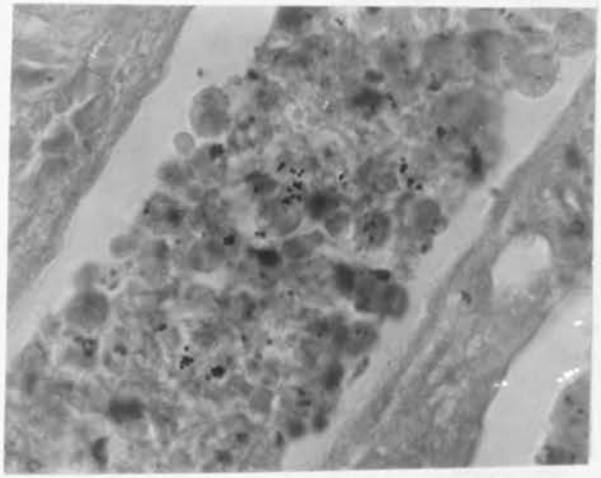


Aut. 615-20. Focal renal abscesses.

Figure 24

R45. Focal renal necrosis. X100.

Figure 25



R45. Gram stain of renal abscess, showing diplococci and pus cells. X500.

Case 6. (Aut. 683-20.). Mr. H. B., aged forty years, had complained for the last month of headache and knife like pains in the body. Urinary suppression suddenly supervened and decapsulation of both kidneys was done. The patient died in coma. At autopsy the anatomical diagnosis was as follows:

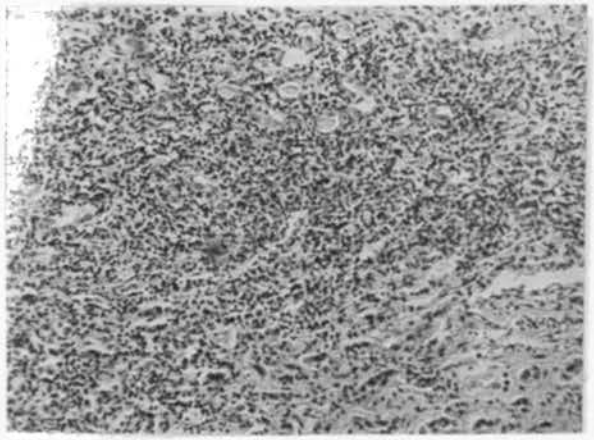
Bilateral bronchopneumonia, thrombosis of the veins tributary to the right renal vein, anemic infarction of both kidneys with early abscess formation, acute splenitis with hemorrhagic infarction and subperitoneal hemorrhages. Cultures from the blood, spleen and kidney yielded a gram-positive anaerobic bacillus (not bacillus Welchii).

Rabbits 46 to 49 inclusive were injected with this organism and the following protocol is typical of the results obtained in the animals:

Rabbit 46, weighing 2000 gm., was injected intravenously with 5 c.c. of a glucose brain broth culture of the patient's kidney. Death occurred twenty-four hours later. Necropsy revealed hemorrhagic peritonitis, and acute nephritis with multiple abscesses, in which there were found gram-positive bacilli as in the patient's kidney (Compare Figures 26, 27 and 28). Cultures from the spleen, peritoneal fluid, kidneys, urine and blood, yielded an organism with identical cultural and morphologic characteristics as the one isolated from the patient. Urine contained a large amount of albumin, pus cells and granular casts.

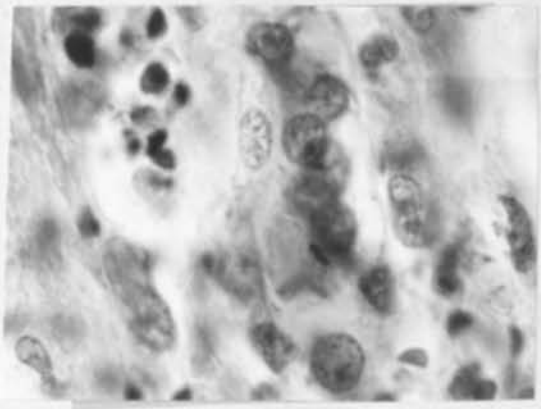
In these animals not only was the chief lesion of the patient reproduced (kidney abscesses), but also the contributory complications. On second animal passage similar but less extensive lesions were obtained. On the third animal passage, no lesions were found; this shows that the organism lost its specificity.

