THE ROLE OF PENICILLIN IN OBSTETRICS

By L. Marshall Harris, Captain, MC, USN, and
Daniel M. Shook, Lt. (j.g.), MC, USN

(From the Department of Obstetrics and Gynecology, U. S. Naval Hospital, Great Lakes, Illinois)

PRIOR to the year 1935, sterilization of the blood by chemical means was looked upon as an unattainable ideal, and the occurrence of obstetric complications attended by infection constituted a major hazard reflected in high maternal and fetal morbidity and mortality rates. In 1935, the advent of the sulfonamides represented the first of the chemotherapeutic agents and probably the greatest therapeutic discovery in modern medicine. While the sulfonamides served as a powerful weapon for combatting infections in general at a time when such a drug was so much in demand, there remained much to be desired to meet all the requirements—more especially those problems of infection in the field of obstetrics. It is believed that penicillin, from experience gained thus far in its use, will solve many of these problems.

RELATIVE FREEDOM FROM UNDESIRABLE REACTIONS

Experience with the sulfonamide preparations has demonstrated their limitations and contraindications in the presence of such conditions as severe anemia, nephritis, hepatitis, agranulocytosis and nausea, as well as their incompatibility with other drugs.

The purpose of this paper is to present some of the advantages offered by penicillin in the treatment of infections in pregnancy and its use in the management of obstetrical difficulties. From a review of the literature and from a study made during the past two years, it is desired to point out the wide therapeutic range of penicillin and its freedom from toxic and undesirable side reactions as well as its compatibility with other therapeutic agents.

Within the first year or two following discovery of the valuable antibacterial properties of penicillin and its use as a therapeutic agent, the question was raised by Stokes and others[6,8,13] as to its possible abortifacient action. It is significant that clinical observations made at that time of cases of threatened and actual abortion complicating the administration of penicillin in pregnancy were made in the early days of its usage and primarily on patients undergoing antiluetic treatment. It is now believed that those untoward reactions resulted not so much from the penicillin itself, but from the impurities contained in the

logic diagnosis and sensitivity, is to establish and maintain a blood concentration above that considered clinically necessary to destroy the offending pathogen. In our experience maximal therapeutic efficiency has been obtained in the average infection by the three hourly intramuscular injection of 50,000 to 100,000 units of penicillin in aqueous solution.

Blood level determinations have been considered of therapeutic significance in that they provide the following: (1) information as to when penicillin is present at maximally effective bacteriostatic concentrations; (2) when lower, more slowly bacteriostatic concentrations are found; and (3) when concentrations are not sufficient to inhibit growth *in vitro* but great enough to act *in vivo*.[3] This explains the apparent discrepancy between reported *in vitro* sensitivities and the clinical response of the infectious process in many cases of infection with "resistant" organisms.

Penicillin differs in its action from that of the general protoplasmic poisons, such as certain halogens, heavy metals and phenols, in that it interferes with a specific biologic mechanism in the growth process of a select group of organisms causing ultimate destruction. The action of penicillin is exerted directly on the invading organism and is, therefore, not dependent upon interaction with the bodily defense mechanisms. Very high concentrations of penicillin may also be bacteriocidal to some organisms. Since penicillin has been found to be virtually nontoxic, it may be administered by any known avenue or route which will bring it in contact with the pathogen.

The intramuscular route is the method of choice in the average or more severe infections. On our service all cases which require penicillin are admitted to the hospital in order that they may receive injections every three hours. The continuous intramuscular drip may be used in more severe infections where higher and more sustained levels are required.

Intravenous administration has been reserved for overwhelming infections where exceptionally rapid and high blood levels are desired. By the continuous intravenous drip, penicillin enters the blood stream continuously and produces high levels despite its rapid excretion by the kidneys.

Subcutaneous administration of penicillin in aqueous solution is feasible with the highly purified crystalline preparations now available. The rate of absorption is slower than with the intramuscular and intravenous routes, and blood levels are uncertain. There may also be pain at the site of injection.

