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THE COMBINED USE OF PENICILLIN AND HEPARIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS*

By Leo Loewe, A.B., M.D.

Brooklyn, N.Y.

EXPERIMENTAL medicine is no longer the work of any single individual. Each research is dependent upon the labours of many men. More often than not, the pioneer work done by the scientist with the greatest vision remains obscured and hidden through the very fundamental nature of his contribution whilst acclaim comes to the less important individual, visible only because he stands on the shoulders of his predecessors.

It was the fate of Louis Gross, in whose name this Lectureship was founded, to be amongst those who pursued fundamental researches in the fastness of his laboratory, far from the glare of the public view. He occupied himself with studies of the circulation of heart muscle and of the heart valves; with the experimental conditions under which infections involve the circulatory structures, and the manner in which these structures react. When his tragically premature death occurred, he had not as yet been able to transmute his many accomplishments into the currency of therapeutics.

It is a source of profound regret to me that Louis Gross could not have lived to see the beginning of the conquest of the disease in which he was so vitally interested. I should like to think that the Louis Gross Memorial Lecture may serve a dual purpose; to keep alive the memory of a friend and associate, and to stress the importance of cultivating and nurturing those who, like Louis Gross, give promise of aiding in man's eternal struggle to conquer disease.

HISTORICAL

The subject of subacute bacterial endocarditis requires few introductory remarks before an audience of this character. Since 1906 and culminating with the publication of his monograph[1] in 1941, Dr. Emanuel Libman has described the clinical syndrome in all its ramifications and clearly delineated the difficulties imposed upon the therapeutic attack; he established the fact that the disease, with few exceptions, was of streptococcal origin; he demonstrated, as far back as 1910, that it was possible to obtain positive blood cultures in 73 of his first 75 cases; he astutely assumed that the portal of infection was "about the teeth or their roots, the tonsils and accessory sinuses or other parts of the upper respiratory tract"; he stressed the importance of the previously existing valvular defect, whether acquired or congenital, as a predisposing factor in the production of the disease; he described fully the usual and the bizarre pathological changes associated with the disease; he emphasized, throughout his clinical thesis, the pathognomonic features particularly referable to the eruptive phenomena, changes in skin colour, the frequent embolic complications and the wide range of forms in which the disease might masquerade.

Early in the course of his studies, Dr. Libman recognized that severer forms of the disease occasionally progressed to spontaneous recovery and estimated that this happy outcome was encountered in at most 3 to 5% of the afflicted; he also recognized that there was a milder or bacteria-free stage of the disease in which the patient might not be seen until recovery had occurred. Dr. Libman noted that an occasional recovery was reported using any one of a variety of chemotherapeutic or physiotherapeutic modalities. With his usual perspicacity, he cautioned that the lack of consistent effect from any one given remedial agent suggested that the isolated "cure" may have been more likely an

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From the Department of Medicine and the Department of Laboratories, Jewish Hospital, Brooklyn, N.Y.
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instance of the spontaneous recovery that is occasionally noted in the severe forms or of an example of the milder bacteria-free syndrome.

Dr. Libman's monograph concludes with the statement of the status of therapy in 1941; in his own words:

> "At the present time, therapy in subacute bacterial endocarditis remains unsatisfactory. . . . A chemotherapeutic agent more effective on the streptococcus viridans than any at present available is needed and may be found; . . . The future looks more promising than ever before."

It is my purpose this evening to add a chapter to Dr. Libman's monograph; we shall present data which indicate that combined therapy using an anti-infective agent and an anticoagulant produced what appears to be clinical cure in approximately 75% of a consecutive series of 54 unselected patients.

LABORATORY DATA

The basis of the present clinical investigation is dependent upon experimental thrombotic bacterial endocarditis[2] as it is produced in the rabbit according to techniques devised in association with my colleagues Drs. Rosenblatt and Lederer. This work indicated that fibrin and blood elements served as an impenetrable barrier to effective chemotherapeusis; the offending organisms, lying deep in the vegetation, were well protected from circulating anti-infective agents. To accomplish disappearance of vegetations, the combined use of a suitable chemotherapeutic agent and an anticoagulant was required. Heparin was successfully employed, in these experimental animals, to arrest the deposition of blood platelets and fibrin which served as a protective nidus and as a stimulus for bacterial growth; relatively fresh, artificially induced thrombi in the animal could be dissipated following the use of the anticoagulants. In corroboration of the experimental investigations, were the observations obtained from human post-mortem material which indicated that heparin has a possible erosive effect on endocardial vegetations.

EVOLUTION OF THE CLINICAL STUDIES

The attempt to translate experimental investigation into terms of clinical therapeusis was at first disappointingly unsuccessful. The intravenous administration of heparin was fraught with danger and the expense was prohibitive in many instances. Whether given by continuous venoclysis or fractional intravenous injection, heparin therapy was cumbersome, accompanied by severe reactions and associated with treatment deaths in altogether too many instances to justify its continuance. To overcome these shortcomings, a special method[3] was devised for the subcutaneous deposition of the drug, through adoption of the Pitkin menstruum, composed of gelatine, dextrose, glacial acetic acid and water in definite proportions, which was developed to regulate the rate of release of water-soluble drugs injected intramuscularly or subcutaneously. By this technique, a slower and more equable absorption of heparin was accomplished.

When this portion of the clinical technique had been solved, a combined attack was inaugurated, using the sulfonamides in association with the heparin. A group of 17 patients with subacute bacterial endocarditis was treated, but there were no more than two apparently authentic "cures", insufficient to justify the conclusion that a specific therapeutic result had been obtained beyond what might be noted with the occasional spontaneous cure or the development of Dr. Libman's bacteria-free state. Nevertheless the two successful issues were sufficient to justify a continued project, more particularly since one of the necropsied cases showed an apparent diminution in the size of vegetations, which were smaller and more discontinuous than might have been anticipated.

With the introduction of penicillin therapy, we were sufficiently fortunate to obtain supplies through the courtesy of Mr. John L. Smith of the Charles Pfizer Company and later, also, through the co-operation of the Committee on Penicillin Therapy of the National Research Council under the ægis of Dr. Chester S. Keefer. The technique was modified by the replacement of sulfonamide with penicillin; continuation of subcutaneous depositions of heparin was made possible by the co-operation of Drs. Ralph D. Shaner and Leo Pirk of Roche-Organon, Inc., which company gratuitously furnished all heparin preparations.

As a preliminary to the inauguration of penicillin-heparin therapy, experiments were devised to determine the effects of heparin on solutions of penicillin (Table I). The data indicated clearly that the anticoagulant had no measurable effect on the anti-infective potentialities of the penicillin; indeed, there was some suggestion of possible synergism or potentiation.

TABLE I.

USE OF HEPARIN IN PENICILLIN ASSAYS

Experiment No. 1, (1-4-44)

	ml. Penicillin solution		*mgm. Heparin*	*mgm. Heparin-O.U. ratio in 10 ml.*	*Series—dilution test results*
A.	9	+	0.5 in 1 ml. H_2O	0.5 mg./1,120 O.U.	124 O.U./ml.
B.	9	+	1.0 in 1 ml. H_2O	1.0 mg./1,120 O.U.	145 O.U./ml.
C.	9	+	5.0 in 1 ml. H_2O	5.0 mg./1,120 O.U.	145 O.U./ml.
D.	9	+	10.0 in 1 ml. H_2O	10.0 mg./1,120 O.U.	124 O.U./ml.
Control	9	+	1.0 ml. H_2O		126 O.U./ml.

Experiment No. 2, (1-8-44)

	ml. Penicillin solution		*mgm. Heparin*	*mgm. Heparin-O.U. ratio in 6 ml.*	*Series—dilution test results*
A.	5	+	0.5 in 1 ml. H_2O	0.5 mg./640 O.U.	128 O.U./ml.
B.	5	+	1.0 in 1 ml. H_2O	1.0 mg./640 O.U.	128 O.U./ml.
C.	5	+	5.0 in 1 ml. H_2O	5.0 mg./640 O.U.	135 O.U./ml.
D.	5	+	10.0 in 1 ml. H_2O	10.0 mg./640 O.U.	128 O.U./ml.
Control	5	+	1.0 ml. H_2O		128 O.U./ml.

DOSAGE SCHEDULE—TREATMENT STATISTICS

The administration of heparin and the determination of optimum dosage are easily gauged by the tilt-tube Lee-White modification of Howell's method[4] for determining blood coagulation time. A reading of 30 to 60 minutes is regarded as satisfactory evidence of an effectual anticoagulant level. Coagulation times above one hour are wasteful of the drug and may indeed be hazardous, particularly if the clotting time is prolonged to two or more hours. Effectually to heparinize the blood necessitates subcutaneous deposits of 300 mgm. every second or third day or approximately 200 mgm. daily of the aqueous commercial product when incorporated in the venoclysis. Hyper-reactors require lesser amounts of heparin and hypo-reactors need additional dosage.

