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The Management of Staphylococcal Disease

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I. THE MANAGEMENT OF STAPHYLOCOCCAL DISEASE

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Prior to the modern era of antibiotic therapy the lack of specific treatment for straphylococcal infections was reflected in the exceedingly high mortality rate for patients with septicemia, and the frequent suppurating and disabling disease that occurred in those individuals that recovered. Skinner and Keefer[1] documented a large series of cases of Straphylococcemia occurring in the preantibiotic period, and pointed out that the mortality rate was 81.97 per cent. This high death rate was particularly applicable to adults over 30 years of age. The mortality rate of children with straphylococcal bacteremia was much lower, but chronic osteomyelitis of the long bones often occurred as a complication.

Studies on staphylococcal disease were initiated in the Department of Medicine in 1937. That also was the year when sulfanilamide first became available. There was no doubt that sulfanilamide, sulfapyridine, and particularly, sulfathiazole, suppressed the in vitro growth of Staphylococci. Sulfathiazole appeared to be of some value in the less serious staphylococcal diseases such as urinary tract infections. Initial observations indicated that sulfathiazole was quite beneficial in cases of staphylococcal bacteremia, but subsequent observations tempered this enthusiasm[2]. The sulfonamides often failed to eradicate, or even to control Staphylococci in the tissues for at least two reasons. First, the exudate and the products of tissue necrosis inhibited the antistaphylococcal action of the sulfonamides. Second, the use of the sulfonamides was often followed by the appearance of sulfonamide-resistant Staphylococci[3]. A study of the nature of this resistance revealed that the resistant staphylococcal cells produced para-aminobenzoic acid which blocked the antistaphylococcal action of the sulfonamides[4]. The results of the management of staphylococcal disease at the University Hospitals in the five-year period of 1937-1942, during which time the sulfonamides were available, demonstrated that well-timed surgical intervention for the drainage of suppurative lesions, especially for osteomyelitis of the long bones, was still of major importance in the recovery of patients. Additional factors that sustained the patient in his recovery were good nursing care and a sufficient caloric intake of food. The sulfonamides were utilized simultaneously, especially sulfathiazole, both locally and systemically. While the results of chemotherapy were difficult to quantitate, the drugs did appear to benefit some patients, but it became quite obvious that the sulfonamides were not the answer to the proper treatment of staphylococcal disease.

Limited supplies of penicillin were made available for investigations in 1942 through the National Research Council. Very fortunately, strains of Staphylococci isolated from patients before penicillin became available had been kept in the laboratory, and when the penicillin did arrive an opportunity presented itself in which to test the comparative in vitro effect of penicillin and sulfathiazole against 68 strains of coagulase-positive Staphylococci. Of considerable importance is the fact that while 28 per cent of these strains were highly resistant to sulfathiazole, not a single strain required 1 unit or more of penicillin to inhibit growth of the organisms[5]. While a slight degree of penicillin resistance was encountered with some strains, the resistance was inconsequential compared to what is being encountered today. Penicillin was administered for the first time at the University Hospitals to a 7 year old girl on July 11, 1942. She was desperately ill with staphylococcal bacteremia, pulmonary abscesses and acute osteomyelitis. While her recovery was remarkable in itself, of equal interest is the amount of penicillin that was used, all administered intravenously! She received 10,000 units of amorphous penicillin every 4 hours for 4 doses; 5000 units every 4 hours for 32 doses; 2500 units every 4 hours

for 20 doses; a total of 252,500 units in 15 days! During the period 1942-1944, 57 patients having staphylococcal disease were treated with penicillin[6]. There were 28 patients with staphylococcal bacteremia, and the over-all mortality rate was 28 per cent, which represented a precipitous drop from the 80 per cent rate of the prepenicillin days. It is of interest that even in adults the total dose of penicillin used rarely exceeded 1 million units. In view of the experience to date, it is now recognized that this mortality rate might very well have been reduced still further if larger doses of penicillin had been used. Further observations with penicillin therapy at the University Hospitals revealed gratifying results in the management of patients having staphylococcal meningitis[7].

For more than five years after the introduction of penicillin into the University Hospitals, highly satisfactory results were obtained in the treatment of primary and secondary staphylococcal disease. This therapeutic success was reflected in the absence of chronic and suppurating staphylococcal infections, such as osteomyelitis, from the hospital beds. Three years after penicillin had been first used in the University Hospitals we stated that the appearance of penicillin-resistant strains of Staphylococci was a minor cause of failures with penicillin[8]. But there were rumblings in various parts of the world to the effect that penicillin-resistant strains of Staphylococci were appearing with increasing frequency, and that this was becoming a serious therapeutic problem. This also became quite apparent in 1948 and 1949 at the University and affiliated hospitals. More and more patients were being encountered who did not respond as satisfactorily to penicillin as previously, and a study of the organisms isolated from these individuals demonstrated a marked increase in the incidence of strains highly resistant to the in vitro action of penicillin. In the latter part of 1949 and beginning of 1950, an in vitro study was made of 104 strains of coagulase-positive Staphylococci isolated from patients at the University Hospitals[9]. Over 50 per cent of these strains were found to be resistant to penicillin, and the resistance demonstrated by the vast majority of strains was extraordinarily high. Furthermore, a considerable number of these strains were also resistant to streptomycin. The interesting feature was that the degree of resistance that these strains manifested against aureomycin, oxytetracycline (terramycin) and chloramphenicol was negligible. At approximately the same time, similar results were reported from various other groups in the United States and from abroad.