Topical applications in the form of aqueous solutions or in ointment

TABLE IV. CASES RECEIVING PROPHYLACTIC PENICILLIN

Indication	Number Cases	Average Dose	Average Total	Number Morbid	Comment
Antepartum gonorrhea	1	30	1.5	1	Temp. to 102° ppd; 101° ppd4, Norm ppd4
Uterus packed	9	60	1.4	0	6 patients temp to 100°—one day only
3rd degree laceration	4	80	2.5	0	Afebrile, no signs of infection
Vaginal exams before delivery	6	40	0.6	0	2 patients temp. to 100°—one day only
Manual removal of placenta	1	40	0.6	0	Afebrile, gross contamination suspected
Premature rupture BOW	6	80	3.2	0	1 patient temp. rise to 100°—one day only
Total Cases	27	—	—	1	

threatened abortion was the chief complaint. The group of "Incidental Infections" includes a variety of types of infection not related to the pregnancy except by coincidence. These are included in Table I.

The second category, "Cases Admitted Intrapartum," includes all patients who were delivered of a viable infant. Only those patients were considered to be "normal" who exhibited no evidence of infection, did not receive penicillin or other specific chemotherapy, and who had no temperature elevation sufficient to be classed as "Morbid." The group of genital tract infections includes pelvic cellulitis and perineal infections following episiotomy as well as frank endometritis. Those patients listed under "Prophylactic Penicillin" received this drug for a variety of reasons; these indications are tabulated in Table IV. "Incidental Infections" again is that group of patients who had infectious processes not related to the pregnancy, and all those in this category had upper respiratory infections.

"Cesarean Sections" are listed separately because it was felt that these constitute a special complication and that the results in these cases should be considered apart from the vaginally delivered patients.

INDICATIONS IN TREATMENT AND PROPHYLAXIS

The various indications for the prophylactic use of penicillin of patients delivered vaginally are listed in Table IV. These twenty-seven patients constitute 3.2 per cent of the vaginally delivered cases. Only one patient had a morbid puerperium. She had acute gonorrhea during the eighth month of pregnancy, and received 30,000-unit dosage of penicillin for a total of 3.2 million units during the acute phase of the infection with apparent recovery except for a moderately profuse

TABLE V. CESAREAN SECTIONS

	Morbid				Not Morbid				Total		
	A		B		A		B		Total Morbid		
	No.	%	No.	%	No.	%	No.	%	No.	No.	%
Section during labor	2	9.5	0	0	2	9.5	1	4.8	5	2	40
Elective section	3	14.3	1	4.8	7	33.3	5	23.8	16	4	25
Total	5	23.8	1	4.8	9	42.8	6	28.6	21	6	65

A—With penicillin
B—Without penicillin

nonspecific vaginitis. When this patient was admitted in labor, penicillin was again begun in 30,000-unit dosage and was given for six days. In spite of this she had a morbid course with temperature to 102° on the third postpartum day and 101° on the fourth postpartum day, with the usual signs and symptoms of acute endometritis. It is probable that the 30,000-unit dosage used at the time of delivery in this patient was inadequate, and suggests that some resistance to penicillin had been acquired by the organisms responsible for her vaginitis. This does not reflect our current policy in this respect. During the past six months we have administered 100,000 units every three hours as the prophylactic dose whenever such prophylaxis was thought indicated. In general, the results as presented in Table IV were satisfactory since in all of these situations the likelihood of infection is, theoretically at least, much increased.

While it is true, as pointed out by Mengert,[9] that basic causes of intra-uterine fetal death remain largely unknown, infection as a possible cause has received relatively brief mention in the literature. Again referring to Dr. Mengert's paper of last year, he listed infection as the cause of fetal and neonatal death in 3.1 per cent and 4.7 per cent in Sloane and Chicago Lying-In Hospitals, respectively.