The estimation of penicillin dosage presents greater difficulty and requires the co-operation of the laboratory. Probatory sensitivity tests must be done on the offending organism. In general, the causative agents are inhibited within the dilutions of 0.007 to 0.5 Oxford units of pencillin per c.c. of test broth. Under these circumstances, the daily dosage of penicillin varies from 40,000 to 1,000,000 Oxford units (Table II); total individual unitage may range between the low of 867,000 and a high of 48,930,000 Oxford units. It may be observed parenthetically, as a tribute to the non-toxicity of the presently available preparations of penicillin, that the latter amount could be introduced without significant toxicological phenomena.

TABLE II.

TREATMENT STATISTICS—SUMMARY

DOSAGE

Penicillin sodium salt (Oxford units)

	Range	
	Low	*High*
Daily dosage	40,000 to	1,000,000
Total dosage	867,000 to	48,930,000
Heparin sodium salt (milligrams)		
Total dosage	400 to	11,500

COURSES OF PENICILLIN-HEPARIN THERAPY

NUMBER OF COURSES REQUIRED IN EACH CASE OF THE SUCCESSFULLY TREATED GROUP

No. of courses	*No. of patients*
1	27
2	8
3	4
4	1
Total	40

At the outset, through limitations in the supply of penicillin, an effort was made to reduce the span of treatment to an absolute minimum so that material might be available for as many patients as possible. Originally, a two-week course of treatment was projected and was actually found adequate for the accomplishment of the disappearance of early endocardial lesions. Unfortunately, this two-week course alone was insufficient for patients who had been ill for longer periods of time and a three-week course was regarded as essential for those who had been ill for two to four months; a four-week course was believed necessary for those who had had the disease for more than four months. It is our present opinion that our current practice

of a five-week course must be made the standard minimum when the supplies of penicillin justify treating the individual patient in optimum fashion. Additional courses are given whenever necessary and are well tolerated. Multiple courses are not uncommon in the advanced cases.

Based on penicillin-sensitivity tests, it appears that an average daily dose of at least 200,000 Oxford units is required. Increased dosage or a more prolonged span of treatment is necessary for patients who have deteriorated, or who show severe clinical manifestations of bacterial activity such as embolization, marked splenomegaly and violent temperature reactions. Additional factors that enter into the determination of the dosage level are the sensitivity of the offending organism to penicillin and the capacity of the patient to develop and maintain an adequate level of the anti-infective agent in the blood.[5] To be therapeutically effective, penicillin blood levels must be far in excess of the *in vitro* bactericidal requirement; the best clinical results are achieved when the average unitage of penicillin is sufficient to develop and maintain a blood serum level of five to ten times the sensitivity figure. Inadequate dosage invites treatment failure and the organisms may acquire resistance that is so high as to render future therapeutic levels virtually unattainable. In at least one instance, we observed a forty-fold increase in the resistance of the organism to penicillin.

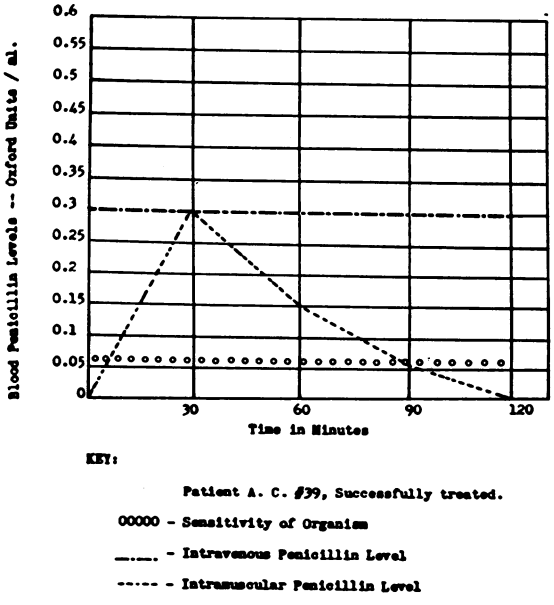
THE TECHNIQUE OF TREATMENT

It is our custom to devote the first few days of therapy to the determination of penicillin levels following intramuscular and intravenous administrations of the drug. During this probationary period, heparin is withheld primarily to obviate any dislodgment of loosely attached vegetations.

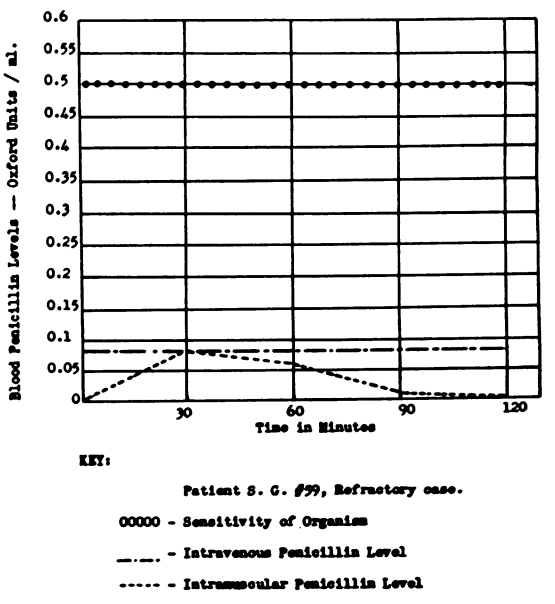
Our experience indicates that intravenous injection of penicillin is decidedly the method of choice (Graphs I and II); intramuscular injections result in the attainment of a higher peak which cannot be maintained and which is fol-

COMPARATIVE EFFECTIVENESS OF FRACTIONAL INTRAMUSCULAR PENICILLIN THERAPY VERSUS CONTINUOUS VENOCLYSIS.

Total Daily Dosage = 240,000 Oxford Units.



Graph I.



Graph II.

Graph I.—Patient A.C. Subacute bacterial endocarditis, *Streptococcus viridans* inhibited by 0.06 O.U. per c.c. of test broth. Penicillin blood level of 0.3 O.U. per c.c. serum with daily dosage of 240,000 O.U. given by continuous venoclysis. One three week course of treatment accomplished successful result. Intravenous blood level of 0.3 O.U. per c.c. of serum achieved only a small fraction of treatment period when penicillin was administered fractionally, 20,000 O.U. units every two hours.

Graph II.—Patient S.G. Subacute bacterial endocarditis due to *Streptococcus viridans* of the resistant variety, requiring 0.5 O.U. per c.c. test broth for complete inhibition. Therapeutic penicillin blood levels could not be obtained with daily dosage of 240,000 O.U. by either intravenous or intramuscular route. Patient was completely refractory to treatment even when daily dosages were stepped up to 1,000,000 O.U. per day.

lowed by a prompt and abrupt decline so that, for a sizable fraction of the treatment day, the blood is virtually free of detectable amounts of penicillin. In contrast, the intravenous injection produces a constant and sustained level. Only rarely, when the patient is in congestive failure so that the additional intravenous administration of the bulk of fluid seems more than the circulation can maintain, do we resort to intramuscular introduction; at the earliest possible opportunity, then, we revert to the continuous intravenous drip employing minimum amounts of diluent. In all instances, when available, Ringer's solution is employed as the vehicle; the patient is placed on a salt-poor intake and heparin is deposited subcutaneously as soon as the preliminary steps have been completed.

Accessory therapeutic measures include the use of high caloric, high vitamin diets, supplementary multivitamin preparations, the use of hæmatinics in liberal dosage where there is anæmia and the resort to frequent transfusions when indicated. The latter require temporary interruption of heparinization and hence are postponed, if possible, till the termination of treatment.

TOXICITY

Reactions to treatment occur frequently, Those of minor importance include chills, fever, local pain, regional angiitis, regional adenopathy, urticaria and vesicular eruptions (Table III).

Febrile reactions are rather common and may be ascribed to a variety of factors. There are the obvious pyrogenic factors such as air-borne contaminants. This is controlled by using sterisol bottles and periodic refrigeration. The substitution of viscose instead of rubber tubing eliminates a small fraction of reactions but does not justify its universal use. The incidence of troublesome regional angiitis with its attendant rigors and sharp rises in temperature can be reduced by changing veins and apparatus every 3 or 4 days. Wherever possible a vein about the wrist or forearm is used to allow freedom of movement.

Thrombophlebitis seldom occurred in our heparinized patients even when this was a troublesome complication of the early penicillin era. Elaborate immunological tests done with early crude and progressively purer products of penicillin have failed to elicit any instance of allergy in any of our patients despite multiple courses of intensive and extensive therapy.