Figure 26



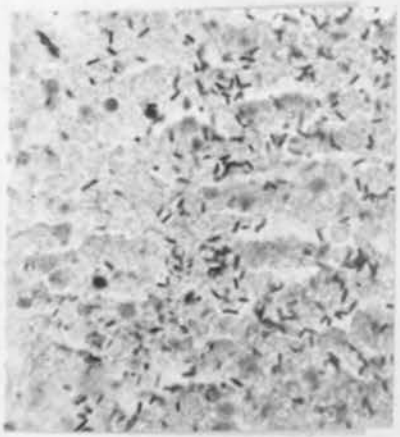
R46. Focal necrosis in kidney. X100.

Figure 27



Aut. 683-20. Gram-positive bacillus in renal abscess. X1000.

Figure 28



R46. Gram-positive bacilli in renal abscess. X500.

Endocarditis

Perhaps the first one to demonstrate the presence of bacteria in vegetative endocarditis was Winge,[38] in 1869. Rosenbach,[39] in 1878, induced the disease in animals by passing a sound down the carotid artery and injuring the aortic valve. Later, Ribbert[40] produced endocarditis by injecting staphylococci simultaneously with an emulsion of potato, while Orth[41] and Wyssowitsch,[42] and Fulci[43] obtained similar results by using pulverized carbon simultaneously with staphylococci or streptococci.[44] The following year, Bonome, and Josserand and Roux[45] produced ulcerative endocarditis by injecting staphylococci alone intravenously.[46] Dreschfeld, using streptococci, obtained similar results which were later confirmed by Poynton and Paine,[47] Davis,[48] Jackson,[49] and Rosenow.[50] The last mentioned attributed to the organisms a selective affinity for the endocardium. The observations of Weiselbaum,[51] Stokes and Wright,[52] Flexner,[11] and Henrici[53] have definitely proven that no one organism is specific of the lesion, although some may produce endocarditis more frequently than others,[49] as pointed out by Poynton and Paine, and by Rosenow. The possibility that endocarditis and rheumatic fever were secondary to focal infection was first definitely proven by Poynton and Paine, and corroborated by Rosenow's[50] extensive research on foci of infection including teeth, tonsils and pharynx.[54] Later, Hartzell and Henrici, and Moody,[55] demonstrated that alveolar infection around the teeth contains organisms of variable degrees of virulence which, when injected intravenously into experimental animals, would produce definite lesions that closely resemble those that existed in the patient.

The following two cases, studied experimentally, are of interest not only in the relation of focal infection to endocarditis, but also because they illustrate that the same condition can be produced in man and experimental animals by different strains of organisms, and they may also throw some light upon the etiology of rheumatic endocarditis and other allied conditions.

Case 7 (Aut. 500A) gave the history of having had recurring attacks of cardiac failure associated with fever. One month before death the patient was

