PENICILLIN IN THE TREATMENT OF ESTABLISHED SURGICAL INFECTIONS*

A SYSTEMATIC STUDY OF 744 INCLUDING 82 SEPTICEMIAS

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IN THE FALL OF 1943 when penicillin became available for clinical study, the Committee on Chemotherapy of the National Research Council assigned a limited quantity to several of the units which had been studying the prevention of infection in civilian accidental wounds and burns under the direction of the Subcommittee on Surgical Infections. These units then undertook to observe the effect of penicillin in the treatment of established surgical infections. These cases were reported to Doctor Keefer and they have been included in the all-inclusive reports which he has made from time to time, but the Subcommittee on Surgical Infections believed that it would be profitable to study the surgical cases separately, going into the details of the cases and recording in a systematic manner the circumstances of each case with the hope that a review and analysis of a fairly large number, might determine what circumstances contributed toward and what circumstances interfered with, a favorable outcome. It was thought that this might logically lead to methods of treatment which would improve the results by increasing the favorable circumstances and eliminating the unfavorable factors.

With the advice and council of Drs. Lowell Reed and John Fertig, Chairman and member, respectively, of the Subcommittee on Biostatistics of the National Research Council, the Subcommittee on Surgical Infections devised a summary sheet on which the items were listed which, it was thought, might play an important rôle in determining the outcome of the treatment. A copy of the summary sheet is enclosed with this report. The chief items have to do with the diagnosis of the surgical infection, its duration and its seriousness before instituting penicillin treatment, the nature of the previous surgical and drug therapy, the dosage and duration of penicillin and the method of its administration, the nature of associated medical or surgical treatments, the clinical symptoms and signs of infection and their persistence or disappearance, and the bacteriologic analyses before and after penicillin treatment. Finally, a well-considered judgment regarding the value of penicillin, in view of the previously noted factors, was recorded in each individual case.

The Committee recognized that there is often a great deal of difficulty in estimating the rôle played by any drug when it is used in conjunction with a surgical procedure, for a condition which in times past may have

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responded satisfactorily to the surgical procedure alone. Surgical infections differ from medical infections in certain fundamental respects which make them less likely to respond to drug treatment. These differences have been described in detail in a number of recent publications but they may be profitably enumerated here because they must be considered in the appraisal of penicillin or of any other drug. Surgical infections are characterized by (1) a local spontaneous or traumatic breakdown of tissue or a localized exudation of leukocytes either into a body cavity, such as a joint or the pleura, or into the substance of solid tissues or organs, such as muscle or liver. This broken down tissue or cellular exudation must either be evacuated or absorbed before health is restored. (2) The blood vessels in the wall of an abscess are thrombosed and any medication coming *via* the blood stream may have difficulty penetrating or diffusing into the focus far enough to reach the offending organisms. (3) At the same time, in a well-localized lesion, the opportunity is afforded for the local application of the drug in question. (4) The bacterial species in surgical infections are often multiple and there may be a synergistic action between them. One or more of the species in any given infection may be either resistant to the bacteriostatic action of the drug or antagonistic to it. (5) When surgical infections are under control there is always the necessity for removal of the débris and repair of the tissue which may require more nutritive elements than are needed for the recovery from a medical infection. (6) Spontaneous surgical infections in contradistinction to those following injury are in the very beginning, before there has been any breakdown of tissue, similar to medical infections, in other words, there is a diffuse inflammation which may be called a cellulitis. Some surgical infections remain in the stage of cellulitis for several days and the tissue breakdown is slow. In others it is rapid. If drugs can be given before there is a breakdown of tissue it is reasonable to believe that they do not meet with the difficulties mentioned above but have a more favorable opportunity to contact and control any susceptible organisms.

The Subcommittee also realized that the complexity of a surgical infection made it almost impossible to run concurrently, a series of controls without any drug treatment or with some other form of drug treatment, the number of factors in any given case being so great, the time factor alone (duration of the infection before treatment) being infinitely variable. Surgical infections may be acute or chronic and there is no sharp line between them. The committee arbitrarily chose 30 days as the dividing line. Among the chronic cases there are those which go on for months or years without much change and those with acute exacerbation so that they must be classified as both acute and chronic. This is particularly true in cases of osteomyelitis. During the course of any chronic infection there may have been any number of operations as well as numerous local and general forms of medication — no two cases being alike. It is, therefore, impossible to obtain for study two parallel series, either by a process of alternating all cases or

by selecting two similar cases and assigning one to the treated series and the other to the control series.

In such circumstances the Subcommittee felt that it would be necessary to let certain chronic and subacute cases, in their previous course, be their own controls. In other cases it would be necessary to show some results in the drug-treated patients not seen in previous surgical experience when the drug under study was not available. For example, when an infection remains for days or weeks or months *in statu quo* or goes progressively down hill and then shows an abrupt improvement following the administration of a drug, it is reasonable to believe that the drug was responsible for the change. If this happens, not once, but many times it becomes more and more convincing. In the category of results not previously seen, we may list: (1) Those cases of surgical infection, formerly always requiring a surgical procedure, in which that procedure was completely obviated. (2) Those cases in which a limited surgical procedure with the aid of drug sufficed to effect a cure when formerly, without drug, a radical procedure would have been necessary. (3) Those cases requiring a surgical procedure but in which the healing time was definitely shortened by the use of drug. (4) Those cases permitting primary closure after incision or excision concurrently with the administration of drug and (5) those cases permitting an earlier successful secondary closure with drug than could have been obtained without drug.