Febrile reactions due to heparin are frequent, for the most part due to excessive anticoagulant activity. These are overcome readily by the mere withdrawal of the drug. One patient under combined penicillin-heparin therapy developed clinical manifestations of sensitivity to heparin. Attempts to resume the conjoint therapy were followed by episodes of chills and fever, the last one being associated with generalized urticaria. Intracutaneous tests were negative to penicillin but gave a moderate reaction to heparin. He has since received as much as 1,000,000 Oxford units of penicillin daily intravenously for some weeks without untoward reactions.

Urticaria has, at times, been troublesome, mostly post-therapy and is almost invariably attributable to penicillin.

TABLE III.

REACTIONS OCCURRING DURING THERAPY—SUMMARY

	Chills and fever	*Fever*	*Local pain*	*Regional angiitis*	*Regional adenopathy*	*Urticaria*	*Vesicular eruptions*
Penicillin intravenous..	Rare	Rare	0	Frequent	0	Occasional	Occasional
Penicillin intramusuclar	0	0	Common, degree variable	0	Occasional	0	0
Heparin subcutaneous..	0	Common	Common, degree variable	0	Occasional	0	0
Heparin intravenous...	0	Common	0	0	0	0	0
Penicillin and heparin combined.....	Not Uncommon*	Common	Uncommon	Occasional	Uncommon	Occasional	Occasional

*Causative factor(s) not clear.

RESULTS OF THERAPY

The results of therapy of subacute bacterial endocarditis, using the combination of the intravenous introduction of the anti-infective agent and mostly subcutaneous implants of the anticoagulant, have been tabulated according to the

records of 54 consecutive and unselected patients (Table IV). Many of our patients were in pitiful condition when therapy was inaugurated. In certain instances, congestive failure had reduced them to the point where any form of therapy was associated with considerable hazard. Other patients were in the ulcerative phase of the endocardial disease and were throwing off emboli from friable and necrotic vegetations. Despite the precarious manifestations of many of the afflicted, we had no choice other than to inaugurate therapy, since refusal was tantamount to the imposition of a death sentence. Had we chosen to treat only those patients in the earlier stages of the disease and to eliminate

TABLE IV.

RESULTS WITH PENICILLIN-HEPARIN IN SUBACUTE BACTERIAL ENDOCARDITIS

Total number of cases (consecutive and unselected).		54	% 100
Duration of illness prior to to penicillin-heparin therapy (weeks).....	1 to 78		
Penicillin sensitivity of causative organisms (Oxford units).....	0.007 to 0.5		
Number of cases in which therapy was successful..		40	74
Patients living.....	37		
Patients deceased—other causes.....	3		
Post-therapy period of observation (months).....	2 to 15		
Number of cases in which therapy failed.....		14	26

those with manifestations of circulatory failure, ulcerative lesions and embolic complications, a considerably higher incidence of favourable accomplishment might have been reported.

As the records now stand, 54 patients were treated by a combination of anti-infective, anticoagulant therapy. The duration of illness prior to treatment varied from one to seventy-eight weeks; the penicillin sensitivity of the etiological organism varied from 0.007 to 0.5 Oxford units (readily inhibitable to very resistant). Fourteen, or 26% of the group are recorded as failures; 40, or 74% may be regarded as satisfactory results. In the latter group, 37 of the 40 are alive and many have resumed useful occupations; 3 have died of other causes. In the group of treatment failures, there have been 13 deaths from progressive circulatory failure, coronary occlusion, embolization and lobar pneumonia, or a total of 16 fatalities in the original roster of 54.

TREATMENT FAILURE

Treatment failure may be attributed to patient-factors, refractoriness of the causative organism or reinfection with the original or a different type of organism.

Of the 14 treatment failures (Table V), it is

TABLE V.

ANALYSIS OF FACTORS IN FAILURES OF PENICILLIN-HEPARIN THERAPY—SUMMARY

	No. of cases	%
1. Patient factors:		
a. Cardiac failure.....	4	28.5
b. Cerebral embolism.....	3	21.4
c. Inanition.....	1	7.2
d. Intercurrent infection.....	2	14.3
2. Organism refractory.....	3	21.4
3. Reinfection.....	1	7.2
Total.....	14	100.0

our opinion that 10 might be attributed to inability of the patient to withstand the ravages of the infection and to utilize the full benefits of combined anti-infective, anticoagulant therapy. At least 4 of the patients suffered from circulatory failure, 3 encountered cerebral embolizations, 1 had profound inanition and 2 had intercurrent infections, notably lobar pneumonia.

A second cause for treatment failure in 3 patients was the refractoriness of the organism. In unreported studies made by Prof. J. M. Sherman of Cornell University, an attempt was made to establish a correlation between streptococcus typing, penicillin sensitivity and the clinical response. Of our series of 54 patients,

TABLE VI.

VARIETY OF STREPTOCOCCUS AS A POSSIBLE INFLUENCE ON PROGNOSIS

PRELIMINARY REPORT ON WORK IN PROGRESS
(Kindness of Prof. J. M. Sherman, Cornell University)

Causative organism	*No. of cases*	*Treatment successful*	*Reinfection*	*Fatal outcome*
Streptococcus sp....	4	0	1	3
Streptococcus mitis.	7	6	0	1
Streptococcus bovis.	2	2*	0	0
Total.....	13	8	1	4

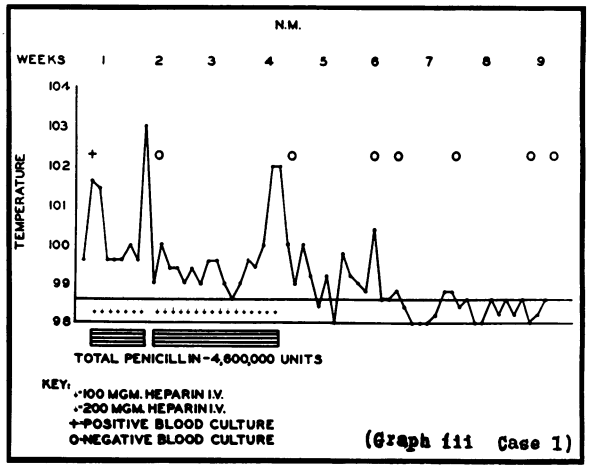
Streptococcus sp.: Apparently a new and distinct variety of streptococcus. Strains belonging to this variety show rather homogeneous cultural and biochemical reactions.

Streptococcus mitis: The common throat viridans streptococcus.

Streptococcus bovis: Similar to so-called "Bargen streptococcus".

*One of these patients, N.M.—Case 32, subsequently died of heart failure. No evidence of bacterial activity at autopsy.

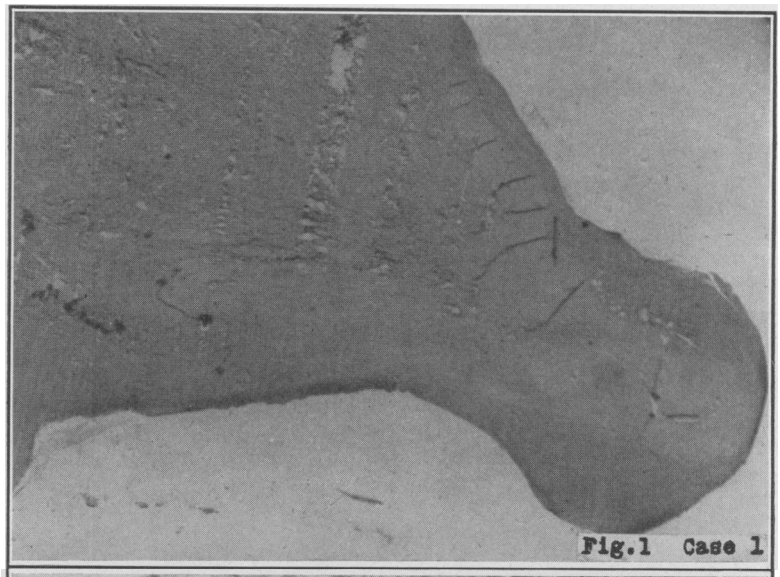
Prof. Sherman worked with 13 different organisms and established the presence of three different species (Table VI). Three patients, infected with a previously unidentified streptococcus, were resistant to therapy and all three succumbed. The blood of 7 patients disclosed a *Streptococcus mitis,* apparently more sensitive to penicillin since six of the seven recovered and there was but one fatality; the remaining two victims were infected by *Streptococcus bovis* and one of these recovered while the other died. Significantly, the autopsy on the fatal streptococcus bovis infection revealed evidences of a healed endocarditis.