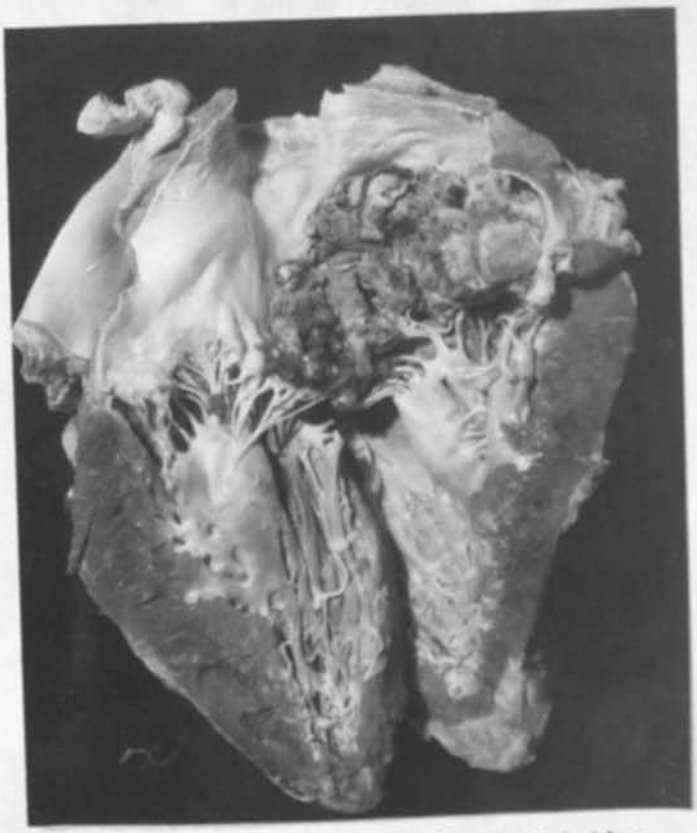
taken with chills and fever and shortness of breath. Examination revealed a fairly well nourished woman, about thirty years old. The teeth were found by roentgen-ray examination to be definitely diseased, having ten periapical abscesses. The heart was enlarged and a presystolic murmur was present. The condition gradually became worse and two days before death there appeared petechial hemorrhages in the skin and right hemiplegia. During the whole illness, at no time did the patient complain of pain in the joints. Autopsy performed five hours after death revealed an extensive chronic and acute vegetative endocarditis (Figure 29) infarction of the left cerebral hemisphere, spleen and both kidneys. Cultures from the blood, brain, spleen and kidney yielded a pure culture of hemolytic streptococci.

Six of ten infected teeth were removed and cultures made from the infected granuloma of four, all of which yielded hemolytic streptococci which corresponded culturally and morphologically to the organisms recovered from the blood and other organs.

Four rabbits were injected intravenously with organisms recovered from the infected granuloma. In three of the four animals there were present multiple purulent arthritis, vegetative endocarditis, and focal myocarditis, while in the fourth animal only a few hemorrhages were found along the line of closure of the mitral valve. The organism was recovered and passed through another series of three rabbits, with similar results in all. The abstracted protocol appended is typical of the results obtained in this case. The associated lesions and their distribution in other animals of the series are indicated in Table V, pages 38 and 39.

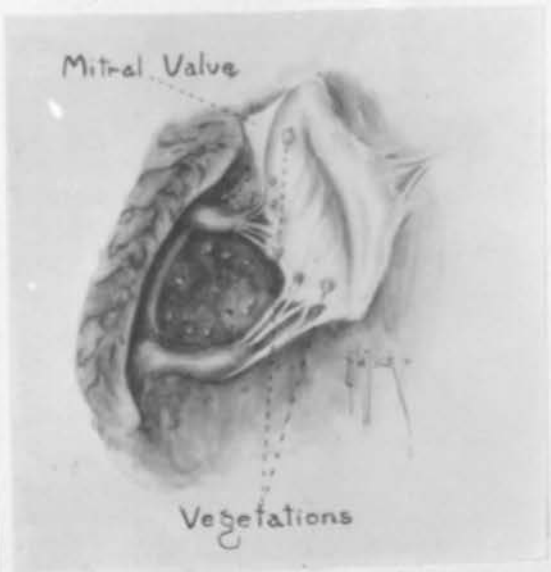
Rabbit 27, weighing 850 gm., was injected intravenously with 3 c.c. of twelve-hour old glucose brain broth culture from an infected granuloma of tooth. Three days after inoculation the right knee joint was swollen and painful on slight pressure. The animal did not touch the ground with the right limb. The next day it became very ill, and was killed with chloroform. Scattered throughout the endocardium of the left ventricle there were found numerous grayish areas varying from

Figure 29



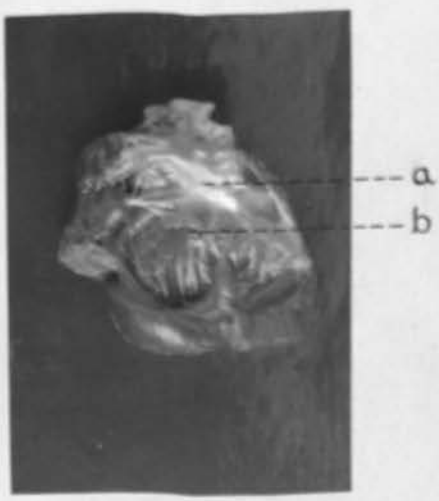
Aut. 500A. Showing extensive vegetative mitral endocarditis with mural invasion.