When it became apparent that less than one-half of the patients with staphylococcal sepsis would respond satisfactorily to penicillin, more and more attention was turned toward aureomycin and oxytetracycline, and less so toward chloramphenicol. These antibiotics were initially highly effective in the therapy of staphylococcal disease, but then the problem of drug-resistant strains of Staphylococci began to manifest itself again. In 1952 another group of 100 strains of coagulase-positive Staphylococci isolated from patients at the University Hospitals was investigated for their in vitro sensitivity toward several antibiotics. It was shown that approximately 60 per cent of the strains were resistant to penicillin, with a similar degree of resistance manifested against streptomycin. But most significantly, it was now observed that up to 40 per cent of the strains were resistant to aureomycin, and to oxytetracycline. Fewer strains were resistant to chloramphenicol, and no resistant strains were encountered for bacitracin, erythromycin and carbomycin. A similar experience has been reported at the Mayo Clinic by Needham and Nichols[10]. In the latter part of 1951, approximately 60 per cent of the strains of Staphylococci isolated from patients manifested resistance to penicillin, and 36 per cent of these resistant strains were also resistant to aureomycin and to oxytetracycline. More recently, Finland and Haight[11] have studied 500 strains of Staphylococci isolated from material at the Boston City Hospital

during the latter part of 1951 and early part of 1952, and found that about 75 per cent were resistant to penicillin, and 25 per cent resistant to aureomycin and to oxytetracycline. Similarly, of 915 strains isolated from individuals in Sydney, Australia, 64.7 per cent were resistant to penicillin, and less so to aureomycin and oxytetracycline[12].

Without documenting the literature any further, it is apparent that all over the world in the larger centers where penicillin has been used extensively, an increasing number of strains of Staphylococci are being isolated that are resistant to penicillin. When clinicians then turned to other antibiotics, such as streptomycin, aureomycin and oxytetracycline, the same story of antibiotic resistance was repeated. The Staphylococcus appears to be the only bacterium that has rapidly produced progeny that are permanently resistant to penicillin and to other antibiotics. While the basic factors responsible for the appearance of resistant strains cannot be detailed here, it is generally accepted that penicillin, and the other antibiotics, have acted upon staphylococcal cells by selecting out the resistant variants, thus permitting these resistant cells to multiply, and killing off the more sensitive organisms. The resistant strains have then been kept going in the nasopharynx of healthy carriers, especially in hospital personnel. This epidemiologic factor explains the high incidence of cross infections in patients in large hospitals with penicillin-resistant Staphylococci. Rountree and Thomson[12] surveyed the nasal carrier rate in 200 persons of a hospital staff and found that 54.5 per cent were carriers of Staphylococcus progenes. Eight of every 10 carriers were harboring penicillin-resistant strains. One of the most treacherous problems afflicting the larger hospitals today is that of cross infections from patient to patient and from staff to patient with highly penicillin-resistant strains of Staphylococci. And more and more of these strains harbored in the nasopharynx are manifesting resistance to several antibiotics.

Once again, staphylococcemia has become a major problem in the University and affiliated hospitals. This report is concerned with 22 cases of staphylococcal bacteremia. At this time we wish to summarize the clinical features of these patients with particular reference to the bacteriology, complications, in vitro resistance studies with several antibiotics, and the results of therapy.

Since November 1951 to May 1953, a period of 18 months, 22 cases of severe staphylococcal sepsis have been studied at the University of Minnesota Hospitals, Minneapolis General Hospital and the Minneapolis Veterans Administration Hospital. Summaries of the cases are in Table I.

TABLE I

Summary of 22 Cases of Staphylococcal

Patient	Primary Disease	Portal of Entry	Complications	Blood Culture Bacteria per ml.
1. 8 yr. Male	Pyelonephritis	Genito-urinary system	Bacteremia	Positive
2. 26 yr. Female	Endocarditis Mitral valve	(Unknown)	Aortic insuffic iency; pulmonary edema	Positive
3. 70 yr. Male	Prostatism Transuretheral resection	Genito-urinary system	Bacteremia abscess	24
4. 42 yr. Male	Carcinoma of esophagus	Alimentary tract Esophagectomy	Bacteremia	Too many to count
5. 67 yr. Male	Carcinoma of esophagus	Alimentary tract Esophagectomy	Bacteremia	150
6. 77 yr. Male	Prostatism Transuretheral resection	Genito-urinary system	Bacteremia	250
7. 38 yr. Male	Endocarditis	(Unknown)	Renal damage	(1) 3 (2) Too many to count

TABLE I (Cont.)