The last treatment failure in a surviving patient is an instance of reinfection with another strain of streptococcus. Studies by Prof. J. M. Sherman indicate that the organism recovered from the blood stream during the initial and the subsequent attack were different. This suggests that the patient was cured of his disease, but not necessarily immunized to subsequent bacterial invasion. The original strain is *Streptococcus salivarius,* whereas the more recent strain is significantly the unidentified streptococcus found, as previously mentioned, only in patients who were resistant to therapy. It will be especially interesting to observe the response to the current course of treatment.

DEATHS

In the series of the 54 original patients, there were 16 deaths. Thirteen of the deaths occurred in the group of treatment failures as previously indicated, three of the fatal issues occurred in those who had been satisfactorily treated. The autopsies of two of the satisfactorily treated patients have afforded an interesting insight into the disputed problem of a temporary sterilization of the blood versus actual cure. Evidence in favour of actual cure is afforded by the de-



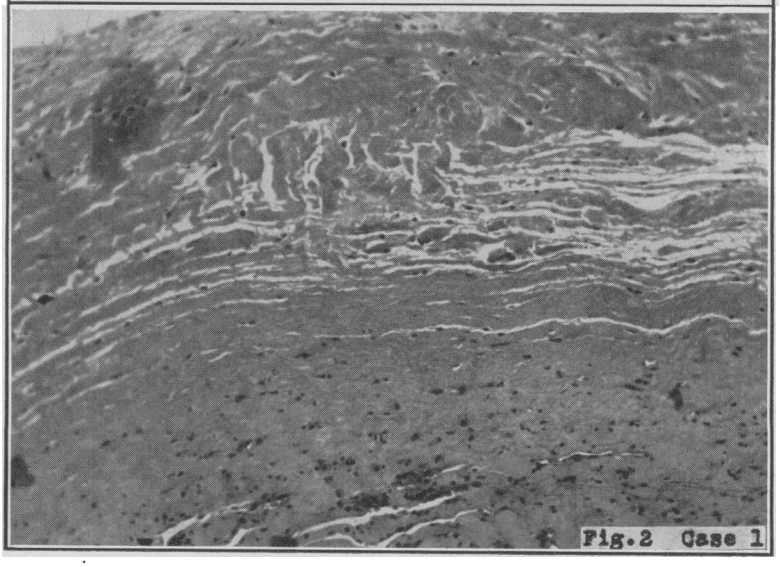


Fig. 1.—Aortic valve. Note stump-shaped cusp which is fibrotic and completely endothelialized. **Fig. 2.**—Stump of aortic cusp (higher magnification). Note that there is no evidence of active inflammation or any indication of bacterial activity.

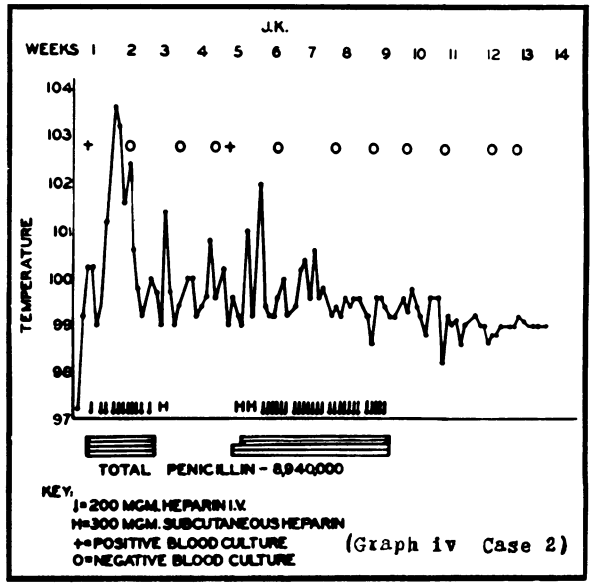
scriptions of the heart valve as recorded in one instance by Dr. E. S. Maxwell of the Good Samaritan Hospital in Sterling, Kentucky, and in the other by Drs. J. W. Denton and A. F. Heyl of the New Rochelle Hospital.

CASE 1

N.M. (Graph III), aged 29, female. Subacute bacterial endocarditis, 12 weeks; *Streptococcus viridans* (penicillin sensitivity 0.031 O.U.): chronic rheumatic cardiovalvular disease, aortic; aphasic on admission due to cerebral embolus; responded well to one 23-day course of penicillin-heparin therapy; developed intractable congestive heart failure which resisted all therapy; blood stream sterile for more than six months until death. Dr. Maxwell reports that the right aortic cusp was almost completely destroyed and replaced by short fibrotic stubs. A congenital aneurysm was present near the origin of the aorta. It was Dr. Maxwell's opinion that death was due to cardiac failure with marked visceral passive congestion. Histological study showed fibrosis and hyalinization of the aortic stubs with no evidence of bacterial inflammation (Figs. 1 and 2).

CASE 2

J.K. (Graph IV), aged 33, female. Subacute bacterial endocarditis, 28 weeks; *Streptococcus viridans*; chronic rheumatic cardiovalvular disease, aortic and mitral; two courses of penicillin-heparin therapy, 14 and 28 days respectively; discharged from hospital in mild congestive heart failure which progressed unfavourably, clinical behaviour same as Case 1; blood stream sterile for more than three months until death. In this case, autopsied by Drs. Denton and Heyl, they reported that there was a shredded, partially calcified anterior cusp of the aortic valve with marked insufficiency of the orifice. The heart was hypertrophied and dilated. There was severe chronic passive congestion of the viscera. It was the opinion of the pathologist that death was due to congestive heart failure and there were no histological evidences of active bacterial endocarditis (Figs. 3 and 4).



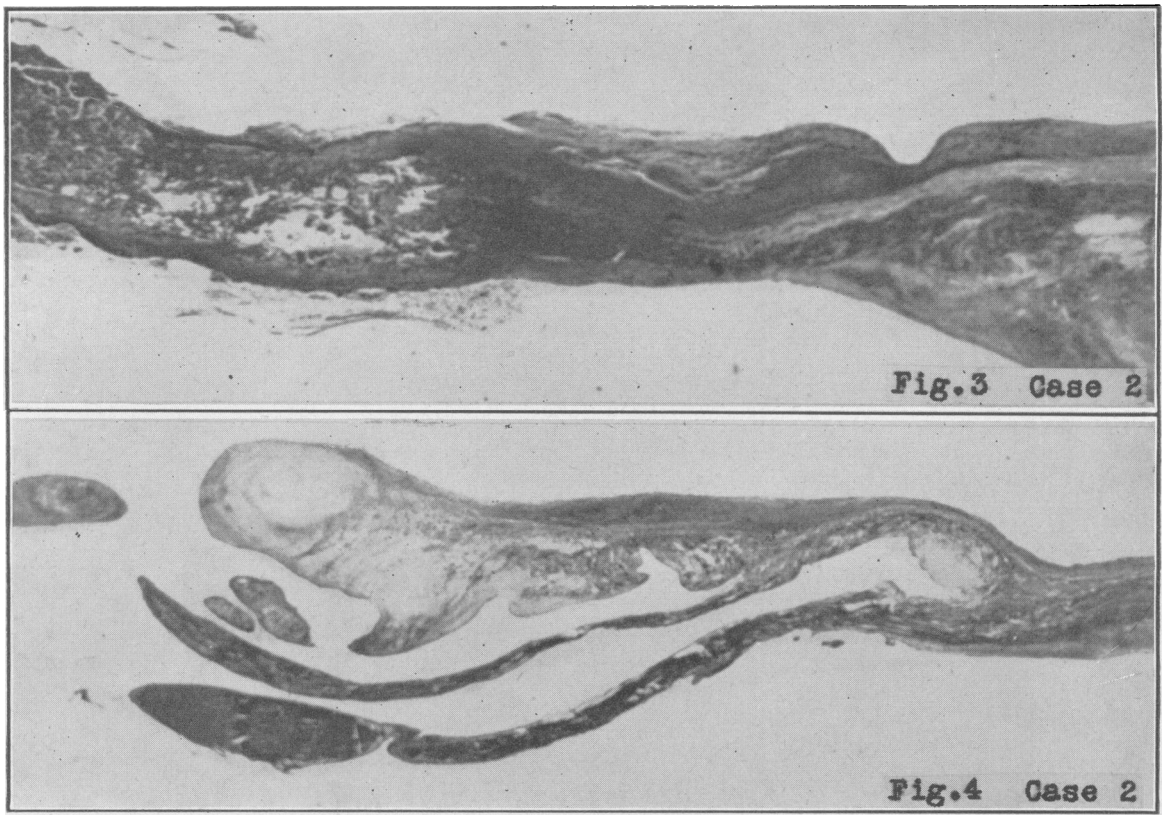
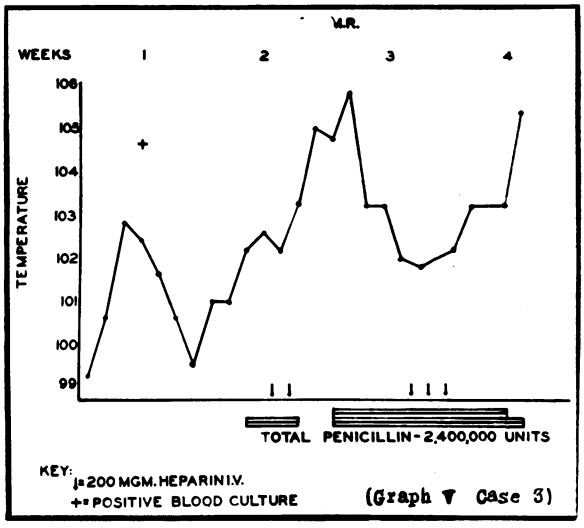


Fig. 3.—Aortic valve. Note the dense fibrotic character of the stroma and central fragmentation of the connective tissue. Note that the surfaces are completely endothelialized. **Fig. 4.**—Mitral valve nodule. Note composition of moderately cellular fibrous tissue. There is no evidence of active inflammatory change.