Figure 30



R27. Mitral vegetative endocarditis.

Figure 31



R34. Mitral endocarditis. (a) Vegetation. (b) Mitral valve.

1 to 2 mm. in diameter, surrounded by red zones. In the base of the mitral valve and along the line of closure as well, there were raised reddish areas varying from 1 to 3 mm. in diameter (Figure 30). The right knee joint was swollen and contained about 3 c.c. of cloudy fluid. The joints of the right and left front limb also contained cloudy fluid. In the smears made from the joint fluid were found pus cells and gram-positive streptococci. Cultures from the blood, spleen and joint fluid all yielded hemolytic streptococci in pure cultures.

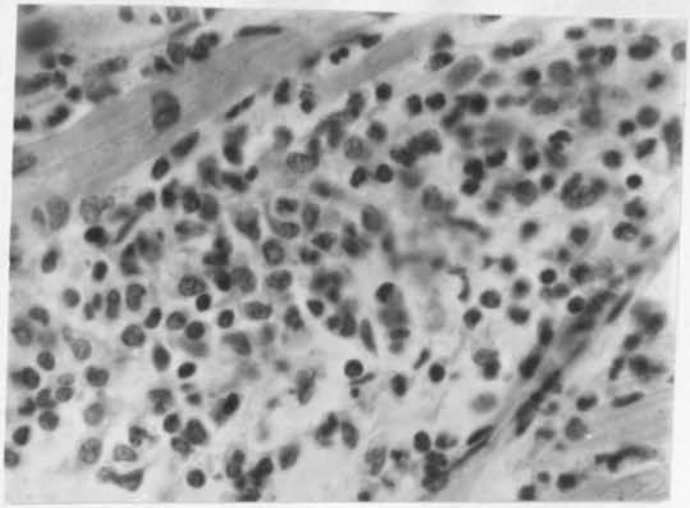
Case 8 (Aut. 515-21). This patient had attacks of rheumatic fever with involvement of joints and definite mitral stenosis with auricular fibrillation. Necropsy revealed healed and fresh vegetations along the line of closure of the mitral valve. Three teeth were removed with two definite infected granulomata which yielded pure cultures of green producing streptococci. Rabbits were injected accordingly with the technic described. The appended protocol is typical of the results obtained. The lesions in the remaining animals injected are tabulated in Table V.

Rabbit 34, weighing 1200 gm., was injected intravenously with a twelve-hour old glucose brain broth culture containing green producing streptococci.

Two days later the animal was chloroformed. Necropsy revealed discrete areas of hemorrhage in the endocardium of the mitral valve and left ventricle. In the line of closure of the mitral valve there was a definite area of ulceration 2 mm. in diameter (Figure 31), and scattered through the wall of the left ventricle were present discrete grayish areas.

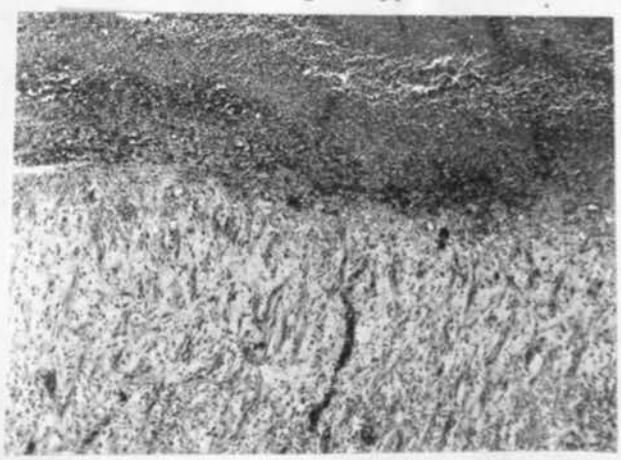
The punctate grayish areas described in the endocardium of the left ventricle in Cases 7 and 8, microscopically were found to extend for a short distance into the myocardium in the intermuscular septa. The areas were focal and made up of groups of large endothelioid cells, lymphocytes, and an occasional polymorphonuclear leukocyte arranged close to a vessel. (Figure 32). No bacteria could be demonstrated in these areas. The vegetations were made up of necrotic tissue, fibrin, leukocytes and large numbers of streptococci (Figures 33 and 34). The lesions found in the myocardium of the rabbits corresponded identically to those of the patient, in being