In 1945 Douglas[2] pointed out the value of prophylaxis in puerperal infection over any known curative agent once the disease was established, and stated at that time "that sulfadiazene or penicillin given early may be efficacious, while late in the course of the disease they may be relatively ineffective." Since then, some very interesting work has been done on the bacteriology of the uterus during labor and the puerperium. Guilbeau[4] and others on Dr. Eastman's service at Johns Hopkins Hospital have just completed a study of the effect of penicillin on the bacterial flora of the postpartum uterus. This investigation consisted of a study of the uterine cultures from eighty-six postpartum patients and indicates that relatively high doses of penicillin administered ante-partum and postpartum may eliminate penicillin-sensi-

TABLE VI. POSTPARTUM MORBIDITY

Diagnosis	Number of Cases				Total	
	Morbid		Not Morbid			
	A	B	A	B	No.	% Morbid
Normal	—	—	—	736	736	0
Mastitis	18	0	6	0	24	75
Endometritis	3	0	5	2	10	30
Pelvic cellulitis	2	3	3	0	8	63
Perineal infection	2	0	3	0	5	40
Urinary tract infection	2	2	8	6	18	22
Prophylactic penicillin	1	0	26	—	27	4
Upper respiratory infection	0	0	5	—	5	0
Total	28	5	56	744	833	3.96

A—With penicillin
B—Without penicillin

tive organisms from the postpartum uterus for seventy-two hours or longer. Even single doses, given early in labor, may be effective forty-eight hours after delivery. This very excellent work not only helps to confirm the opinion that penicillin therapy is more effective when instituted early, but will undoubtedly stimulate further interest in the study of the prophylactic use of penicillin in obstetrics.

Table V lists the patients who were delivered by cesarean section. The section rate, 2.46 per cent, is comparable to the over-all section rate for this hospital, 2.66 per cent. It is interesting to note the increased morbidity among those patients who were sectioned after labor had started, namely, 40 per cent in that group, as compared to 25 per cent in the group sectioned electively before the onset of labor. This suggests that the onset of labor is a factor in the spread of infection as reported by Guilbeau. Most probably this related to the extension of pathogenic organisms from the lower reproductive tract to the interior of the uterus and probably also to the parametrial tissue. The incidence of morbid patients in this group who had received penicillin, as compared to those who had not, would seem to contradict our thesis that penicillin is efficacious in reducing the effects of an infectious process. However, those patients who received penicillin were, for the most part, obviously infected before delivery was accomplished. Also, during the early part of the series relatively small dosages of penicillin were given, namely, 30,000 or 40,000 units every three hours. Since we have begun to use large doses of penicillin, that is, 100,000 units every three hours, the results have been much more gratifying. This series of twenty-one sections is, of course, too small to permit any statistically sound comparison. It is, however, interesting to note that among the fourteen patients in whom there was an indication for penicillin treatment, only about one-third actually had a morbid postoperative course.

ADVANTAGE OF ADEQUATE DOSAGE

Among the vaginally delivered patients, thirty-three (3.96 per cent) had puerperal morbidity (Table VI). The largest group of morbidity was in a series of patients having mastitis. Two patients of this group were of special interest. These women had acute mastitis eight and eleven days respectively after delivery and were treated with 40,000 units of penicillin every three hours for a total of 800,000 units, and both had a fall of the temperature to normal within thirty-six hours. Both of these patients, however, had recurrences of the infection in the same breast within four days after the initial course of penicillin was discontinued. The second course of penicillin therapy consisted of 100,000 units every three hours for periods of four and five days, respectively. Both patients had a good clinical response and no further recurrences. We have noted that in cases of mastitis the most important factor as regards the duration of the febrile reaction and of course, concomitantly, the toxicity of the patient, is the time at which penicillin treatment was started as was concluded by Douglas.[2] This factor seems to have been of more importance than the dosage. When penicillin was begun with the earliest signs of inflammation in the breast, the clinical course was much more benign than in those patients who had developed a marked febrile reaction before the onset of therapy. The infections cleared more rapidly, and there was less induration in the first group of patients. The dose of penicillin used seemed, by and large, to be related to the rapidity with which the inflammatory process resolved; that is, the period of convalescence was less and the duration of definite indurated areas was less in most patients receiving large doses. There was no case of recurrence in any patient who had received either 80,000 or 100,000 units of penicillin during the initial course of treatment.