Sepsis Observed November 1951 - May 1953

In vitro Sensitivity Tests with Concentrations of Antibiotic* in Units or Micrograms Necessary to Inhibit Growth									Treatment in Order in Which Antibiotics Were Given			
Peni.	Strepto	Aureo	Oxytet	Chloro	Bacit	Erythro	Carbo	Neo.	Antibiotic*	No. Days	Total Dose*	Result
7.8	>62.5	>62.5	62.5	7.8	1.0				Aureo. Chloro. Bacit. Peni. Sulfadiaz.	3 8 9 17 9	3.0 gm 12.0 gm 180000 u 20.4 ml 13.5 gm	Recovered
125.0	15.6	3.1	7.8	15.6	1.0	(0.5)	(1.9)	1.9	Aureo. Terra. Peni. Strepto. Bacit. Peni.	10 3 11 11 8 2	11.0 gm 5.0 gm 21.0 ml 11.0 gm 800000 u 40.0 ml	Expired
15.6	>10,000	62.5	156.0	7.8	7.8	0.05	1.9	3.9	Aureo. Terra. Peni. Strepto. Chloro. Erythro.	20 4 6 10 10 17	25.0 gm 8.0 gm 9.6 ml 20.0 gm 20.0 gm 20.4 gm	Recovered
2000.	>10,000	62.5	62.5	7.8	0.5	0.5	1.9	3.9	Peni. Strepto. Aureo. Terra. Chloro. Erythro. Bacit.	45 34 32 25 4 21 5	46.4 ml 34.0 gm 32.0 gm 25.0 gm 4.0 gm 25.2 gm 150000 u	Expired
>15.6	62.5	0.5	62.5	Resis.	Sens.				Peni. Strepto. Sulfadiaz. Bacit.	12 12 4 2	9.0 ml 21.0 gm 24.0 gm 160000 u	Expired
>15.6	>62.5	>62.5	>62.5		0.5	0.5			Aureo. Peni. Strepto. Terra. Bacit. Erythro.	11 25 21 11 7 5	10.5 gm 151.5 ml 29.0 gm 22.0 gm 420000 u 6.0 gm	Expired
6.3	12.5	3.1	1.5	12.5	3.1	0.38	1.9	1.5	Carbo. Terra. Erythro. Peni. Bacit.	11 3 114 75 3	46.0 gm 1.5 gm 228.0 gm 286.8 ml 240000 u	Not improved

TABLE I (Cont.)

Patient	Primary Disease	Portal of Entry	Complications	Blood Culture Bacteria per ml.
8. 48 yr. Female	Septic arthritis	(Unknown)	Bacteremia	(1) 2 (2) 19
9. 47 yr. Male	Endocarditis	Abscess of neck	Myocardial abscess Multiple abscesses	(1) 6 (2) Too many to count
10. 38 yr. Male	Endocarditis Cirrhosis	(Unknown)	Congestive failure Anemia	(1) 3 (2) Too many to count
11. 22 yr. Female	Endocarditis Aortic valve	Abscess of hand	Congestive failure	Positive 4 X
12. 48 yr. Female	Intestinal obstruction	Indwelling plastic tube in vein	Bacteremia	Positive 3 X
13. 21 yr. Male	Staphylococcus septicemia	(Unknown)	Septic arthritis Vitreus abscess	Positive 4 X
15 61 yr. Male	Rheumatoid arthritis Cortisone Endocarditis Mitral valve	(Unknown)	Rupture of mitral valve. Pericarditis. Abscesses. Meningo-encephalitis	600
16 38 yr. Male	Lymphoblastoma Duodenal ulcer	Indwelling plastic tube in vein	Bacteremia Abscesses of myocardium, lungs, liver, spleen. Pyelonephritis Pericarditis	Positive

TABLE I (Cont.)

Peni.	Strepto	Aureo	Oxytet	Chloro	Bacit	Ery-thro	Carbo	Neo.	Anti biotic*	No. Days	Total Dose*	Re-sult
50.0	12.5	1.5	1.5	12.5	1.5	0.75	1.0	1.5	Peni.	36	25.2 ml	Re-
									Terra.	55	110.0 gm	cov-
									Strepto.	10	10.0 gm	ered
									Carbo.	3	6.0 gm	
									Erythro.	23	27.6 gm	
									Bacit.	20	1.2 ml	
									Neo.	19	14.25gm	
0.09	3.1	1.5	1.5	12.5	0.75	0.38	0.75	0.75	Peni.	23	134.0 ml	Ex-
									Terra.	2	3.0 gm	pir-
									Aureo.	1	0.25gm	ed
									Carbo.	4	18.4 gm	
									Erythro.	12	24.0 gm	
0.09	1.5	0.75	0.75	6.3	1.5	0.19	0.75	1.5	Carbo.	7	32.8 gm	Not
									Peni.	57	342.0 gm	im-
									Bacit.	4	320000 u	prov-
									Erythro.	36	72.0 gm	ed
0.38	12.5	1.5	1.5	12.5	1.5	0.38	0.75	0.09	Peni.	22	96.3ml.u	Ex-
									Erythro.	5	6.0 gm	pir-
									Carbo.	6	24.0 gm	ed
									Terra.	1	3.0 gm	
1250.	>10,000	7.8	31.2	31.2	1.0	0.25	1.0	3.9	Peni.	4	3.2ml.u	Re-
									Strepto.	6	6.0 gm	cov-
									Aureo.	4	4.0 gm	ered
									Carbo.	27	51.0 gm	
									Bacit.	22	880000 u	
<0.5	>62.5	3.9	15.6	7.8	15.6	0.5	0.25	3.9	Bacit.	1	25,000 u	Re-
									Carbo.	15	45.0 gm	cov-
												ered
0.5	7.8	1.9	3.9	7.8	7.8	<0.5	1.9	15.6	Peni.	2	16 ml.u	Ex-
									Terra.	2	4 gm	pir-
												ed
>2000	>10,000	31.2	156.0	7.8	31.2	1.9	1.9	15.6	Gantrisin	6	24 gm	Ex-
									Neo.	1	4 gm	pir-
									Peni.	16	38.2 ml	ed
									Strepto.	9	18.0 gm	
									Terra.	11	11.0 gm	
									Erythro.	5	8.0 gm	
									Carbo.	5	1.5 gm	
									Bacit.	2	80,000 u	

TABLE I (Cont.)