Figure 32



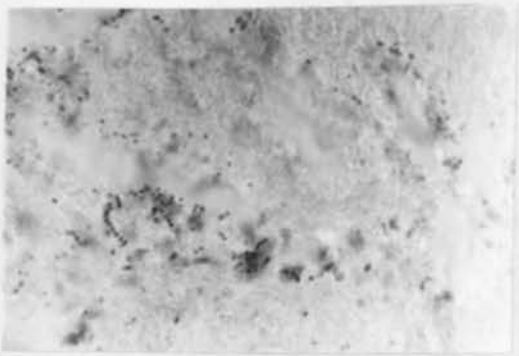
Aut. 500A. Aschoff's body. X500.

Figure 33



Aut. 500A. Necrotic tissue in vegetation of mitral valve. X120.

Figure 34



Aut. 500A. Gram positive diplo-streptococci in section of vegetation. X1000.

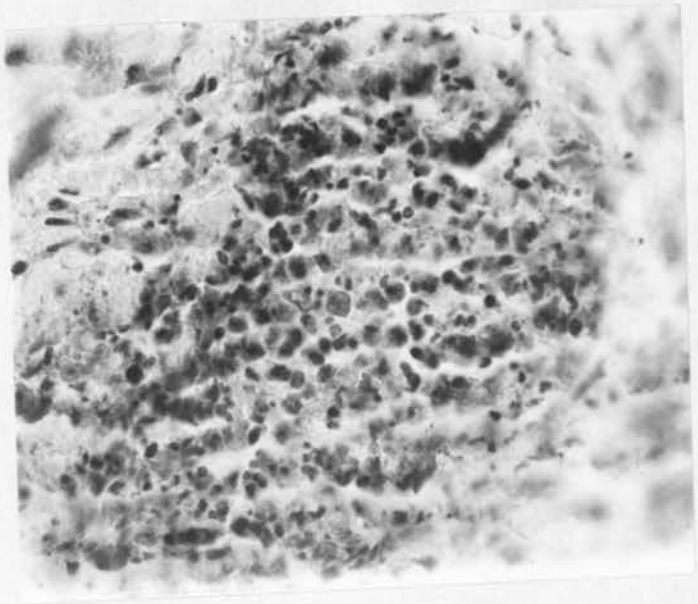
focal in type, perivascular in distribution, but the predominating cells were polymorphonuclear leukocytes and lymphocytes. Stained by Gram's method, large numbers of diplo-streptococci were found in the center of the lesions.(Figures 35 and 36).

Discussion

The myocardial lesions associated with endocarditis have given rise to considerable discussion in regard to their resemblance to the Aschoff bodies which, according to some authors are believed to be specific of rheumatic endocarditis. Aschoff,[56] in 1904, first described a focal myocardial lesion associated with rheumatic endocarditis and called it "submiliary endocarditis of rheumatic fever". The lesion which he described was multiple and occurred in the intermuscular septa closely associated with a blood vessel; composed of a group of large oval or spindle-cells which occasionally were multinuclear and arranged in the form of a rosette or fan shape. These cells were surrounded by lymphocytes and few polymorphonuclear leukocytes. Geipel,[57] a year later, described similar nodules in rheumatic fever although he did not admit the specificity of these nodules since he also found them in a case of nephritis associated with interstitial myocarditis. Thalheimer and Rothschild[58] believe that the presence of Aschoff bodies in the myocardium is a strong presumptive evidence of rheumatic fever, even though no history is available.