We should like to note here that we are opposed to the practice of reducing the dose of penicillin when the acute phase of an infectious process has apparently been overcome. We believe that this will increase the incidence of recurrence, since organisms beginning to develop a resistance to penicillin will not be affected when the smaller dose is used. It will be noted from Table VI that all patients with mastitis received penicillin treatment. In this small series of twenty-four cases there was no patient who developed abscess. It should be further noted that penicillin was the only specific treatment used in these cases; neither sulfonamides nor x-ray was employed as an adjuvant. We believe that the high incidence of morbidity in this group of infections in spite of penicillin treatment is only a reflection of the seriousness of the condition.

SELECTIVE ACTION OF PENICILLIN

The group of pelvic infections, i.e., endometritis, pelvic cellulitis and perineal infection, is interesting in view of the response which these patients made to penicillin treatment. In endometritis the principal offending organism was Staphylococcus aureus in those cases which were not morbid and E. coli in all three cases which were morbid. It will be noted that these three patients all received penicillin. Secondly, in perineal infections the organism was E. coli in both morbid cases and one of the cases which was not morbid, and a nonhemolytic streptococcus in the other two cases which were not morbid. Cases of pelvic cellulitis include those patients without definite signs of endometritis, but who did have lower abdominal tenderness and fever. In three cases large doses of penicillin were given with the onset of the earliest signs with a good response. In two patients penicillin was started only after two days of fever, and they also made a good clinical response. Three patients had relatively low grade fevers, 100.6° and 100.8°, for two or three days with minimal signs, and were not treated with penicillin but received sulfonamides.

Among the urinary tract infections, two of the ten cases receiving penicillin were morbid. In these two cases sulfonamides were not given. In the eight cases which were not morbid, five had received sulfonamides and three had not. The two morbid patients with urinary infections who did not receive penicillin did receive sulfonamide therapy.

In the upper respiratory infections, five in number, all received penicillin treatment with the earliest signs of the disorder. All made excellent clinical response.

In reviewing these cases, several things seem to be suggested. First, in urinary infection, sulfonamides were apparently of more therapeutic value than was penicillin, even in large doses. Second, with a frank endometritis, large doses given early were effective except in those cases in which E. coli was present, and in those penicillin seemed to be relatively ineffective. Third, in the group of perineal infections, the same situation obtains. This would seem to indicate that postpartum infections the important factors are, first, early treatment with adequate dosage of penicillin, and second, recognition of those cases in which a penicillin-resistant organism is present, and in such cases to use other drugs in addition to penicillin. We believe that penicillin is indicated in all cases of puerperal infection even when the principal pathogen present is known to be penicillin resistant. This means the effects of other organisms present will be kept at a minimum. Treatment should, of course, be instituted to combat the penicillin-resistant organisms.

TABLE VII. PELVIC INFECTION AS A FACTOR IN ABORTION

	A (1)						Total		B				Total	
	Total		a		b				a		b		a	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
AB 59	1	1.2	1	1.2	0	—	58	67.5	31	36.1	27	31.4	32	37.3
TAB 27	2	2.3	2	2.3	0	—	25	29.0	16	18.6	9	10.5	18	20.9
86	3	3.5	3	3.5	0	—	83	96.5	47	54.7	36	41.9	50	58.2

(1) Under "AB" only those cases are included who received penicillin before abortion occurred
A—With penicillin
B—Without penicillin
a—With pelvic inflammatory disease
b—Without pelvic inflammatory disease