Interpretation of autopsy findings and the evaluation of gross pathological phenomena invite a discussion also of the significance of embolization occurring during the course of treatment. It is a well-established fact that embolization is a common complication of subacute bacterial endocarditis, but embolization has also been attributed to heparinization, particularly in the presence of thrombotic vegetations on the heart valves. To clarify this point, we have charted (Table VII) the relationship of embolization to therapy in eight of our patients. In four, embolic phenomena were present

TABLE VII.
GROSS EMBOLIC INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

Time of occurrence with respect to penicillin-heparin therapy	*No. of of cases*	*Successfully treated*	*Fatal outcome*
Before treatment.....	4	4	
During treatment.....	3		3
After completion of treatment.....	1	1	
Total.....	8	5	3



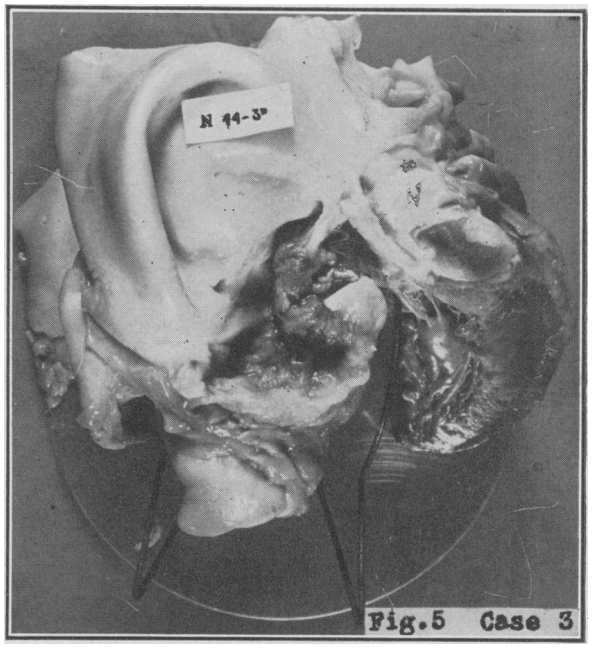


Fig. 5.—Aneurysm of sinus of Valsalva viewed from above. Note severe ulcerative lesion.

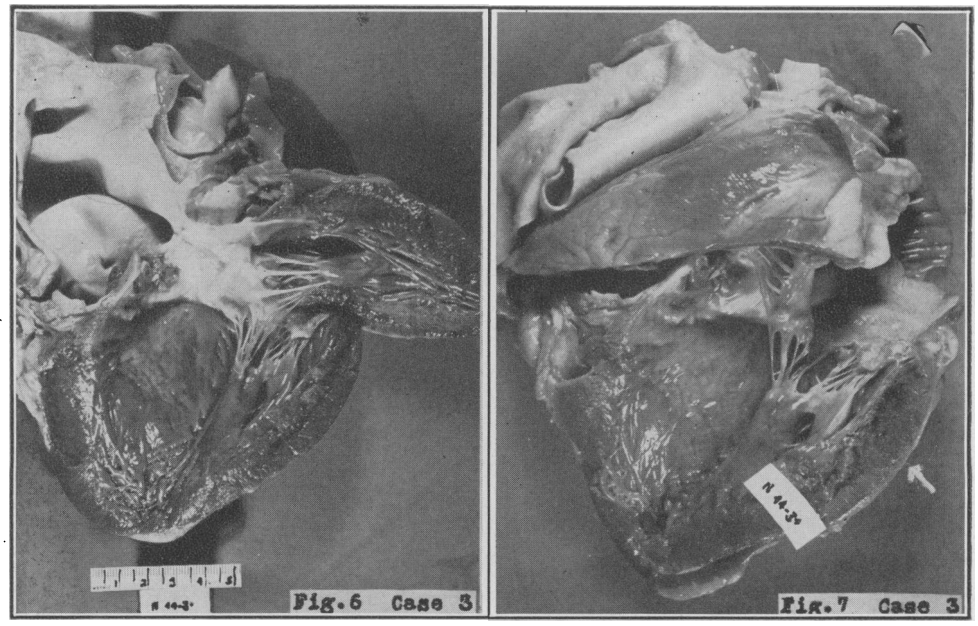
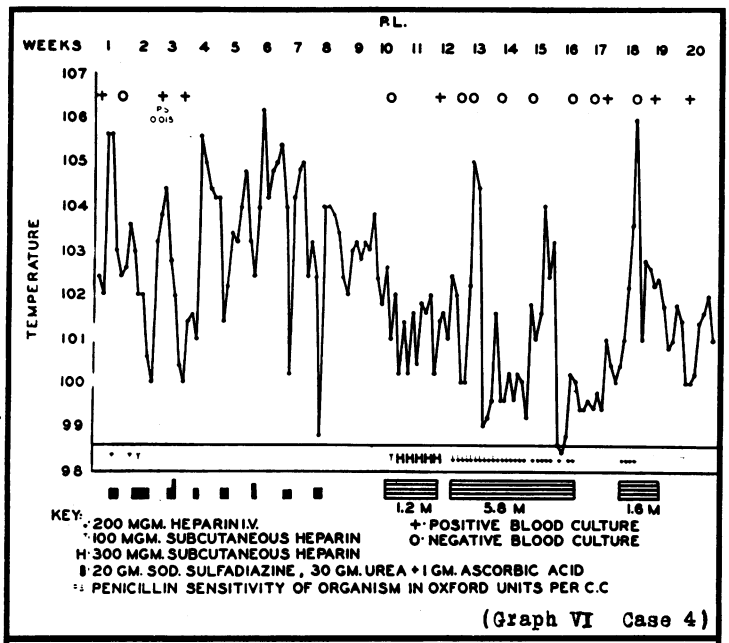
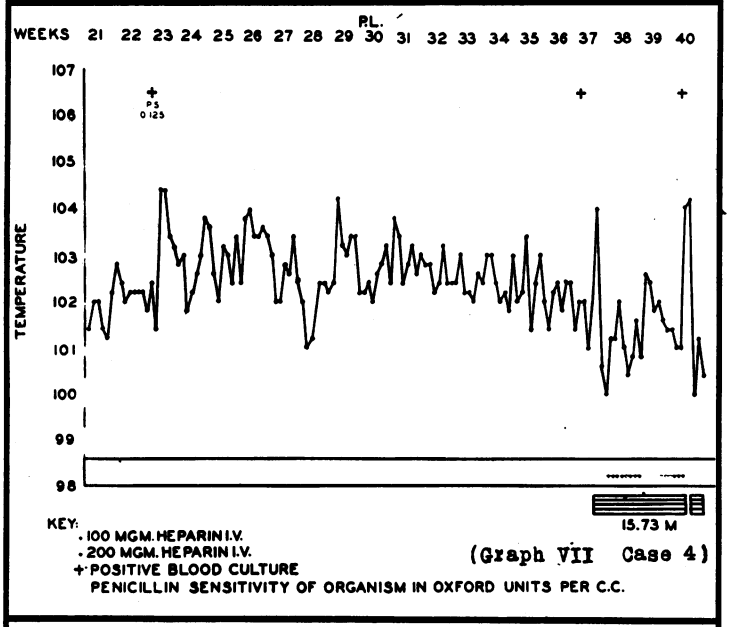


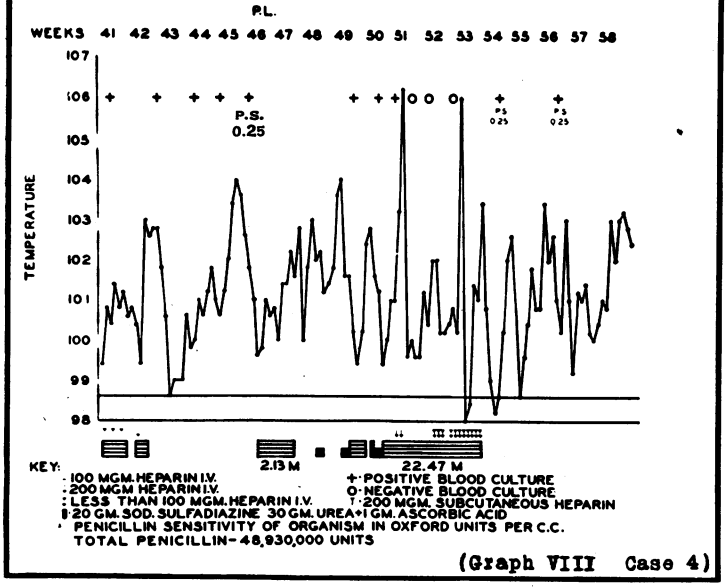
Fig. 6.—Aortic and mitral thrombo-ulcerative endocarditis. Note extensive myomalacia cordis, especially on cut surface. **Fig. 7.**—Myomalacia cordis. Gross fragmentation of myocardium.