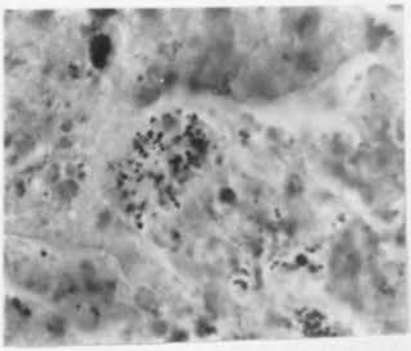
The experimental evidence submitted by various researchers disagrees to a certain extent. Bracht and Wachter[59] claim to have reproduced these bodies in rabbits inoculated with streptococci isolated from rheumatic fever patients. The lesions described were focal in character, and made up of lymphocytes. Jackson[49] made a similar study of myocarditis produced by injecting a strain of hemolytic streptococci isolated from a milk epidemic. The organism, when injected intravenously, had a marked tendency to produce purulent arthritis and focal myocarditis. The age of the lesions studied in this series varied from two days to about two months, and it is of interest to note that the early lesions contained numerous polymorphonuclear leukocytes and bacteria as well, while as the lesion progressed

Figure 35



R27. Perivascular necrosis in myocardium. X200.

Figure 36



R27. Gram positive diplo-streptococci in same area as in Figure 46. X1000.

in age, lymphocytes and oval cells predominated with occasional giant cell and finally in old lesions, only fibrous scars remained. Thalheimer and Rothschild, as stated above, believe that the Aschoff bodies are characteristic only of those found in rheumatic fever and chorea, but absent in cases of subacute endocarditis, due to streptococcus viridans. They admit that these organisms, when injected intravenously into rabbits, produce focal myocarditis, but they insist that these lesions are different in structure and staining reaction of the cells with pyronin methyl-green. Further, they believe that the focal myocardial lesions are of toxic origin since they were unable to demonstrate bacteria in them. Hartzell and Henrici, in a recent study on the specificity of streptococci, found that by injecting various strains of streptococci of low virulence, a certain percentage of these produce focal myocardial nodules which, although not always of similar character, could not be histologically differentiated from Aschoff bodies, and concluded that the lesion is not specific since they were produced by several strains of streptococci. However, they agree with Thalheimer that the myocardial lesions are of toxic character, since they also were unable to demonstrate bacteria in them.

The two cases quoted represent two different clinical and pathologic pictures, namely one of vegetative endocarditis (Case 7), and the other, what is clinically classed as rheumatic fever associated with endocarditis (Case 8). Both cases are probably secondary to periapical dental infection, and in the myocardium of both cases, there were found focal perivascular lesions which, histologically resemble the "submiliary endocarditis of rheumatic fever" described by Aschoff. The organisms recovered from each case are culturally different, and when injected intravenously into animals, tended to localize in the myocardium and endocardium producing focal, perivascular miliary necrosis containing streptococci. The arthritis produced by the hemolytic streptococci was distinctly more pyogenic in character than that produced by the green-producing streptococci.

It would appear, then, from the review of the literature and my own few

experiments, that in all probability, the Aschoff bodies are not specific of rheumatic fever. Perhaps the reason for disagreement that has arisen in the comparison of the lesion, is, that the time factor has not been emphasized. Possibly the earliest lesion is a focal perivascular necrosis in which polymorphonuclear leukocytes predominate, due to the chemotactic substances liberated. During this stage, bacteria can be demonstrated. As the lesion becomes chronic, the bacteria are destroyed, the lymphocytes and endothelial cells predominate and eventually only a scar is left.

Summary

1. There is definite evidence that organisms recovered at postmortem from foci of infection and specific lesions may exhibit a selective localizing power.
2. Such selectivity is comparable in all its phases including animal inoculation with that which has already been proven by other studies.
3. This fact constitutes an additional argument in favor of careful routine and exhaustive bacteriologic examinations of all cases studied at postmortem.

Bibliography

1. Rosenbach, F. J.: Mikro-Organismen bei den Wund-Infektions-Krnakheiten des Menschen. Wiesbaden, Bergmann, 1884, 132 pages.

2. Wurtz, R. and Herman, M.: De la presence frequente du bacterium coli commune dans les cadavres. Arch. de med. exper. et d'anat. path., 1891, iii, 734-745.

3. Hauser, A.: Bacterienbefunde bei Leichen. Ztschr. f. Heilk. 1897, xviii, 421-455.

4. Gradwohl, R. B. H.: Importance de l'examen bacteriologique pratique sur le cadavres. Ann. de l'Inst. Pasteur, 1904, xviii, 767-773.

5. Birch-Hirschfeld, A.: Ueber das Eindringen von Darmbakterien, besonders des Bacterium coli commune in das Innere von Organen. Beitr. z. path. Anat. u. z. allg. Path., 1898, xxiv, 304-326.