PELVIC INFECTION AND ABORTION

In our clinic we see a large number of patients who have pelvic inflammatory disease. Most of these patients have a relatively benign type of infection, chronic in nature, which we classify as low grade types of infection. They rarely develop an acute exacerbation. It was our impression in the clinic, and on the gynecological and obstetrical services, that many patients with this type of infection presented fertility problems and that abortions and threatened abortions were fairly frequent. It was thought, therefore, that perhaps the infectious process *per se* was a significant factor in these two conditions. If this were true, elimination of such an infectious process could probably be of benefit both as regards fertility and the occurrence of abortion. We have no figures available on the effect, if any, of penicillin on patients with infertility problems, but it was possible to analyze our series of hospital cases of abortions, complete, incomplete, and threatened, with regard to the occurrence of concomitant pelvic inflammatory disease in respect to the effect of penicillin treatment. These figures are presented in Table VII. It will be noted that eighty-six patients are included in this series. Of these, fifty (58 per cent) had clinically recognizable pelvic inflammatory disease, while thirty-six (42 per cent) did not. Among the first group of patients who aborted—including complete abortion or incomplete abortion necessitating dilatation and curettage—there were a total of fifty-nine cases. Of these fifty-nine, thirty-two patients had pelvic inflammatory disease and twenty-seven did not, or 54 per cent and 46 per cent, respectively. Among patients without pelvic inflammatory disease, none received penicillin before abortion, and among the patients with pelvic inflammatory disease, only one patient had received penicillin before abortion (v.s.). In the group of patients with threatened abortions, nine were without pelvic inflammatory disease, and eighteen patients had pelvic inflammatory

disease. In the former group no patient received penicillin treatment. In the latter group two patients did receive penicillin.

An analysis of these figures can only suggest a relationship since the series is very small, but the suggestions are quite definite. The fact that there is a relatively small difference between the number of patients with and without pelvic infection who aborted would indicate that probably this infection was not the most important factor but that such abnormalities as defective ova and faulty implantation were more signficant. However, among the patients with threatened abortion, the difference between these groups is considerable. Twice as many patients had pelvic infections as did not. This tends to support the hypothesis stated above. The study of this possible relationship is being continued on our service.

In view of the clinically proven value of penicillin when used alone or as combined therapy in not a few conditions which, before its discovery, were for the most part treated expectantly—and frequently unsuccessfully—a criticism that it is used promiscuously would seem unjustified. Until an antibiotic or chemotherapeutic agent with superior antibacterial activity and with equal freedom from toxicity is discovered, it is believed that penicillin administered for the proper indications, either prophylactically or early in the course of infectious disease, and in adequate dosage will continue to serve in revolutionizing the management of obstetrical problems attended by infection.

SUMMARY AND CONCLUSIONS

1. The advantages in the use of penicillin in obstetrics over other chemotherapeutic agents are discussed, as well as its efficacy and compatibility with other agents in combined therapy.

2. The possibility of abortifacient or oxytocic properties of penicillin is discussed, and clinical evidence is presented which suggests that such reaction reported early in its use, for the most part in patients undergoing antiluetic treatment, was the result of impurities in the drug or of therapeutic shock.

3. The significance of bacteriologic diagnosis and sensitivity is discussed with their relation to dosage and therapeutic efficiency of penicillin. Penicillin resistance may rise in the presence of inadequate dosage.

4. The modes of administration and relative efficacy are discussed. The intramuscular route has been found to be the method of choice in all but the most severe infections.

5. An evaluation of the results of penicillin therapy in the various infections complicating pregnancy is presented in a statistical analysis.

The value of the prophylactic and very early use of penicillin in sufficiently large doses when it is indicated has been fairly well established.

6. The possibility that pelvic inflammatory disease might be a factor in certain cases of infertility and in some cases of premature termination of pregnancy is suggested. While there are insufficient data from the study to prove such a thesis, further investigation may reveal that such infections are sufficient indications for active therapy. With our present armamentarium this includes penicillin.

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DISCUSSION

Dr. R. T. LaVake, Minneapolis, Minn.—This excellent paper is of great practical importance. Drs. Harris and Shook have well emphasized what our experience would corroborate: that pregnancy is not a contraindication to the use of penicillin, that the earlier it is administered the more effective it tends to be, and that the dosage should be adequate from the beginning. The method of administration and dosage outlined has in our experience given excellent results.

In regard to when to stop the penicillin, we have found that it is well to continue the penicillin until all visual and palpatory signs of the inflammation have subsided and temperature and leukocyte count have been normal for forty-eight hours. It is hoped that there will be more discussion on this important point.