In any group of surgeons there might be a difference of opinion regarding the classification of cases in any of these five categories. For example, in a case of cellulitis one might say that surgery was obviated, while another might say that he had seen similar cases which subsided spontaneously. Probably there would be more unanimity of opinion with reference to a condition such as acute suppurative arthritis which formerly almost invariably required incision and drainage to effect a cure and a return to normal function. There might be the greatest difference of opinion about cases in the third category, that of the shortening of healing time because no one can tell how long any given case will take to recover. One can estimate the healing time of a carbuncle following incision or excision but in both drug-treated and non drug-treated carbuncles there must be a separation of the tissue already destroyed when treatment began. This tends to equalize the healing time for cases in the two groups. The value of the drug treatment can sometimes be more clearly indicated by the disappearance of the causative organisms from the culture during the course of therapy, for in non drug-treated cases the cultures are almost invariably positive until the wound is healed.

Primary closure of a wound which has been made for the drainage of a purulent exudate was rarely successful before the advent of drugs. If that can now be done repeatedly with the aid of a drug, we may be fairly certain of the drug's efficiency. Secondary closure was not infrequently successful in World War I after a wound had been cleared of its slough and had been covered with healthy granulations. If with the aid of drug now there can be a strikingly higher percentage of successful wound healing or if sec-

ondary closure can be done earlier than formerly, the drug must be given credit for its share in the successful result. This is probably the most difficult criterion to weigh and measure accurately, in any particular case.

Bearing all of these things in mind, it is obvious that it may be difficult to appraise the value of a drug in any given case. However the Subcommittee felt that some approach to a satisfactory estimate could be made with regard to penicillin if the results could be classified as follows:

1. *Excellent* in cases responding abruptly or definitely within the first 72 hours after treatment began.
2. *Good* in cases clearly showing the benefit of the drug but over a longer period of time, perhaps a week or ten days.
3. *Questionable* in cases which might have done just as well without the drug as a result of the surgical procedure or some other associated treatment.
4. *No effect* in cases in which the infection was not altered in any way but ran its usual course.

These criteria were followed in the cases herewith presented. The largest single group of cases were observed by the author, and his associates, Dr. Harold Harvey and Dr. Robert H. E. Elliott at the Presbyterian Hospital in New York City. The next largest group were studied at the Pennsylvania University Hospital in Philadelphia by Dr. John Lockwood, Dr. Jonathan Rhoads and Dr. William White. The third largest group was cared for by Dr. William Altemeier at the Cincinnati General Hospital. The rest of the cases in smaller groups were treated in Detroit Receiving Hospital by Dr. John Hirshfeld, and his associates, at the Henry Ford Hospital by Drs. McClure and Lam and at the Charity Hospital by Drs. Ochsner and Caldwell, and their staffs. It has not seemed profitable to divide the cases into groups according to the units studying the problem. It may be assumed that they were treated in a similar manner and the summary sheets make certain that the factors associated with the case were recorded in a uniform manner. These data have been transferred to the McBee System punch cards for the purpose of analysis and the results of the study are given below.

There were approximately 1,000 cases of established surgical infections treated in all of the units put together. Approximately one-quarter of these cases were treated with various forms of sulfonamide or with zinc peroxide or some other antibacterial agent, but the treatment was too diversified to warrant analysis. This presentation will be limited to the cases which were treated with penicillin of which there were 744 with data sufficiently complete to yield a satisfactory analysis. These cover a wide variety of surgical diagnoses.

The accompanying tables give a list of the surgical lesions represented by five or more cases. The results are given in percentages in the four categories of "Excellent," "Good," "Questionable," and "No Effect." The first two may be considered favorable and the last two unfavorable. In the

Questionable group there may be cases in which the penicillin played a favorable rôle but it was not apparent to the observers and so we cannot score them to the credit of the drug.

It will be seen in Table I, giving the results for the series as a whole, that penicillin is of benefit in surgical infections and yet it is not a panacea. In about 15 per cent of the cases the response could be called dramatic or excellent, in 50 per cent definite or good, in 18 per cent doubtful or questionable, while in 18 per cent no effect could be demonstrated. It is necessary to study the cases carefully from many angles to determine what the conditions are for its success and why it often fails.

When the cases are divided into diagnostic groups it is seen that the results in some are very good, in others, intermediate and in others, poor.