Patient	Primary Disease	Portal of Entry	Complications	Blood Culture Bacteria per ml.
19. 78 yr. Female	Staphylococcus pneumonia	Respiratory system	Bacteremia	Positive
20. 63 yr. Male	Multiple myeloma Treatment urethane	(Unknown)	Bacteremia	125
21. 42 yr. Male	Lymphoblastoma	(Unknown)	Bacteremia	(1) 4 (2) 176
22. 29 yr. Male	Ureteral calculus Right ureteral lithotomy	Ureteral lithotomy wound	Bacteremia	Positive?
23. 44 yr. Female	Carcinoma of cervix with metastasis Cholecystectomy Abd. fistulae	Recto-vaginal fistula	Becteremia	(1)Positive (2) 2
24. 33 yr. Male	Lymphosarcoma	Indwelling plastic tube in vein	Bacteremia Thrombo-phlebitis	
25. 72 yr. Male	Osteomyelitis of hip	(Unknown)	Bacteremia	Positive?

TABLE I (Cont.)

Peni.	Strepto	Aureo	Oxytet	Chloro	Bacit	Ery-thro	Carbo	Neo.	Anti-biotic*	No. Days	Total Dose*	Re-sult
>50.0	>50.0	>50.0	>50.0	6.3	3.1	0.38	1.5	3.1	Peni.	9	6.0 ml	Re-
									Terra.	9	14.0 gm	cov-
									Erythro.	23	46.0 gm	ered
									Bacit.	8	640000 u	
>15.6	>62.5	3.9	62.5	7.8	0.25	1.9	1.9	7.8	Peni.	9	14.4 ml	Ex-
									Strepto.	9	18.0 gm	pir-
									Aureo.	2	2.0 gm	ed
									Terra.	2	2.8 gm	
>100.	Resis.	0.39	0.39	Resis.	6.25	1.56			Peni.	36	43.2 ml	Ex-
									Strepto.	14	20.0 gm	pir-
									Erythro.	9	7.2 gm	ed
									Terra.	8	13.0 gm	
>100	Resis.	100.	100.	6.3	1.56	0.78			Peni.	6	1.8 ml	Re-
									Aureo.	3	6.0 gm	cov-
									Erythro.	20	22.8 gm	ered
									Terra.	2	1.0 gm	
>500	>62.5	125.	125.	3.1	0.5	0.25	1.9	3.9	Sulfasuxi	8	64.0 gm	Im-
									Aureo.	13	13.0 gm	prov-
									Peni.	17	13.5 ml	ed of
									Strepto.	11	11.0 gm	infec.
									Bacit.	5	400000 u	Expir.
									Neo. (O)	16	36.0 gm	ed of
									Erythro.	26	49.2 gm	pri.
									Terra.	4	4.0 gm	dis-
												ease
>62.5	>62.5	7.8	62.5	7.8	0.25	1.0	3.9	7.8	Aureo.	12	3.6 gm	Ex-
									Terra.	9	9.0 gm	pir-
									Strepto.	3	3.0 gm	ed
									Peni.	3	6.0 ml.u	
									Bacit.IM	1	80,000 u	
									ErythroIV	5	5.0 gm	
>50.0	12.5	1.5	.75	12.5	3.1	.38	0.75	1.5	Peni			Not
									Terra.			im-
									Erythro.			prov-
									Bacit.			ed

* ABBREVIATIONS:

Peni. - Penicillin
Strepto. - Streptomycin
Aureo. - Aureomycin
Oxytet. - Oxytetracycline (Terramycin)
Chloro. - Chloramphenicol (Chloromycetin)
Bacit. - Bacitracin
Erythro. - Erythromycin
Carbo. - Carbomycin (Magnamycin)
Neo. - Neomycin
Sulfadiaz. - Sulfadiazine
Sulfasuxi. - Sulfasuxidine
ml - - million units
u - - units
gm - - grams

Age Distribution

The ages of the patients are presented in the following table:

TABLE II

Age in Years	Number of Cases
1-10	1
10-20	0
20-30	4
30-40	4
40-50	6
50-60	0
60-70	4
70-80	3

Most of the cases represented adults which is not an accurate distribution of cases of staphylococcal sepsis. This disparity in the present series is due to the fact that all of the cases from the Pediatrics Services are not included. There were 16 males and 6 females.

The portals of entry in some of the cases were difficult to determine; however, in some cases a specific site was indicated. These are presented in Table III.

TABLE III

Portal of Entry		No. of Cases
Abscess of hand		1
Abscess of neck		1
Infection at site of insertion of polyethylene catheter into vein		3
Alimentary tract		2
Genito-urinary system		3
Pyelonephritis	1	
Post-transurethral resection	2	
Respiratory tract		1
Operative wound, ureteral lithotomy		1
Rectovaginal fistula		1
Unknown		9

In 2 of the 6 patients with endocarditis, abscesses of the skin were present. In the patients with thrombophlebitis near the insertion of plastic tubes, Staphylococci were cultured from the sites in 2 cases.