That the incidence of abortion is definitely increased by all types of infection is borne out by clinical experience, and serologic data has suggested the likely mechanism that brings about this increase. It seems, therefore, that the essayists are logical in their reasoning that by eliminating infection by penicillin the incidence of abortion should be reduced. The prevention and elimination of infection in pregnancy has been an essential part of prenatal care for many years, with the lessening of abortion incidence as one of its major aims.

It would seem from Dr. Harris' cesarean statistics that he wishes to make it clear that the idea of prophylactic penicillin should not lead one to change in any way one's rules governing the safest condition, method and time for performing cesarean; and that the idea should not be interpreted as permitting any reduction of previously recognized standards favoring perfect asepsis, or as permitting increased latitude in regard to the safety of operative interference. With these views we heartily concur.

It has been our experience also that urinary infections are most frequently of a type more amenable to the sulfonamides than to penicillin. Thus the sulfonamides are tried first, before results from cultures can be obtained, and if ineffective, penicillin is substituted.

I wish to thank Dr. Harris for his courtesy in giving me plenty of time to study his findings and conclusions.

DR. LOUIS H. DOUGLASS, Baltimore, Md.—Captain Harris has presented the results of a painstaking piece of work, and deserves our congratulations for its completeness and the clarity with which it is put forth. Among the statements which he makes, there are several which will bear repeating for the sake of emphasis: First, penicillin is not a panacea for all types of infection met with in obstetrics. There are organisms which are extremely resistant to the drug, and little or no benefit would follow its use when dealing with infections from these. Therefore, cultures should be obtained at the onset of treatment, and additional therapy added when indicated; or better still, since the colon bacillus is so frequently encountered, one of the sulfa drugs might be included at the beginning of treatment. This is a point which has been, and still is, woefully neglected in many places. When the essayist speaks of the phophylactic use of penicillin, it would appear that he has learned well the inadequacy of small doses and at the present time is actually using it therapeutically; and this is as it should be. When a patient is potentially or actually infected, it means that her tissues are being invaded by pathogenic organisms of unknown virulence and susceptibility to penicillin. Since it is safe to use penicillin in large dosage, it would seem better judgment to give enough to care for all contingencies. In this way there will also be much less danger of resistance to the drug occurring.

Captain Harris, when he speaks of cesarean section, does not state whether these were classical, low or extraperitoneal, and in this he is probably wise, since the relative safety of these various approaches is still being debated. Probably the simplest conclusion today is that, in the presence of infection, any type of section is hazardous, and that the sulfa drugs and penicillin have materially reduced the risk but have not completely eliminated it.

The experiments in the use of penicillin in cases of relative sterility and repeated abortions are most interesting, and it is to be hoped that the work will be continued. It might be extended with benefit to include the husbands as well as the wives.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—On January 1, 1947, we initiated a study on the efficacy of penicillin as a substitute for silver nitrate in the prophylaxis of gonorrheal ophthalmia. The object of that study, of course, had to do with ophthalmia and not with puerperal infection, but we were interested to know the results with regard to the latter. Each mother received 200,000 units of penicillin intramuscularly at the onset of labor. If her labor extended beyond eighteen hours, this was repeated. Our puerperal morbidity in 1947, judged by usual standards, was 3.8 per cent. In 1946 our puerperal morbidity had been 8.2 per cent, and in 1945, 9 per cent, and has never been below a figure of 8 or 9 per cent except for the year of 1947.