TABLE I

SHOWING THE OVER-ALL RESULTS OF PENICILLIN TREATMENT IN SURGICAL INFECTIONS

	Results in Percentage					
	Favorable			Unfavorable		
Total Number of Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
744	14.8	49.9	64.7	17.8	17.6	35.4

TABLE Ia

SHOWING THE MOST FAVORABLE RESULTS OF PENICILLIN TREATMENT ACCORDING TO DIAGNOSIS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Furuncle	26	53.9	38.4	92.3	7.7	0	7.7
Cellulitis	36	64.0	27.7	91.7	8.3	0	8.3
Mastoiditis	6	0	83.3	83.3	0	16.7	16.7
Carbuncle	28	39.3	42.9	82.2	14.3	3.6	17.9
Suppurative arthritis	22	18.2	63.5	81.8	4.5	13.6	18.1
Lung abscess	11	0	81.7	81.7	0	18.3	18.3
Superficial abscess	32	25.0	56.3	81.3	6.3	12.5	18.8
Brain abscess	5	0	80.0	80.0	0	20.0	20.0
Osteomyelitis	153	8.5	68.0	76.5	13.7	9.8	23.5

These are shown in Tables Ia, and Ib and Ic. Table Ia indicates that the best scores in the favorable columns were obtained by furuncles, cellulitis, mastoiditis, carbuncles, suppurative arthritis, lung abscess, superficial abscess, brain abscess and osteomyelitis, in that order, all of these lesions responding favorably in more than 75 per cent of the cases. The most brilliant results were obtained in the cases with cellulitis or furuncles and it is of interest that these two diagnoses are the only ones with zero in the "no effect" column.

The intermediate group shown in Table Ib includes deep abscess, thrombophlebitis, sinusitis, infected soft-part wounds, infected operative wounds, otitis media, infected compound fracture and ulcers of the skin. Favorable results were obtained in from 50 per cent to 75 per cent of these cases.

The poorest results, revealed in Table Ic, were obtained in empyema, burns, gas gangrene, actinomycosis, gangrene of the skin, miscellaneous surgical infections, postoperative pneumonia, peritoneal abscess, and, worst of all, diffuse peritonitis.

TABLE Ib

SHOWING THE INTERMEDIATE RESULTS OF PENICILLIN TREATMENT ACCORDING TO DIAGNOSIS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Deep abscess	58	15.5	53.4	68.9	22.4	8.6	31.0
Thrombophlebitis	12	8.3	58.4	66.7	16.7	16.7	33.3
Sinusitis	6	0	66.7	66.7	0	33.3	33.3
Infected soft-part wound	37	13.5	51.3	64.8	21.6	13.5	35.1
Infected operative wound	70	5.7	55.6	61.3	21.4	17.2	38.6
Otitis media	7	28.6	28.6	57.2	14.3	28.6	42.9
Infected compound fracture	9	0	55.6	55.6	11.1	33.3	44.4
Ulcer of the skin	22	0	50.0	50.0	18.2	31.6	50.0

TABLE Ic

SHOWING THE LEAST FAVORABLE RESULTS OF PENICILLIN TREATMENT ACCORDING TO DIAGNOSIS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Empyema	34	0	47.0	47.0	26.5	26.5	53.0
Infected burn	31	3.2	42.0	45.2	29.0	25.8	54.8
Gas gangrene	9	11.1	33.3	44.4	33.3	22.2	55.5
Actinomycosis	7	0	42.9	42.9	28.6	28.6	57.2
Gangrene of skin	10	10.0	30.0	40.0	50.0	10.0	60.0
Miscellaneous	66	13.6	25.8	39.4	16.7	43.9	60.6
Postop. pneumonia	18	11.1	27.8	38.9	38.9	22.2	61.1
Peritoneal abscess	11	9.1	27.3	36.4	45.5	18.2	63.7
Diffuse peritonitis	18	5.5	22.2	27.7	22.2	50.0	72.2

All of these groups must be broken down in order to determine if possible why some cases succeeded and some failed, but first it would seem profitable to present the other factors which may play a rôle in the favorable outcome. It is generally believed that penicillin is more effective in acute than in chronic infections. Our cases may be divided into acute, chronic, with acute exacerbation, and chronic, without flare-up. The results are shown in Table II and they bear out the general impression but the difference is not as great as one would suppose. The chief difference is not in the combined figures for favorable results but in the figures for a prompt response in the "excellent" column. This clearly indicates that a larger pro-

portion of the acute cases respond dramatically to penicillin. Furthermore, the chronic cases with an acute exacerbation seem to give better results than those which smolder along without much change. However, other factors come into play in these two groups (particularly the nature and time of a surgical procedure) so that the over-all figure should not be given too great weight because these groups are not really comparable.

TABLE II

SHOWING THE RESULTS ACCORDING TO THE ACUTENESS OF THE PROCESS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Acute	477	20.1	46.6	66.7	17.4	16.0	33.4
Chronic, with acute flare	49	8.2	63.3	71.5	14.3	14.3	28.6
Chronic, without acute flare	218	4.6	54.1	58.7	19.3	22.0	41.3

TABLE III

SHOWING THE RESULTS IN THE ACUTE CASES ACCORDING TO THE DURATION OF SYMPTOMS BEFORE INITIATING TREATMENT

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Four days or less	145	26.9	43.4	70.3	14.5	15.2	29.7
Five days or more	319	17.9	47.6	65.5	19.1	15.4	34.5

In the acute cases the duration of the infection before the initiation of treatment bears an important relationship to the favorable outcome as is shown in Table III. In the chronic cases other factors are of more importance.