Primary Disease Preceding Staphylococcal Infection

Most of the patients had other associated diseases which preceded the onset of sepsis. In many instances this very likely contributed to the high mortality rate in the present series of cases. Some of the associated diseases are as follows:

TABLE IV

Primary Disease	No. of Cases
Arthritis, Charcot's joint	1
Rheumatoid arthritis undergoing cortisone therapy	1
Carcinoma of cervix with metastasis and abdominal fistulae	2
Carcinoma of esophagus, esophagectomy	2
Intestinal obstruction, multiple operations	1
Lymphoblastoma	2
Lymphosarcoma	1
Multiple myeloma	1
Fracture of hip	1
Transurethral resection of prostate	2
Respiratory infection, influenza	1
Pyelonephritis	1
Ureteral lithotomy	1

Antibiotic Resistance

The cultures, which were isolated from the patients, were tested in vitro for sensitivity to the antibiotics. They were considered to be resistant if the culture grew in 3.1 or more units or micrograms of antibiotic per ml. The results are shown in Table V.

TABLE V

Results of in vitro Sensitivity Tests of the Cultures (Isolated from patients) to the Antibiotics, Showing Sensitivity Ranges and Percentage of Cultures Resistant to 3.1 or More Units or Micrograms of Antibiotics per Ml.

Total No. Cultures	Antibiotic	No. of Cultures Inhibited by Each Concentration Range in Units or Micrograms of Antibiotic per Ml. <1.0	1.5-3.1-3.9*	6.3-15.6	>15.6	% Resistant* to 3.1 or More
22	Penicillin	5		2	15	77.2
22	Streptomycin		2	6	14	95.4
22	Aureomycin	2	9	3	8	63.6
22	Oxytetracycline	3	6	1	12	68.1
21	Chloramphenicol		1	17	3	100.0
22	Bacitracin	10	7	4	1	36.3
20	Erythromycin	17	3			0
17	Carbomycin	7	10			5.8
17	Neomycin	2	11	4		52.9

*Two different dilution techniques were used, one resulting in dilution of 3.1 and the other 3.9.

The cultures were very resistant to penicillin and streptomycin. Some of the patients developed staphylococcal sepsis while undergoing therapy with these antibiotics. In cases 3, 4, 12 and 16 of Table I the isolated Staphylococci grew in broth containing 10,000 mcgm. of streptomycin per ml. In the case of oxytetracycline and aureomycin there was increased resistance of 68 and 64 per cent respectively. All of the strains were resistant to chloramphenicol. But it should be pointed out that the resistance for chloramphenicol was not beyond that which might be overcome therapeutically, although this drug has not been too effective in cases of staphylococcal sepsis. Eight of the 22 strains were resistant to bacitracin. However, the amounts necessary for bacteriostasis was over 15.6 units per ml. in only one instance. Erythromycin and carbomycin were similar and equally effective in the in vitro studies. In one case 3.9 mcgm. of carbomycin was necessary for bacteriostasis.

Report of Cases

Case #3. , a 70 year old white male was admitted to the University Hospital April 8, 1952 with acute urinary retention and history of alcoholism and prostatism of one year. Shortly after admission he developed fever which improved following treatment with penicillin, streptomycin and aureomycin. A transurethral resection of the prostate was performed on April 16, 1953 which was followed by shock, chills and fever. He improved and became afebrile during treatment for 5 days with penicillin, streptomycin and aureomycin. Severe diarrhea and jaundice occurred during therapy and subsided. He was discharged 14 days after discontinuance of therapy.

Eight days later he was readmitted with chills and fever. His temperature subsided during therapy with penicillin, dihydrostreptomycin and chloromycetin and he was discharged after 6 days.

The third admission was 4 days later

with chills and fever. Three consecutive blood cultures were positive for coagulase-positive hemolytic Staphylococcus aureus with 24 bacteria per ml. of blood. He did not respond to aureomycin. Sensitivity studies revealed the culture to be very resistant to streptomycin, terramycin, aureomycin and penicillin, but very sensitive to erythromycin. He was treated with erythromycin with satisfactory response. An abscess of the right deltoid area was found to contain Staphylococci. The abscess and blood became sterile and the patient was discharged June 25, 1952. No relapse occurred during one month out-patient follow up.

Case #9. ., a 47 year old white male roofer was admitted to Minneapolis General Hospital on December 19, 1952 and expired on January 11, 1953. He had a history of alcoholism and an abscess of the neck 2 weeks prior to admission. Four days prior to admission he developed headache, malaise and fever. Mental confusion occurred with hallucinations and periods of unresponsiveness. No history of rheumatic fever was known.

Physical examination revealed T. 103; P. 144; B.P. 130/98; disorientation; petechial hemorrhages of extremities, buccal mucosa and right eye, and splenomegaly. An aortic diastolic murmur was heard on the 4th day.

Six consecutive blood cultures revealed too many colonies to count of coagulase-positive hemolytic Staphylococcus aureus. WBC was 43,200 with 95% neutrophils. The organism was sensitive to the antibiotics. except chloromycetin. He was treated with penicillin, 6 million units per day; with carbomycin for 5 days and then with erythromycin for 11 days. Temperature remained elevated. He developed a paralysis of the left arm. Pulmonary edema developed suddenly on the 18th hospital day and he expired.

Autopsy revealed acute pulmonary edema, endocarditis with a ruptured aortic valve, and abscesses of the myocardium, meninges, liver, spleen and kidneys.