(Graph VI Case 4)



(Graph VII Case 4)



(Graph VIII Case 4)

before the inauguration of treatment and four of these patients were successfully treated. Three patients in the first 30 of the series of 54 cases had embolization during treatment and succumbed. These are included among the treatment failures.

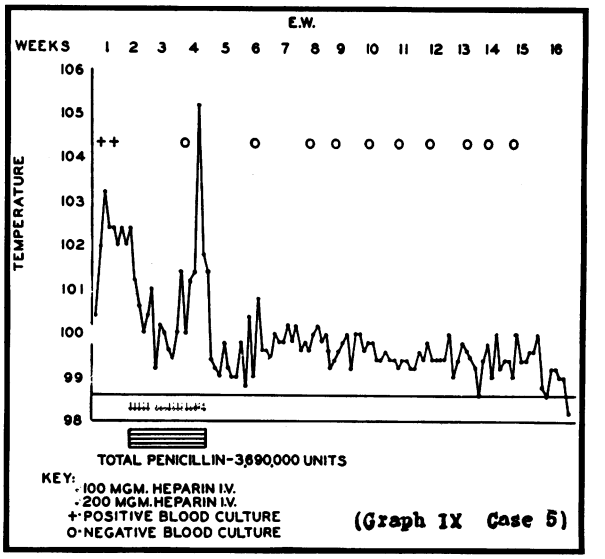
It may be more than fortuitous that, since introducing a probationary 3-day course of intramuscular penicillin treatment, there has been no intra-therapy cerebral embolization. In only one instance has there been a post-therapy embolization and that occurred in a patient who made a splendid recovery both from the infection and from the hemiplegia which resulted from the vascular occlusion. From these figures it would seem fair to conclude that pre-treatment embolization is not a contra-indication to the inauguration of anticoagulant, anti-infective therapy and that embolization occurring during and following treatment is more likely a manifestation of the continued progress of the underlying disease than a result of the utilization of the anticoagulant.

SATISFACTORY RESULTS

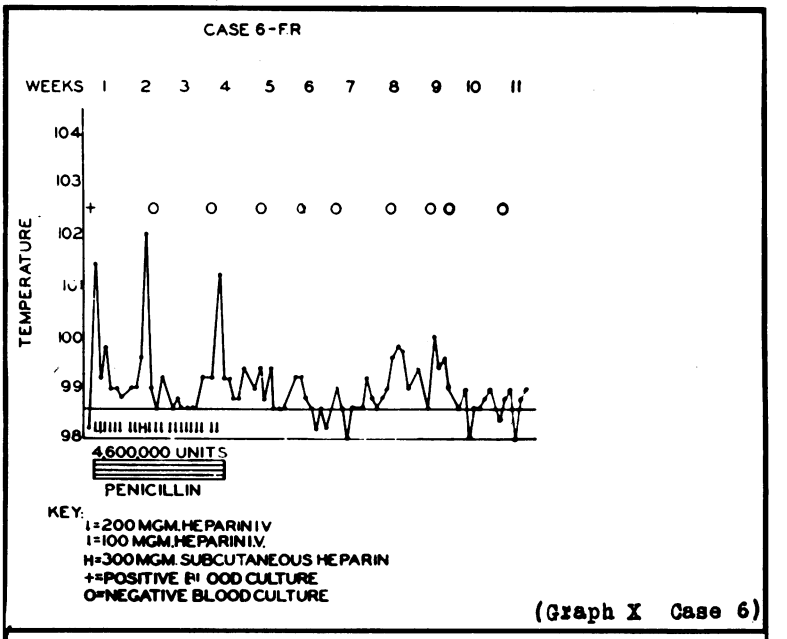
We have recorded satisfactory results in 40 patients, of whom 37 are still alive, many having resumed their normal activities. The most recent patient has been observed for only two months, but the oldest member of the group was discharged from the hospital fifteen months ago. In the favourable instance, the temperature falls to a normal level, the patient experiences a sense of well-being though, naturally, the mechanical deformities of the heart valves result in varying degrees of diminution in cardiac reserve. As in the instance of fatalities and treatment failures, the outcome of therapy is dependent upon patient- and organism-factors. Those patients who are seen soon after the onset of their bacteræmia, who have relatively small vegetations, who do not suffer from ulcerative endocarditis or circulatory failure have the optimum chance for cure,

provided that their infection is by a penicillin-sensitive organism.

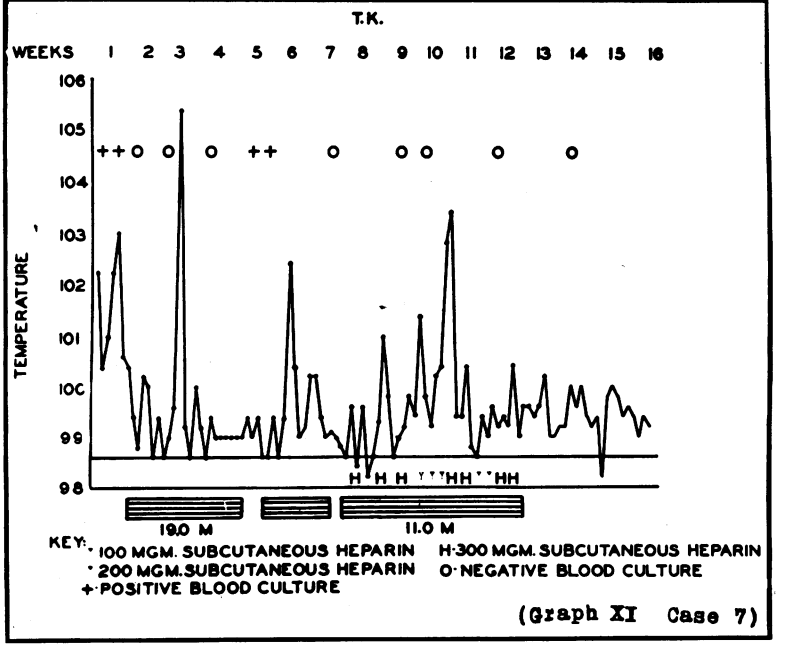
The second variable, so clearly delineated by Prof. Sherman's studies (Table VI), deals with the variety of infecting organisms. Apparently, infection with streptococcus mitis or bovis carries a considerably more favourable prognosis than an invasion caused by the special streptococcus which is presently being subjected to searching inquiry by Prof. Sherman. The accomplishment of a favourable outcome in approximately 3 out of every 4 patients leaves no doubt that the beneficial results observed in this unselected series cannot be attributed to spontaneous recovery. The severity of the manifestations of the disease in our group of patients precludes the possibility that we have been dealing with the bacteria-free stage of the subacute streptococcus endocarditis syndrome.



(Graph IX Case 5)



(Graph X Case 6)



(Graph XI Case 7)

PROPHYLAXIS

Consistent with Dr. Libman's observation concerning the possible portal of entry in the upper respiratory passages and the teeth, we have included in our treatment program the elimination of foci of infection before permitting the patient to leave the hospital. To prevent a recurrence of exacerbation of the bacteræmia, penicillin is administered parenterally and topically before and after the eradication of the focus.