Of these cases, 662 were considered serious infections and 82 trivial. Favorable results were obtained in 64.9 per cent of the serious and in 88.6 per cent of the trivial cases. Of 384 cases which had received some form of sulfonamide prior to penicillin treatment, 65.4 per cent showed a favorable response. One would have expected that the cases which had failed to respond to the sulfonamides or to other drugs would have responded less readily to penicillin but such is not the case. It is of interest that such a large number failed to respond to the sulfonamides. However, we have no indication that during that treatment they developed any increased resistance to penicillin. This is shown in Table IV.

In 393 cases the lesion was closed, and in 351 it was open when treatment began. Favorable results were obtained in 67.4 per cent of the former and in 61.5 per cent of the latter, not a significant difference.

The relationship between penicillin and surgery in the treatment of these cases is revealed in Table V. It may be surprising to note that so many

cases (258) had no primary surgical procedure while under treatment in this study. Some of these were chronic infections and in the others, surgery was obviated by the use of the drug. In this first group, it is seen that there is a high incidence of excellent results and a sum total of favorable results somewhat better than the average. In the second group penicillin was tried first but did not suffice to control the infection and an operation was later resorted to. The results of the penicillin therapy were considered poor but this is a small group and, therefore, of less significance than the others. In the third group surgery was performed at the same time that

TABLE IV

SHOWING THE RESULTS OF PENICILLIN IN RELATIONSHIP TO PREVIOUS FORMS OF TREATMENT OF SURGICAL INFECTION

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
No previous treatment	259	20.1	44.8	64.9	17.8	17.4	35.2
Sulfonamides only	338	11.8	54.7	66.5	15.7	17.8	32.5
Other drugs only	39	25.6	41.0	66.6	20.5	12.8	33.3
Sulf. and other drugs	46	13.0	43.5	56.5	19.6	23.9	43.5

TABLE V

SHOWING THE RESULTS IN THE CASES WITHOUT SURGERY AND WHEN PENICILLIN PRECEDED, ACCOMPANIED, OR FOLLOWED AFTER A SURGICAL PROCEDURE

		Results in Percentage					
		Favorable			Unfavorable		
Time Relationship of Penicillin Administration to the Surgical Procedure	Total Number of Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
No surgery	258	22.8	43.8	66.6	14.7	18.6	33.3
Pen. before surgery	33	9.1	30.3	39.4	21.2	39.4	60.6
Pen. with surgery	230	11.3	59.6	70.9	18.7	10.4	29.1
Pen. after surgery	223	9.9	49.8	59.7	19.7	20.6	40.3

penicillin was started and the best results are found in this category. In the last group the penicillin treatment was initiated after the surgery had been done. These groups are not of course strictly comparable. The chief lesson to be learned from the table is that in many cases of surgical infection, surgery may be obviated by penicillin while in others a surgical procedure is required to effect a cure.

The cases have also been divided into three groups according to the method of penicillin administration. The results are shown in Table VI. These three groups are of course not comparable but the table emphasizes the fact that a large proportion of surgical infections may be controlled by the local application of penicillin which represents a very economical method of using the drug.

The question of dosage is an important and a troublesome one. In the

TABLE VI

SHOWING THE RESULTS IN THE THREE GROUPS REPRESENTING THE LOCAL, GENERAL, AND COMBINED METHOD OF GIVING PENICILLIN

Method of Penicillin Administration	Total Number of Cases	Results in Percentage					
		Favorable			Unfavorable		
		Excellent	Good	Combined	Questionable	No Effect	Combined
General, without local	438	16.7	44.7	61.4	20.0	18.5	38.5
Local, without general	142	16.2	54.2	70.4	15.5	14.1	29.6
Both general and local	164	8.5	59.8	68.3	13.4	18.3	31.7

early months of this study the supply of penicillin was greatly limited, the daily dosage was small and it was often stopped as soon as the infection seemed to be under control. Many of these cases had a recurrence of the activity of the infection and required a renewal of treatment. As time went on, more penicillin became available, larger initial doses were given and treatment was prolonged. In many cases large doses were given in conditions where previous experience had shown that small doses would not suffice, or the doses were doubled and doubled again when there was no response to the initial treatment. When a therapeutic agent of low toxicity is available, as with penicillin, the doctor is tempted to use large doses with

TABLE VII

SHOWING THE FAVORABLE RESULTS IN THE CASES ONLY TREATED SYSTEMICALLY, GROUPED ACCORDING TO THE TOTAL AMOUNT OF SYSTEMIC PENICILLIN EMPLOYED

Total Systemic Dosage	Total Number of Cases	Results in Percentage Favorable	
		Excellent	Good
Less than 500,000 units	118	30.5	31.4
500,000 to 1 million	101	18.8	43.6
1 to 2 million	129	12.4	52.7
Over 2 million	90	2.2	52.3