Case #12. ., a 48 year old white married female admitted to University Hospital November 24, 1952 with a fecal fistula, a Miller-Abbot tube in the small bowel and symptoms of intestinal obstruction and a history of recurrent intestinal obstruction, two laparotomies, wound disruption and the ileum being inadvertently opened in 3 places with development of a fistula. Physical examination revealed T. 100; P. 108; a Grade II systolic murmur at the apex and the fecal fistula. X-ray studies revealed evidence of a mechanical obstruction of the small bowel. Surgical repair was done and she received penicillin and streptomycin. During therapy she developed edema of the left leg and an ileofemoral thrombosis with chills and fever. Blood cultures on 3 successive days revealed coagulase-positive hemolytic Staphylococcus aureus. The culture grew in 10,000 mcgm./ml. of streptomycin and required 1250 units per ml. of penicillin to inhibit it. She was treated with bacitracin and carbomycin with good response except that the sedimentation rate remained elevated. She was discharged. Three months later an abscess in the right hip area was drained and Staphylococci were isolated. She was well at last report 4 months following discharge.

Case #15. , a 61 year old white male was admitted to the University Hospital on April 4, 1952 and expired the next day. He had rheumatoid arthritis of many years duration and had received cortisone for 19 months, taking 62.5 mg. daily. Chills and fever had started 3 days prior to admission. He was observed to be acutely ill with labored respirations; T. 103; R. 32; P. 136; B.P. 88/60; petechiae of conjunctiva; coarse pulmonary ronchi and loud harsh systolic murmur. Blood culture revealed 600 bacteria per ml. of blood. He received penicillin in high dosage and terramycin. At autopsy he was found to have endocarditis with perforation of the mitral valve, fibro purulent pericarditis, multiple hemorrhages of the kidney, an abscess in the right anterior chest wall and suppurative meningo-encephalitis.

Case #19. , a 78 year old female was admitted to Minneapolis General Hos-

pital on February 9, 1953 and was discharged on March 21, 1953. Two weeks prior to admission she had developed cough, dyspnea, anorexia, generalized aches, chills, fever and pleuritic pain for which she had received one injection of penicillin and two penicillin tablets daily for 6 days without improvement. She had a history of a coronary thrombosis 5 years before. Physical examination revealed T.104; P. 112; R. 24; B.P. 134/70. She was restless, groaning, hot and dehydrated with injected sclera and physical signs of a pneumonic process in the right lower chest. X-ray revealed pneumonia in the base of the right lung. Two blood cultures and a sputum culture revealed coagulase-positive hemolytic Staphylococcus aureus. She was treated with penicillin and terramycin. On the 13th hospital day, a chest x-ray revealed multiple areas of infiltration interpreted as necrotizing pneumonitis which were probably abscesses. Treatment was changed to bacitracin and erythromycin with improvement.

Results of Therapy

Of the 22 cases studied, 7 have recovered and show no signs of infection. One of them (Case #11, Table I) had an amputation of a leg because of the persistence of a suppurative focus, and one (Case #13) lost most of his vision. Three cases (Cases #7, 10 and 25) are in the process of being treated. Two of these have been treated with antibiotics for over 6 months. In one of these (Case #7) therapy with the antibiotics was discontinued after the patient was 100 days without fever, but within 6 days he became febrile and blood cultures revealed too many colonies of bacteria to count. The prognosis of the 3 patients now undergoing therapy is poor.

Twelve of the patients have expired, a mortality rate of approximately 54%. One who expired (Case #23) appeared to be cured of her staphylococcal infection but died because of the primary disease and probable myocardial infarction.

It has been observed in a number of these cases that relapses frequently occur even after the patient has been afebrile for several days or many weeks. One of the best indications for insufficient therapy and a continued infection has been an elevated sedimentation rate.

An analysis of therapy used in these patients suggests that the best results were obtained when penicillin was used in combination with bacitracin, or when erythromycin or carbomycin was administered simultaneously with bacitracin.

Recommended Therapy for Severe Staphylococcal Sepsis

It is difficult to lay down hard and fast rules for the therapy of staphylococcal infections, and the following is offered only because experience to date has indicated that such treatment is effective. Penicillin is still the antibiotic of choice for the treatment of staphylococcal disease, providing the causative strain displays in vitro sensitivity. Under these circumstances the following is suggested:

A total daily dose of at least 2 to 4 million units of crystalline G penicillin in aqueous solution administered intramuscularly in divided doses every 4 hours. In addition, "booster doses" of 1 million units in 10 ml. of saline solution may be administered intravenously every 12 hours. Such therapy should be continued for a minimum of 2 weeks in severe cases. If the patient has normal renal function, small doses of bacitracin may be used simultaneously, but a total daily dose of 100,000 units should not be exceeded, and the urine should be examined daily for evidence of albuminuria. The bacitracin may be given intramuscularly in divided doses every six hours. Therapy with bacitracin should be discontinued if nitrogen retention appears.

If the causative organism exhibits resistance to penicillin, it is suggested that erythromycin should be used in a total daily dose of 2 to 3 gms. given orally in divided doses every 6 hours. Again, if normal renal function is present, bacitracin may be used simultaneously as described above.

Other agents that are effective and can be used in selected cases include aureomycin and oxytetracycline, as well as carbomycin. Dihydrostreptomycin and streptomycin are not highly desirable for long term use because of the appearance of resistant variants, but in selected cases these drugs can be effectively used along with penicillin or any of the other agents mentioned above.