6. Fredette, J. W.: Bacteriemias in the agonal period. Jour. Lab. and Clin. Med., 1916-1917, ii, 180-188.

7. Canavan, Myrtelle M. and Southard, E. E.: The significance of bacteria cultivated from the human cadaver. Jour. Med. Res., 1915, xxxi, 339-365.

8. Landsteiner and Austerlitz: Quoted by Canon.

9. Monod, C. and Macaigne: Contribution a l'etude des infections par streptocoques. Rev. de Chir., 1894, xiv, 81-106.

10. Beco, L.: Etude sur la penetration des microbes intestinaux dans la circulation generale pendant la vie. Ann. de l'Inst. Pasteur, 1895, ix, 199-209.

11. Flexner, S.: A statistical and experimental study of terminal infections. Jour. Exper. Med., 1896, i, 559-576.

12. Löw: Quoted by Canon.

13. Canon: Die Bakteriologie des Blutes bei Infektionskrankheiten. Jena, Fischer, 1905, 256 pages.

14. Achard, C. and Phulpin, E.: Contribution a l'etude de l'envahissement des organes par les microbes pendant l'agonie et apres la mort. Arch. de med. exper., 1895, vii, 25-47.

15. Simmonds, M.: Über bakteriologische Blutuntersuchungen an der Leiche. Arch. f. path. Anat., 1904, clxxv, 418.

16. Chvostek, F.: Ueber die Verwertbarkeit postmortaler bacteriologischer Befunde. Wien. klin. Wohnschr., 1896, ix, 1143-1155.

17. Slawyk: Bakteriologische Blutbefunde bei infektios erkrankten Kindern. Jahrb. f. Kinderheilk., 1901, liii, 505-515.

10-20 SM

18. Rosenow, E. C.: The newer bacteriology of various infections as determined by special methods. Jour. Am. Med. Assn., 1914, lxiii, 903-907.

19. Rosenow, E. C.: The etiology of acute articular rheumatism. Jour. Infect. Dis., 1914, xiv, 61-80.

20. Gwyn, N. B. and Harris, N. MacL.: A comparison between the results of blood cultures taken during life and after death. Jour. Infect. Dis., 1905, ii, 514-528.

21. Richey, D. G. and Goehring, C.: Studies on bacteriemias in the agonal period. Jour. Med. Res., 1918, xxxviii, 421-447.

22. Robertson, H. E.: Personal communications.

23. Rosenow, E. C.: The Etiology of articular and muscular Rheumatism. Jour. Am. Med. Assn., 1913, lx, 1223-1224.

23. Idem: Experimental Infectious Endocarditis. Jour. Infect. Dis., 1912, xi, 210-224.

24. Rosenow and Meisser: Personal communications.

25. Evans, J. S.: Focal infection. In: Tice's Practice of Medicine, New York, W. Pryor Company, 1921, 1.

26. Pasteur, L.: Quoted by Duclaux, E. Pasteur; The History of a Mind. Saunders, Philadelphia, 1920, 363 pp.

27. Billings, F.: Focal Infection. New York, D. Appleton and Co., 1916, 178 pp.

28. Rosenow, E. C. and Ashby, W.: Focal infection and elective localization in the etiology of myositis. Arch. Int. Med., 1921, xxviii, 274-311.

29. Israel, J.: Chirurgische Klinik. der Nierenkrankheiten. Berlin, A. Hirswald, 1901, 615 pp.

30. Brewer, G. E.: Some observations upon acute unilateral septic infarcts of the kidney. Surg. Gyneo. and Obst., 1905, ii, 485-497.

31. Jordan: Ueber renale und perirenale Abscesse nach Furunkeln oder sonstigen kleinen peripheren Eiterherden. Verhandl. d. Deutsch. Gesellsch. f. Chir., 1905, xxxiv, 18-22.

32. McKennie, D. W.: Etiology of renal infections, with special reference to urinary stasis in infections of the renal pelvis. Canadian M. A. Jour., 1921, xi, 714-718.

33. Phemister, D. B.: Hematogenous staphylococcus infections secondary to foci in the skin. Jour. Am. Med. Assn., 1922, lxxviii, 480-483.