TABLE VIII

SHOWING THE FAVORABLE RESULTS IN THE CASES ONLY TREATED LOCALLY, GROUPED ACCORDING TO THE TOTAL AMOUNT OF LOCAL PENICILLIN EMPLOYED

Total Local Dosage*	Total Number of Cases	Results in Percentage Favorable	
		Excellent	Good
Less than 10,000 units	37	38.0	54.0
10,000 to 50,000 units	40	15.0	55.0
Over 50,000 units	62	4.8	53.3

* Three cases, exact dosage not recorded.

the idea of having a wide margin above the therapeutic level. Any compilation of dosage figures then, may seem to indicate that the worst results are obtained with the largest doses. A prompt response to an initial dose on the other hand, would permit an early cessation of treatment. Thus, the best results might be associated with the smallest total dosage. Certain

of these points are brought out in Tables VII and VIII. It is noted in Table VII that the excellent or prompt response of systemic treatment decreases as the total dose increases while the good results are in the reverse order. Furthermore, the total favorable results decline sharply over the two million mark.

In Table VIII covering the local treatment, one sees that the same decline in "excellent" responses as the total dosage increases while the "good" responses remain stationary. It is of interest that so many cases responded favorably to simple local treatment with relatively small doses given over a short space of time. This group contains, of course, most of the trivial cases and those in which the infection was well-localized.

Have we any criteria upon which we can base the determination of the necessary or adequate dosage for any given case? It is certainly an individual matter. An "adequate" dose is one that will control the infection and get the patient well. The requirements in any given case depend upon the number and susceptibility of the organisms, the extent and penetrability of the local process, the rapidity of absorption and excretion of the drug and the dosage. An "adequate" dose may range all the way from a few thousand to several million units. The experience of the men working in these study units has indicated that a starting dose of 10,000 units every three hours intramuscularly will be adequate in the average case. The intravenous administration is generally not as acceptable to the patient, is harder to administer from a nursing standpoint and results in more rapid elimination of the drug. In a very sick case a large initial dose of 100,000 units may be given, continuing with 20,000 units every two or three hours. With a plentiful supply of the drug and with the danger of developing resistant strains of organisms by inadequate dosage, so feared by Fleming, it would appear reasonable to start routinely with 20,000 units every three hours and double it once if there is no response in 48 hours. There is very little evidence that larger doses will be any more effective than 320,000 units a day in surgical infections. A single daily dose in oil or wax does not give reliable or consistent blood levels.

If there is a response to the initial dosage which clearly indicates the efficacy of the drug it should be continued at that level until one is certain that the infection has subsided with a margin of safety of five to seven days for systemic treatment or two to three days for local treatment. In certain cases with open wounds or ulcers it may be advisable to continue treatment until the wound has healed or is covered by skin grafts or closed by secondary suture.

The most significant features of the study are revealed when we come to the bacteriologic analysis of the flora of the purulent exudates produced in these established surgical infections. In acute infections it is found that the lesions are usually produced by one species of organism but in chronic infections there is often a mixture of organisms, some causative and other "fellow travelers" which have come into the picture as secondary con-

taminants. In this study it was, therefore, necessary to be prepared to recognize and classify any organism both aerobic and anaerobic, pathogenic or nonpathogenic which might be encountered. It was obvious that if the analyses were to be complete, the classification would have to be carried to species recognition. But for purposes of recording, many of the individual species could be put in larger groups. A code sheet was therefore devised and employed so that the results of the study could be adapted to the punch card system for statistical analysis. A copy of this code sheet for bacterial classification is attached to this report. For purposes of final tabulation this classification has been still further condensed into the following significant groups:

1. The hemolytic streptococci.
2. The coagulase-positive staphylococci.
3. The gram-negative aerobic nonspore-forming rods (including *E. coli, A. aerogenes, Ps. pyocyaneus* and *B. proteus*).
4. *Clostridium welchii.*
5. All other gram-negative aerobic nonspore-forming rods.
6. Micrococci, coagulase test not done.
7. Nonhemolytic streptococci (including the green and indifferent types).
8. All other aerobic cocci.
9. Anaerobic and micro-aerophilic cocci.
10. Aerobic gram-positive rods including the large *B. subtilis* and diphtheroid groups.
11. All other aerobic and anaerobic rods.

In one of the units the hemolytic streptococci were grouped according to the Lancefield classification. Most of the strains fell into Group A, confirming the fact that this is the group of human pathogenicity but a number of strains in other groups clearly demonstrated their activity both in pure and mixed cultures. However, a number of the strains were not grouped and for purposes of this report we have, therefore, put them all together. All of the units have confirmed the importance of the coagulase test as an indication of the pathogenicity of the staphylococci but, again, exceptions were found to this rule. This is more important than hemolysis or the finer classification into *albus, aureus* and *aurantiacus* although most of the pathogenic strains were hemolytic and pigmented.

In any case, it is fair to assume that if any organism is found in pure culture in a purulent exudate that that organism is pathogenic and is the cause of the infection. If it is found in a mixture, it may be pathogenic or nonpathogenic, and it may or may not be taking part in the infection. In evaluating the effect of penicillin on these organisms it is necessary not only to put them to the test in the laboratory to demonstrate whether they are susceptible, indifferent or antagonistic to penicillin, but to note whether they were found in pure or mixed culture in the lesion and whether under treatment they persisted into the second or third week of treatment and whether the infection in which they were found responded favorably or unfavorably to the treatment.