It might appear superfluous to mention as additional therapeutic procedures good nursing care, adequate dietary intake, and the surgical drainage of approachable suppurative areas, but attention to these details may mean the difference between ultimate recovery and chronic disease, or even death.

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J. Lab and Clin. Med., 41:150, Jan. 1953.

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Antibiotic resistance of pathogenic Staphylococci: Study of five hundred strains isolated at Boston City Hospital from Oct. 1951 to Feb. 1952.
Arch. Int. Med., 91:143, Feb. 1953.

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Incidence of antibiotic-resistant Staphylococci in a hospital.
Lancet, 2:262, 1952.

II. MEDICAL SCHOOL NEWS

Coming Event

July 1 Family Doctors' Day; Division of Psychiatry; 12:00 Noon; Powell Hall Recreation Lounge.

* * *

Progress Report

Last year's skeleton has taken on body and form. As the Mayo Memorial Building approaches completion, it forms an increasingly predominant portion of the campus silhouette. Structural steel is now completely covered with brick. Several of the more intrepid members of our faculty have climbed to the top of the structure and have informed the Editor that the view is magnificent. We are all anxiously awaiting the opening of the building, scheduled for April, 1954.

* * *

Doctors Ebert and Chapman to Leave

The Department of Medicine will lose two of its most outstanding teachers and investigators in the field of cardiology during the summer months. Dr. Richard V. Ebert, Clark Professor of Medicine for the past year, will become Professor of Medicine at the Northwestern University School of Medicine on September 1. He will also be Chief of Medicine at the Veterans Research Hospital in Chicago.

Dr. Carleton B. Chapman, Associate Professor of Medicine, will leave at the end of the first summer session to become Professor of Medicine at Southwestern Medical School in Dallas, Texas, where Dr. George N. Aagaard, formerly Director of the Department of Continuation Medical Education and Editor of the Bulletin, is now Dean.

The loss of two such capable people is regretted by the entire faculty. However, we naturally join in offering our congratulations and best wishes to both of them on their new appointments. We are glad that they have been with us even if for an all too brief period.

* * *

Faculty News

Dr. A. B. Baker, Professor, Department of Psychiatry and Neurology and Director, Division of Neurology, will attend the American Neurological Association Meetings in Atlantic City from June 15 to 18 where he will participate in a discussion on neurological education.

At the Annual Cascade County Medical-Surgical Conference at Great Falls, Montana, on June 22 and 23, Dr. Wesley W. Spink, Professor, Department of Medicine, will present two papers on, "The Present Status of Antibiotic Therapy" and "The Management of Patients with Fever of Undetermined Etiology."

Dr. Donald W. Cowan, Associate Professor of Public Health and Assistant Director, Students' Health Service, is leaving this week for Belfast, Ireland, where he will spend several weeks at the university in exchange with Dr. Wilson Johnston who will be coming to the University of Minnesota to observe methods here. Dr. Cowan will also tour the European continent.

Dr. Ramona Todd, Associate Professor of Public Health, has resigned from the University faculty to accept a position in San Francisco with the California State Board of Health.

The University of Minnesota, together with the Minnesota State Medical Association, has sponsored a television program entitled, "How's Your Health?" on which have appeared several members of the full-time staff including: Doctors Richard V. Ebert, Richard L. Varco, Ancel Keys, Robert G. Hinckley, Donald W. Cowan, Robert B. Howard, and John J. Bittner. Clinical members of our faculty who have also participated in these programs are as follows: Doctors C. J. Ehrenberg, O. J. Campbell, Phillip F. Donohue, C. J. Holmberg, and Eugene Rames. Dr. James Rogers Fox, Instructor, School of Public Health, and Physician, Students' Health Service, has been the chairman and moderator of this television program.

Dr. Fox, has also presented several lectures recently. At "Health Day" in Duluth, which was sponsored by the St. Louis County Medical Society, Dr. Fox discussed, "Common Medical Problems." At a Medical Forum in St. Paul he talked on "The Panel System in Great Britain." "The Health Plan in Great Britain" was his topic at the meeting of the American Society of Dentistry for Children, and he talked at the meeting of the Minneapolis P.T.A. on "The Parent's Responsibility for the Health of the Child."

* * *

Thank You, Elva Lavers

After a full year as Editor of the Bulletin, we have come to appreciate even more than ever the outstanding cooperation and interest in its publication manifested by Miss Elva Lavers and her staff. We regret the many inconveniences we have caused them due to delays, changes, and special tables and graphs. We hasten to assure them, however, that their efforts are not unappreciated. Once again, then, Miss Lavers, many thanks to you and your colleagues.

* * *

Summer Best Wishes

With this issue the "Bulletin of the University of Minnesota Hospitals and Minnesota Medical Foundation" ceases publication until next fall. Once again, we have had a series of papers of real interest and originality. Readership of the Bulletin has continued to increase, and today it is found in a good many medical libraries throughout the nation. The faculty is to be commended for the increasingly high quality of the publication.

To students, faculty, and friends of the Medical School and to all members of the Minnesota Medical Foundation, we extend best wishes for the summer season. We look forward to the relaxing activities of the summer months and beyond that to the resumption of full-scale activities next fall.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

June 15 - 20, 1953

Monday, June 15

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom; Todd Amphitheater, U. H.

12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

4:30 - Public Health Seminar; 15 Owre Hall.