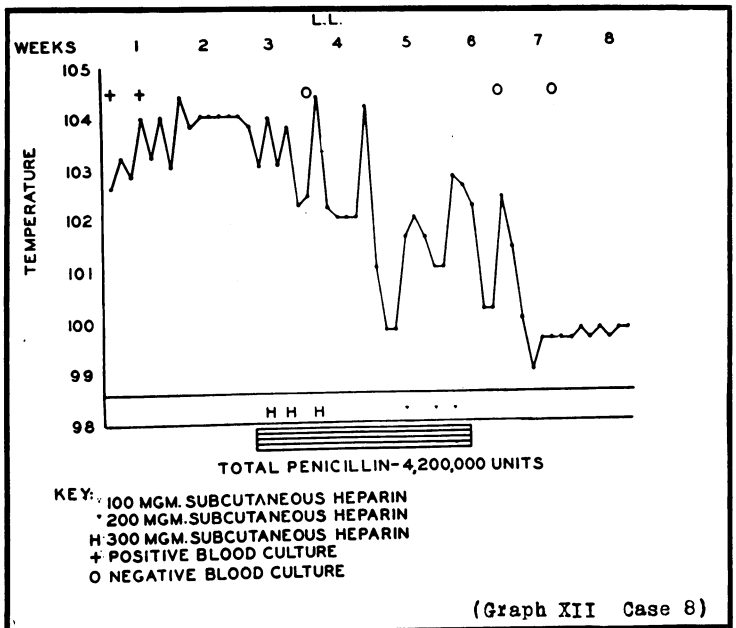
In the time that remains, it may be possible to illustrate the general principles which have been established through a concrete study of individual case records.

A. ANALYSIS OF FAILURE

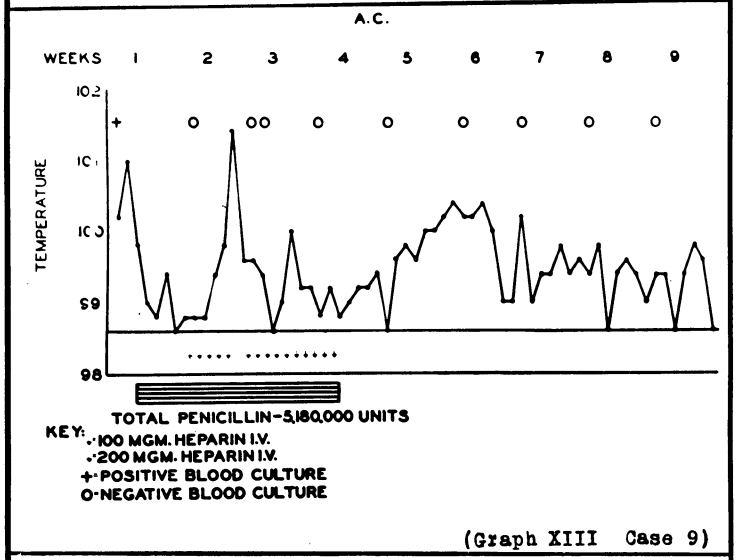
1. *Example of therapeutic failure due to patient factors.*

CASE 3

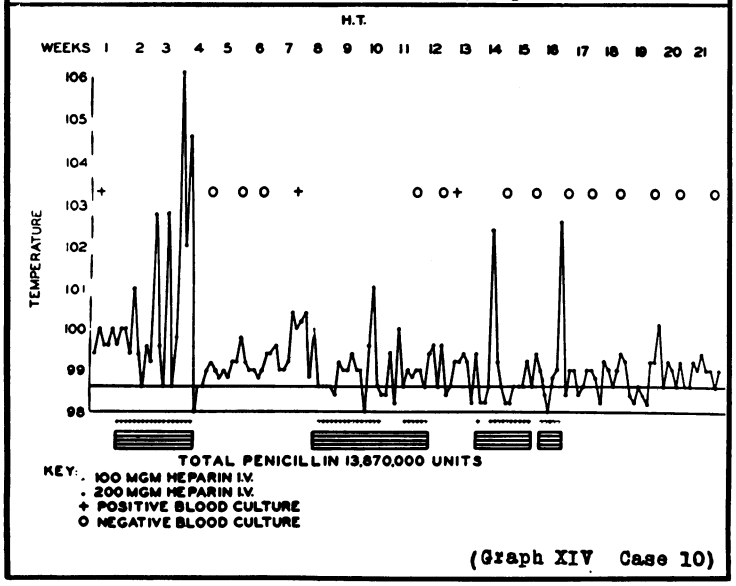
M.R. (Graph V), aged 47, male. Subacute bacterial endocarditis, 6 weeks; *Streptococcus viridans;* chronic rheumatic cardiovalvular disease, aortic and mitral; discontinuous therapy for 12 days, severe myocardial embarrassment, pulmonary and cerebral embolization; progressive downhill course, death from circulatory failure (Figs. 5, 6, and 7).



(Graph XII Case 8)



(Graph XIII Case 9)



(Graph XIV Case 10)

2. *Example of failure due to organism factor. Infection with Streptococcus sp. (Table VI) which acquired resistance to penicillin.*

CASE 4

P.L. (Graphs VI, VII, and VIII), aged 21, male. Subacute bacterial endocarditis; 56 weeks; *streptococcus viridans,* (penicillin sensitivity 0.015 to 0.25 O.U.): chronic rheumatic cardiovalvular disease, aortic and mitral; three courses of penicillin-heparin therapy with but temporary improvement; treatment suspended October 31, 1943, for lack of material; resumed four months later with intensive massive medication; therapy interrupted because of extra-cardiac complications which caused death despite total of 48,930,000 Oxford units given in six courses; organisms recovered after successive courses displayed increasing resistance to penicillin as shown in laboratory assays and reflected by the lack of clinical response; confirmatory autopsy findings were, "thrombo-ulcerative mitral and aortic endocarditis, with lesions predominantly aortic. Valve stenotic and insufficient. Chronic cardiac failure with accumulation of fluid in body cavities and passive congestion of viscera. Death due to ruptured œsophageal varices. Long-standing case with resistant organism".

B. CO-EXISTENT RHEUMATIC VIRUS ACTIVITY

Penicillin-treated patients are apparently susceptible to virus infections, due probably to disturbance of protective barriers by the drug. Reactivation of rheumatic virus in successfully treated patients with subacute bacterial endocarditis may be explained on the same basis.

CASE 5

E.W. (Graph IX), aged 16, female. Subacute bacterial endocarditis; 8 weeks; *Streptococcus viridans,* (penicillin sensitivity 0.015 O.U.); chronic rheumatic cardiovalvular disease, aortic and mitral; one 17-day course of penicillin-heparin therapy sterilized blood stream; continued low grade temperature and elevated ESR, post-therapy, due to persistent rheumatic virus activity uncovered by successful therapy of subacute bacterial endocarditis; confirmatory electrocardiographic findings of protracted rheumatic virus activity; culmination in severe rheumatic pericarditis with effusion six months post-therapy; development of hydro-pneumopericardium and its subsequent disappearance portrayed radiographically; despite all this no recurrence of bacterial endocarditis; blood stream sterile for over nine months; weight gain of 14 pounds, hæmoglobin 82%, ESR 40 mm./hr.; continued active rheumatic suspect.

It was an interesting observation to note that the rheumatic virus continued to operate despite the

presence of sufficiently high penicillin levels to eliminate streptococcal viridans bacteræmia. This and kindred observations tend to point up the recently reported experiences of the Army and Navy[6, 7] which attest to the resistance of rheumatic virus to anti-infective agents.

C. Failure with Penicillin Alone—Success with Combined Penicillin-Heparin. Seven Such Instances to Date

Case 6

F.R. (Graph X), aged 43, female. Subacute bacterial endocarditis, 12 months; *Streptococcus non-hæmolyticus;* chronic rheumatic cardiovalvular disease, aortic and mitral; on continuous intramuscular penicillin therapy for 10 months; totalling almost 9 million units with but transitory sterilization of blood stream; referred for penicillin-heparin therapy; one course interrupted after 3 weeks because of apparent penicillin-heparin sensitivity; striking progressive clinical improvement; no clinical or laboratory evidence of bacterial activity for over 10 months despite complicating upper respiratory infection; prophylactic oral surgery.

Case 7

T.K. (Graph XI), aged 22, male. Subacute bacterial endocarditis, 3 weeks; *Streptococcus viridans,* (penicillin sensitivity 0.03 O.U.); patent ductus arteriosus; recovery from subacute bacterial endocarditis two years ago following sulfonamide-fever therapy; two courses of penicillin *per se,* totalling 19 million Oxford units, ineffective for present recurrence; one five-week cycle of penicillin-heparin, with lower dosage of penicillin, successful; no clinical or laboratory evidence of bacterial activity for over 2 months.