Table IX gives the results for the four principal bacterial groups and it is to be seen at once that all of these groups were found more often in bacterial mixtures than in pure culture, the hemolytic streptococci five times as often, the staphylococci twice as often, the gram-negative rods 19 times as often, while the *Cl. welchii* was found alone only once out of 29 times. The table also shows that the favorable response to treatment occurred much

TABLE IX

SHOWING THE RESULTS OF PENICILLIN TREATMENT ACCORDING TO THE PRINCIPAL BACTERIOLOGIC AGENTS ACTIVE IN SURGICAL INFECTIONS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Hemolytic Streptococcus:							
Pure	16	12.5	56.2	68.7	12.5	18.8	31.3
Mixed	85	12.9	49.4	62.3	21.2	16.5	37.7
Coagulase-positive Staphylococcus:							
Pure	47	25.6	61.7	87.3	10.6	2.1	12.7
Mixed	98	10.2	55.2	65.4	23.4	11.2	34.6
4 Principal gram-neg. rods:							
Pure	5	0	40.0	40.0	40.0	20.0	60.0
Mixed	95	1.1	49.5	50.6	25.2	24.2	49.4
Cl. welchii:							
Pure	1	0	100.0	100.0	0	0	0
Mixed	28	7.1	35.7	42.8	32.2	25.0	57.2

more often when the gram-positive organisms were pure than when they were in mixed culture.

The highest percentage of favorable results are found in the pure staphylococcal infections, and this is perhaps the high point of the study which demonstrates that the organism against which Fleming first demonstrated the activity of penicillin is the one which produces the diseases which respond clinically most satisfactorily to treatment with that drug.

Among the gram-negative rods the results in the few cases in which they were found in pure culture, were generally unfavorable. It is not clear why two of these cases gave a good response. There may have been other factors at work in these cases, such as the operative procedure or, by chance, these organisms of relatively low pathogenicity may have been inhibited by the doses of penicillin employed. In the bacterial mixtures containing these organisms they may have been relatively unimportant and in these cases at least not capable of real antagonism against the penicillin which was credited with definite benefit. In the single case in which the *Cl. welchii* was found in pure culture, the result was listed as good but in all of the other cases where it was found in mixed cultures, the response was generally bad. This is a confirmation of the results obtained with cases of gas gangrene in the army. While in experimental animals, penicillin was found to be effective against pure cultures of the gas gangrene organisms, in war wounds, so highly contaminated by bacterial mixtures including gram-negative aerobic

rods, did not do as well as had been expected or hoped for. It is probable that the good results occurred in those cases in which there were no organisms capable of producing penicillinase.

With organisms in the other more or less heterogenous groups, shown in Tables X and XI, the results are not striking. In general, aerobic cocci in pure culture are susceptible while the anaerobic cocci and rods are gener-

TABLE X

SHOWING THE RESULTS OF PENICILLIN TREATMENT IN THE PRESENCE OF ORGANISMS OF LESS IMPORTANCE IN SURGICAL INFECTIONS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Other gram-neg. aerobic rods:							
Pure	1	100.0	0	100.0	0	0	0
Mixed	29	0	37.9	37.9	37.9	24.5	62.0
Nonhemolytic strept.:							
Pure	10	0	70.0	70.0	30.0	0	30.0
Mixed	109	8.3	43.1	51.4	28.4	20.2	48.6
Gram.-pos. aerobic bacilli:							
Pure	1	0	0	0	0	100.0	100.0
Mixed	102	8.8	56.9	65.8	19.6	14.7	34.3
Staph. coag. test not done:							
Pure	79	30.4	39.3	69.7	12.6	17.7	30.3
Mixed	80	11.2	40.0	51.2	25.0	23.8	48.8

TABLE XI

SHOWING THE RESULTS OF PENICILLIN TREATMENT IN THE PRESENCE OF ORGANISMS OF LESS IMPORTANCE IN SURGICAL INFECTIONS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
All anaerobic and micro-aerophilic cocci:							
Pure	2	0	50.0	50.0	50.0	0	50.0
Mixed	54	7.4	50.0	57.4	24.1	18.5	42.6
All other aerobic cocci:							
Pure	18	5.6	61.0	66.6	5.6	27.8	33.4
Mixed	62	4.8	48.4	53.2	30.6	16.2	46.8
All other aerobic and anaerobic rods:							
Pure	2	0	0	0	50.0	50.0	100.0
Mixed	29	0	41.4	41.4	20.7	37.9	58.6
No Cultures:							
Favorable group	37	46.0	37.8	83.8	5.4	10.8	16.2
Intermediate group	16	6.3	68.5	74.8	18.7	12.5	31.2
Unfavorable group	23	4.4	26.1	30.5	30.5	39.1	69.6

ally resistant to penicillin and do not respond, but there are often exceptions to this rule.