4:30 - 6:00 Physiology 114A and Cancer Biology 140 -- Research Conference on Cancer, Nutrition, and Endocrinology; Drs. Visscher, Bittner, and King; 129 Millard Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Ancker Hospital

8:30 - 10:00 Tuberculosis and Chest Conference; Auditorium.

2:00 - 3:00 Surgery Journal Club; Classroom.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Eldon Berglund; Newborn Nursery, Station C.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Erling Platou; Station K.

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

2:00 - Pediatric Rounds; Robert A. Ulstrom; Stations I and J.

Veterans Administration Hospital

1:30 - Cardiac Rounds; Drs. Ebert and Berman, and Richards.

Tuesday, June 16

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

12:30 - 1:30 Physiology 114D -- Current Literature Seminar; 129 Millard Hall.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

Ancker Hospital

9:00 - 10:00 Medical X-ray Conference; Auditorium.

Minneapolis General Hospital

10:00 - Pediatric Rounds; Spencer F. Brown; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

12:30 - Grand Rounds; Fractures; Willard White, et al; Sta. A.

12:30 - Neuroroentgenology Conference; O. Lipschultz, J. C. Michael and Staff.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:00 - Tumor Clinic; Drs. Eder, Cal, and Lipschultz.

1:00 - Neurology Grand Rounds; J. C. Michael and Staff.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:30 - Infectious Disease Rounds; Drs. Hall and Zinneman.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery-Tumor Conference; L. J. Hay, J. Jorgens; Conference Room, Bldg. I.

1:00 - Review of Pathology, Pulmonary Tuberculosis; Conference Room, Bldg. I.

1:30 - Combined Medical-Surgical Chest Conference; Conference Room, Bldg. I.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

Wednesday, June 17

Medical School and University Hospitals

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U. H.

Wednesday, June 17 (Cont.)

Medical School and University Hospitals (Cont.)

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Surgery Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

12:30 - 1:30 Physiology 114C -- Permeability and Metabolism Seminar; Nathan Lifson; 129 Millard Hall.

1:30 - 3:00 Physiology 114B -- Circulatory and Renal System Problems Seminar; Dr. M. B. Visscher, et al; 214 Millard Hall.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

12:30 - 1:30 Medical Journal Club; Library.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Max Seham; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Seminar; Arnold Anderson; Classroom, Station I.

11:00 - Pediatric Rounds; Erling S. Paltou; Station K.

12:00 - Surgery-Physiology Conference; Dr. Zierold and Dr. E. B. Brown; Classroom.

12:15 - Pediatric Staff Meeting; Classroom, Station I.

1:30 - Visiting Pediatric Staff Case Presentation; Station I, Classroom.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Conference Room; Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker

9:00 - Gastro-Intestinal Rounds; Drs. Wilson, Nesbitt, Zieve, Hay and Goodnow.

12:30 - X-ray Conference; J. Jorgens; Conference Room, Bldg. I.

1:30 - 2:30 Infectious Disease Conference; Wesley W. Spink; Conference Room, Bldg. I.

2:30 - 4:00 Infectious Disease Rounds; Main Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedisc, Conference Room, Bldg. I.

Thursday, June 18

Medical School and University Hospitals

8:00 - 9:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Heart Hospital Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

Thursday, June 18 (Cont.)

Medical School and University Hospitals (Cont.)

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Ancker Hospital

8:00 - 10:00 Medical Grand Rounds; Auditorium.

Minneapolis General Hospital

9:30 - Neurology Rounds; Heinz Bruhl; Station I.

10:00 - Pediatric Rounds; Spencer F. Brown; Station K.

10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. H.

11:30 - 12:30 Clinical Pathological Conference; John I. Coe; Classroom.

1:00 - Fracture - X-ray Conference; Dr. Zierold; Classroom.

1:00 - House Staff Conference; Station I.

2:00 - 4:00 Infectious Disease Rounds; Classroom.

4:00 - 5:00 Infectious Disease Conference; Wesley W. Spink; Classroom.

Veterans Administration Hospital

8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.

1:00 - 3:00 Metabolic Disease Conference; Drs. Flink, Heller, Jacobson, and Bolin.

Friday, June 19

Medical School and University Hospitals

8:00 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:00 Pediatric Grand Rounds; Irvine McQuarrie and Staff; Eustis Amphitheater, U. H.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 1:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Physiology 124 -- Seminar in Neurophysiology; Ernst Gelhorn; 113 Owre Hall.

Friday, June 19 (Cont.)

Medical School and University Hospitals (Cont.)

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Wallace Lueck; Station J.

10:30 - Pediatric Surgery Conference; Oswald Wyatt, Tague Chisholm; Station I, Classroom.

12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

1:15 - X-ray Conference; Oscar Lipschultz; Classroom, Main Bldg.

2:00 - Pediatric Rounds; Robert Ulstrom; Stations I and J.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.

2:00 - Autopsy Conference; E. T. Bell and Donald Gleason; Conference Room, Bldg. I.

Saturday, June 20

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 10:00 Infertility Conference; Louis L. Friedman, David I. Seibel, and Obstetrics Staff; Eustis Amphitheater, U. H.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Urology Staff Conference; T. H. Sweetser; Main Classroom.

11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry, and Staff; Main Classroom

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - 11:15 Hematology Rounds; Drs. Goldish and Bolin, and Howard.

11:15 - 12:00 Morphology . . . . . Dr. Aufderheide; Conference Room.

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