D. Comparative Response of Patients to Therapy

Case 8

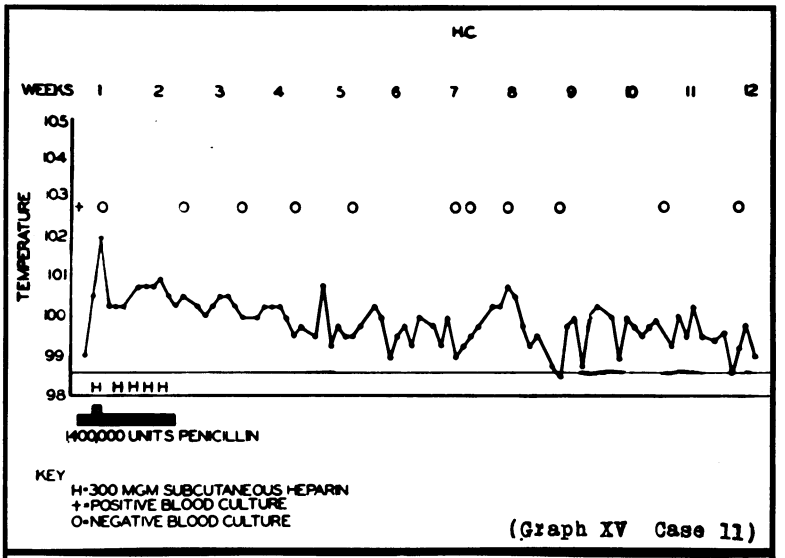
L.L. (Graph XII), aged 33, female. Mt. Sinai Hospital (courtesy of Dr. B. S. Oppenheimer). Subacute bacterial endocarditis, 8 weeks; *Streptococcus viridans,* (penicillin sensitivity 0.03 O.U.); chronic rheumatic cardiovalvular disease, mitral; stormy course characterized by rigors, spiking temperature; continuous intravenous medication impossible because of congestive heart failure necessitating dehydration measures; temperature immediately post-therapy ascribed to rheumatic virus activity, prompt response to salicylate therapy; infected dental foci removed; no clinical or laboratory evidence of bacterial activity for over 7 months; present weight 124 pounds, hæmoglobin 80%; ESR 7 mm./hr.

Case 9

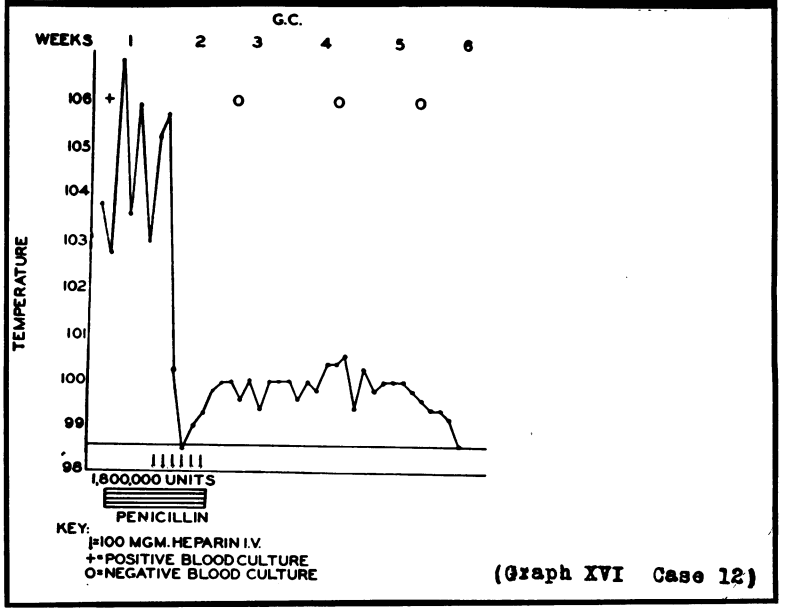
A.C. (Graph XIII), aged 59, male. Subacute bacterial endocarditis, three weeks, *Streptococcus viridans,* (penicillin sensitivity 0.06 O.U.); chronic rheumatic cardiovalvular disease, mitral; therapy well tolerated; uneventful course apart from regional lymphangitis; no clinical or laboratory evidence of bacterial activity for over 5 months; prophylactic oral surgery.

Case 10

H.T. (Graph XIV), aged 27, male. Subacute bacterial endocarditis, 24 weeks; *Streptococcus viridans,* (penicillin sensitivity 0.06 O.U.); chronic rheumatic cardiovalvular disease, aortic and mitral; intensive sulfonamide therapy ineffective, admitted for penicillin-heparin therapy; advanced case, deteriorated, glomerulonephritis, hæmoglobin 45%; marked febrile response after 14 days' therapy; widespread simultaneous embolization to brain, lungs, spleen and kidneys due apparently to fragmentation of vegetations; prompt cessation of embolic phenomena and abrupt defervescence following suspension of therapy after 17 days; second and third courses of penicillin and heparin well tolerated; compare penicillin requirements with previous cases; progressive clinical improvement; no clinical or laboratory evidence of bacterial activity for over 6 months; renal findings negative; prophylactic oral surgery; weight gain of 28 pounds, present hæmoglobin 98%, ESR 6 mm./hr.



(Graph XV Case 11)



(Graph XVI Case 12)

CASE 11

H.C. (Graph XV), aged 52, female. Case 6 of original series;[8] subacute bacterial endocarditis, *Streptococcus hæmolyticus*, 3 weeks; chronic rheumatic cardiovalvular disease, aortic; widespread, almost lethal embolizations; prompt, dramatic response to penicillin-heparin therapy; progressive clinical improvement, and negative blood cultures, 14 months; present weight 163 pounds, hæmoglobin 94%, ESR 7 mm./hr.; has resumed work as a private secretary for past six months.

CASE 12

G.C. (Graph XVI), aged 10½, male. Pneumococcus-type 33 endocarditis referred by Dr. Robert E. Gross of Boston for sterilization of the blood stream prior to operation on a patent ductus arteriosus; ill with chills and fever for 3 weeks prior to admission; no response to sulfonamides; progressed favourably following a short course of therapy and was sent home clinically well; temperature chart shows graphically the spectacular response; hyperpyrexia attributed to overwhelming destruction of organisms and consequent liberation of bacterial proteins; when last seen over nine months post-therapy gained 23 pounds, hæmoglobin 104% and ESR mm./hr.

CONCLUSIONS

A review of these illustrative cases permits of the following conclusions:

1. Age and sex have no bearing on the outcome of therapy.

2. The type of organism, apart from the so-called *Streptococcus sp.* (Table VI), is immaterial to the outcome of therapy, provided it is inhibitable by penicillin within practical limits (0.007 to 0.125 Oxford units).

3. If the patient is in good physical condition, the duration of the disease less than three months, and the causative organism sensitive to penicillin, a satisfactory result may be anticipated, barring accidents, in virtually every case.

The invitation to deliver the Seventh Louis Gross Memorial Lecture has been a source of tremendous personal satisfaction to me. I should be remiss however, were I to conclude without expressing my thanks to my various colleagues and collaborators, among whom are included Drs. P. Rosenblatt, M. Lederer, H. J. Greene, M. D. Levin, M. Grolnick, and E. Alture-Werber, Mr. M. Russell, and Misses R. Kashdan and M. Koslof. I would like also to express my gratitude to Dr. Harold T. Hyman for his invaluable assistance in the correlation of my data for presentation.

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177 New York Ave.,
Brooklyn.

MANAGEMENT OF BREAST TUMOURS*

By Roy D. McClure, M.D. and Laurence S. Fallis, M.D.

Detroit, Mich.

SO well spread has been the information by the various societies organized for the control of malignant disease that many patients now consult their medical adviser for assurance that they do *not* suffer from cancer. The breast is the organ for which advice is sought most frequently because of the relative ease with which changes in texture can be recognized by self-examination. Women who discover a lump in their breast almost universally fear that they have a cancer. These women pursue two divergent courses. One small and fortunately diminishing group, because they feel that there is some stigma attached to cancer, pretend to ignore such a lump. Perhaps this is due to fear and an inability to face the issue. By far the majority of women, however, visit their doctor without much delay; though at the same time it is of the utmost importance never to make an all-out diagnosis of carcinoma, but always to leave the patient with at least a ray of hope that the condition may not be malignant.

The thought uppermost in these patients' minds is: Do I have cancer? Except in the moderately or far advanced cases a definite answer cannot be given. Because these women are at least thinking of the term cancer, if not actually using it, no useful purpose can be served, and much harm may be done by failure of the medical man to discuss the condition quite openly and frankly. We have picked up many unsuspected early cancers of the breast in our diagnostic clinic annual examinations where the patient had felt no lump themselves. Of course there are patients whose mental make-up is such that given a diagnosis of suspected cancer they would be thrown into a state of depression, but these are relatively rare, and easily recognized. Well-meaning relatives in many instances create embarrassing situations for the doctor by requesting that the patient should not be told the truth if cancer is present. Time spent in pointing out the error of this course of procedure to relatives, and convincing them that the

* From the Department of Surgery, Henry Ford Hospital, Detroit, Michigan.

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