In 70 cases no cultures were taken before the administration of penicillin. The great majority of those patients presented early infections in the

stage of cellulitis and there was no opportunity to find out what organism was at fault. If these cases are divided up into three groups according to diagnosis to correspond with the series as a whole, as represented in Tables Ia, Ib and Ic, we find that the results run fairly parallel, so that we may assume that the causative organisms in these cases were roughly similar to those in the whole group, but of this we cannot be certain.

A review of the individual records of the cases in which penicillin was reported to have "no effect" permitted a listing of factors which seemed to be responsible for the failure. These are shown in Table XII. Of the 131 cases in this category, 58 were either infected or contaminated with or-

TABLE XII

GIVING A LIST OF PROBABLE CAUSES OF FAILURE OF THE 131 CASES IN WHICH PENICILLIN HAD NO EFFECT

1. The presence in mixed culture of organisms capable of producing penicillinase			58
Including:			
E. coli	22	*Aerobacter aerogenes*	8
Ps. pyocyanea	18	*Coli* intermediates	3
B. subtilis	18	Other gram-negative aerobic rods	5
B. proteus	15		
2. Tuberculosis			6
3. Tetanus			6
4. Penicillin-resistant staphylococcus			5
5. Penicillin-resistant streptococcus			2
6. Synergism (?) of hemolytic strept. and staph			9
7. Patient *in extremis* on admission			11
8. Too little			9
9. Too late			7
10. Too conservative surgery			9
11. Diabetes and arteriosclerosis			7
12. Metastatic brain abscess, hemiplegia or meningitis			5

ganisms which potentially are producers of penicillinase. In many instances the production of penicillinase was demonstrated in the laboratory. Other causes of failure were the presence and activity or organisms not susceptible to penicillin such as tuberculosis, resistant staphylococci and resistant streptococci. Such overwhelming infections like tetanus and metastatic brain abscess, with hemiplegia or meningitis, often killed the patient before the benefit from penicillin could be appreciated. Diabetes and arteriosclerosis seemed to play a rôle by diminishing the blood supply to the infected part. This prevented the entrance of the penicillin into the focus of bacterial activity as well as the nutritive elements necessary for repair. In some cases too conservative surgery which left behind necrotic bone or other tissue handicapped the effective use of penicillin. In a number of cases penicillin was given in desperation when the patient was *in extremis,* and in a few other cases it could be rightly said that it was given "too little and too late." In a small number of cases there was no obvious cause for failure, nine of these yielded on culture a mixture of *hemolytic Streptococcus* and *hemolytic Staphylococcus aureus.* There may be a synergistic action of these two organisms which is difficult for penicillin to combat.

There were 82 cases in the series with septicemia, eight of these had

more than one organism in the blood stream. These cases have been listed according to the diagnosis of the associated surgical lesion and also according to the bacteriology in Tables XIII and XIV. It is seen that good results were obtained in acute osteomyelitis, suppurative arthritis, cellulitis, a furuncle with pneumonia, a carbuncle and a case of rat bite fever. The *hemolytic Streptococcus* had the best score among the bacteria, with 87.5 per cent good results. The *Staphylococcus aureus* yielded a favorable response in 69 per cent. Before the arrival of the sulfonamides the mortality of *hemolytic Streptococcus* septicemia was in the neighborhood of 50 per cent and of staphylococcus septicemia 80 per cent. We have, therefore, come a long way in protection against blood stream infection with these organisms but

TABLE XIII

SHOWING THE RESULTS OF PENICILLIN THERAPY ACCORDING TO THE ASSOCIATED SURGICAL CONDITION IN THE 82 SEPTICEMIA CASES

	Total Cases	Excellent	Good	Questionable	No Effect
Acute osteomyelitis	21	6	12	1	2
Chronic osteomyelitis	6	0	3	0	3
Suppurative arthritis	6	2	4	0	0
Cellulitis	4	3	1	0	0
Operative wound infection	5	2	2	0	1
Otitis media	2	1	1	0	0
Thrombophlebitis	2	1	1	0	0
Infected rat bite	1	1	0	0	0
Infected burn	4	0	2	0	2
Furuncles and pneumonia	1	0	1	0	0
Carbuncle	1	0	1	0	0
Empyema	3	0	2	0	1
Deep abscess	5	0	2	0	3
Endocarditis	4	0	0	0	4
Peritonitis and perit. abscess	4	0	0	2	2
Miscellaneous	13	1	1	3	8
	82	17	33	6	26