34. Meisser, J. G. and Rosenow, E. C.: Elective localization by methods other than intravenous. In press.

35. Adami, J. G.: Upon the bacteriology of progressive cirrhosis of the liver. Montreal Med. Jour., 1898, xxvii, 565-581.

36. Weaver, G. H.: Hepatic cirrhosis in the Guinea Pig produced by inoculation with a bacillus. Philadelphia Med. Jour.,1889, iii, 283-285.

37. Hektoen, L.: Experimental bacillary cirrhosis of the liver. Jour. Path. and Bact., 1901, vii, 214-220.

38. Winge, E.: Endocarditis (Mycosis endocardii). Nord. Med. Ark., 1870, Bd. ii, N.r. 14 pp., 15-16.

39. Rosenbach: Über artificielle Herzklappenfehler. Hab-Schrift, Breslau, 1878, 39 pp.

40. Ribbert: Ueber experimentelle Myo- und Endocarditis. Fortschr. de Med., 1886, iv, 1-13.

41. Orth, J.: Ueber die Aetiologie der experimentellen myootischen Endocarditis. Arch. f. path. Anat., 1886, ciii, 333-343.

42. Wyssokowitsch, W.: Beiträge zur Lehre von der Endocarditis. Arch. f. path. Anat., 1886, ciii, 301-332.

43. Fulci, F.: Experimentelle versuche über die Existenz einer Endocarditis durch bacterielle Toxine. Beitr. z. path. Anat., u.z. allg. Path., 1908, xliv, 349-361.

44. Bonome, A.: Contribuzione allo studio degli stafilococchi piogeni. Gior. d. r. Accad. di med. di Torino, 1886, xxxiv, 603-615.

45. Josserand and Roux, G.: Note sur un cas d'endocardite infectieuse experimentale. Arch. de med. exper. et d'anat. path., 1892, iv, 469-478.

46. Dreschfeld: Experimental investigations on the bacterial origin of non-ulcerative malignant endocarditis. Brit. Med. Jour., 1887, ii, 887.

47. Poynton, F. and Payne, A.: A Research on Rheumatism. London, 1913.

48. Davis, D. J.: Bacteriologic study of streptococci in milk in relation to epidemic sore throat. Jour. Am. Med. Assn. 1912, lviii, 1852-1854.

49. Jackson, Leila: Experimental "rheumatic myocarditis." Jour. Infect. Dis., 1912, xi, 243-252.

50. Rosenow, E. C.: Immunologic and experimental studies on pneumococcus and staphylococcus endocarditis. Jour. Infect. Dis., 1909, vi, 245-281.

50. Idem: A study of pneumococci from cases of infectious endocarditis. Jour. Infect. Dis., 1910, vii, 411-428.

51. Weichselbaum: Zur Aetiologie der akuten Endocarditis. Wien. med. Wchnschr. 1885, xxxv, 1241-1246.

52. Wright, J. H. and Stokes, W. R.: A report on the bacteriologic investigations of autopsies. Boston Med. and Surg. Jour. 1895, cxxxii, 293-296.

53. Henrici, A. T.: The specificity of streptococci. Jour. Infect. Dis., 1916, xix, 572-605.

54. Hartzell, T. B. and Henrici, A. T.: A study of streptococci from pyorrhea alveolaris and apical abscesses. Jour. Am. Med. Assn., 1915, lxiv, 1055-1060.

55. Moody, A. M.: Lesions in rabbits produced by streptococci from chronic alveolar abscesses. Jour. Infect. Dis., 1916, xix, 514-525.

56. Aschoff, L.: Zur Myocarditisfrage. Verhandl. d. Deutsch. Path. Gesellsch., 1904, viii, 46-53.

57. Geipel, P.: Untersuchungen über rheumatiche myocarditis. Deutsch. Arch. f. klin. Med., 1906, lxxxv, 75-88.

58. Thalheimer, W. and Rothschild, M. A.: On the significance of the submiliary myocardial nodules of Aschoff in rheumatic fever. Jour. Exper. Med., 1914, xix, 417-428.

59. Bracht, E. and Wächter, O.: Beitrag zur Ätiologie und pathologischen Anatomie der Myocarditis rheumatica. Deutsch. Arch. f. Klin. Med., 1909, xcvi, 493-514.