TABLE XIV

SHOWING THE RESULTS OF PENICILLIN THERAPY ACCORDING TO THE BACTERIOLOGY IN THE SEPTICEMIA CASES

	Total Cases	Excellent	Good	Questionable	No Effect
Hemolytic streptococcus	8	2	5	0	1
Staphylococcus aureus	45	11	20	2	12
Staphylococcus albus	6	1	2	0	3
Micrococcus varians	1	0	1	0	0
Nonhemolytic streptococcus	6	0	3	0	3
Anaerobic streptococcus	2	0	0	1	1
Pneumococcus III	1	0	1	0	0
Pneumococcus IV	1	0	0	1	0
E. coli	1	0	0	0	1
B. proteus	1	0	0	1	0
Streptobacillus moniliformis	1	1	0	0	0
Unidentified gram-neg. bacillus	1	0	0	0	1
Staph. aureus and nonhem. strept.	5	1	1	0	3
Staph. albus and nonhem. strept.	1	1	0	0	0
E. coli and *B. proteus*	1	0	0	1	0
E. coli, B. proteus, A. aerogenes, B. subtilis and *Staph. aureus*	1	0	0	0	1
	82	17	33	6	26

our defense is not yet perfect, and when the staphylococcus gets established on the heart valves it is still impossible in most cases to eradicate it. There were no cases, in this series, of recovery after endocarditis had become clinically recognizable.

SUMMARY

The results may be summarized as follows:

1. Penicillin is effective in controlling the disease either alone or as an aid to surgery in about two-thirds of the general run of established surgical infections.

2. It is most effective in cases of furuncle, cellulitis, mastoiditis, carbuncle, suppurative arthritis, lung abscess, superficial abscess, brain abscess, and osteomyelitis.

3. It is moderately successful in cases of deep abscess, thrombophlebitis, sinusitis, infected soft-part wound, infected operative wound, otitis media, infected compound fracture and ulcer of the skin.

4. It is not so successful in cases of empyema, infected burns, gas gangrene, actinomycosis, gangrene of skin, miscellaneous surgical infections, postoperative pneumonia, peritoneal abscess and diffuse peritonitis.

5. It is more successful in the treatment of acute than of chronic infections and if given early rather than late in the course of the disease.

6. It is often effective when the sulfonamides have failed to control the infection.

7. Many cases of well-localized surgical infection can be successfully treated with local injection of penicillin solution or local application of penicillin in ointment form.

8. "Adequate dosage" (which is defined as that necessary to control the infection) may vary from a few thousand to several million units.

9. Surgical infections are frequently caused by mixtures of organisms.

10. Penicillin is not as successful in mixed infections as in those caused by a pure culture of a susceptible organism.

11. Surgical infections caused by a pure culture of a coagulase-positive staphylococcus yield the best results, responding favorably to penicillin in the great majority of cases.

12. The *Clostridium welchii* (the common bacillus of gas gangrene) is so often found in a mixed culture with other intestinal organisms that clinical cases of gas gangrene often fail to respond to penicillin.

13. An analysis of the cases in which penicillin had no appreciable effect reveals the fact that in a large proportion of the cases, the cultures showed organisms capable of producing penicillinase.

14. Other important causes of failure were:

    a. Resistant strains of staphylococci or streptococci.

    b. Too little or too late administration of penicillin.

    c. Associated tuberculosis or diabetes with arteriosclerosis.

    d. Too conservative surgery.

15. In the septicemia cases, the results were better in those due to the hemolytic streptococcus than in those due to the staphylococcus, probably due to the fact that in the latter type the infection more quickly produces deep metastatic abscesses and vegetations on the heart valves.

Four points warrant special emphasis:

1. Penicillin is a very valuable adjunct to surgery in the treatment of surgical infections and in many instances it can obviate surgery, but it is not a panacea.

2. Penicillin is effective when applied locally to well-localized surgical infections if the organisms are susceptible and not antagonistic.

3. "Adequate dosage" is the amount which will bring the infection under control and get the patient well, and it cannot be determined in any given case before the beginning of treatment.

4. A careful and complete bacteriologic analysis is essential to obtain the best results.

COMMENT.—If the bacteriologic analysis of the surgical infection reveals the presence of organisms which are antagonistic to penicillin, some measure will have to be found to offset their action or else the penicillin will not be permitted to inhibit the associated more important organisms. Fortunately, most of the penicillinase producers are relatively nonpathogenic and are not invasive, so that local application of agents which have been found to interfere with their action, may be sufficient to permit the penicillin to function at the site of the infection, whether it is given systemically or locally. It has been found, in these study units, that parachlorophenol in a dosage of .25 of 1 per cent, 9-aminoacridine in a concentration of 1:1000, 5-nitro-2-furaldehyde-semicarbazone in a dilution of 1:1000 and streptothrycin and streptomycin in a concentration of 500-5,000 units per cc. may be successfully employed.

If the resistant or antagonistic organisms are invasive, some agent must be found which will perform this function when used systemically. At present, streptomycin is the only one that we know of that can be used systemically, and is just beginning to be available. There is some hope that new antibiotics will be found which will not have the handicap of inactivation by associated resistant organisms.

Bacitracin, which was discovered in the author's laboratory and is now being developed by a number of commercial firms, is not inhibited by these gram-negative bacteria, although it is not potent against them. It is not yet available in a form suitable for human systemic injection. The author believes that the ultimate control of such mixed infections will come when we can find some chemotherapeutic or antibiotic agent which will destroy or inhibit these second-rate organisms and which can be combined with penicillin for either systemic or local application. These facts are presented with the hope that they may clarify some of the points in the use of penicillin so that it may be more successful in your hands than it has been heretofore.