After trying to explore other explanations for this reduction of puerperal morbidity by one-half, we felt that the injection of penicillin was probably the factor. Some plausibility to this hypothesis was lent by the following circumstance. On January 1, 1948, we gave up the maternal injection of penicillin

in labor and, for the first six months of this year, our puerperal morbidity has returned to the previous figure of 8 or 9 per cent. This is in agreement with Dr. Plass' report, and it was this clinical study that led us to the laboratory and prompted the study that Dr. Guilbeau and his associates made, to which Dr. Harris referred this morning. They found that puerperal uterine cultures were sterile in 75 per cent of cases in which penicillin had been administered routinely in labor, whereas in patients who had not received penicillin the great majority showed pathologic organisms. This leads us to believe that penicillin is lethal to most organisms that commonly cause puerperal infection. The clinical implications are plain enough; and it is our feeling that any woman who has been in labor for eighteen hours or more, or any woman who has had ruptured membranes for twelve hours or more, or who in any way seems to be headed for trouble, should have penicillin administered prophylactically. This is especially advisable if there is any likelihood of cesarean section being performed.

DR. E. D. PLASS, Iowa City, Iowa.—In an attempt to determine the effectiveness of penicillin given during labor in reducing the incidence of puerperal febrile reactions, my associate, Dr. W. C. Keettel, carried on a clinical experiment during the year ending in February, 1948. Alternate patients were given 300,000 or 600,000 units of penicillin in oil and wax as soon as they were definitely in labor, and 300,000 units every twenty-four hours thereafter until delivery, with a single 300,000 unit dose post partum, twenty-four hours after the last antepartum injection. There were 465 patients in this series and 430 in the control group which received no antepartum antibiotics.

All temperatures were taken by mouth five times daily, every four hours except at 2:00 a.m. Any elevation to 100.4° or higher was considered febrile. "One-day fever" was diagnosed when the elevation persisted for less than twenty-four hours. The same criterion was employed in determining "intrapartum fever."

There was no significant difference in the incidence of "one-day fevers" and "intrapartum fevers" in the two groups, possibly indicating that they are not commonly due to infections, or that if infectious in origin, the etiologic organisms are not penicillin sensitive.

Fevers lasting two or more days occurred in 10.2 per cent of the control series, as against 7.0 per cent in those receiving an initial penicillin dose of 300,000 units, and 3.0 per cent for the series given 600,000 units at the onset of labor. In the whole series there were twelve untreated patients who had fever for more than three days, as compared with only two in the treated series. This appears to indicate that the more persistent puerperal fevers are more likely to be due to aerobic Gram-positive bacteria that are sensitive to penicillin. The evidence also appears to support the concept that a fair proportion of post partum infections of the generative tract are the result of the invasion of anaerobic bacteria that generally are resistant to penicillin.

This work is being continued in an effort to determine whether there is any value in prophylactic administration of this antibiotic to normal women with the prospect of normal parturition. At present, we are skeptical. On the other hand, we are already convinced that in prolonged labor, the administration of penicillin is reasonable and probably useful, particularly for the protection of the child from the dangers of amnionitis.

On the basis of our limited experience, we are also impressed by the value of antepartum penicillin injections as a means of eye prophylaxis in the new-

born. Conjunctivitis neonatorium appears to be less common following this form of indirect prophylaxis than after local applications of either 1 per cent silver nitrate solution or of penicillin-containing ointment.

DR. OTTO H. SCHWARZ, St. Louis, Mo.: I just spoke to Dr. Douglas and asked him to say something on anaerobic streptococci but he was too modest to respond. I was very glad that Dr. Plass mentioned the anaerobic streptococci in his discussion, and was especially pleased to hear Dr. Eastman's discussion. Bacteriologic studies done years ago, not only in our clinic but at New York Lying-In, Hopkins and Chicago Lying-In as well, showed very conclusively that anaerobic streptococci are the chief offending organisms in such services. I have for some time made an effort to find out just what the penicillin would do to the anaerobic streptococci and found nothing definite. Sulfa drugs are of no use against anaerobic streptococci. Dr. Plass stated that they are not sensitive to penicillin, and Dr. Eastman pointed out they were. This causes further confusion, but since Dr. Eastman's statement is based on actual bacteriological work, we must accept it, and I therefore feel this is a most valuable contribution.

DR. L. MARSHALL HARRIS, Great Lakes, Ill. (closing).—I wish to express my appreciation to the members of the Association for the invitation to present this paper.

Dr. LaVake has raised the question as to what constitutes adequate penicillin therapy. In our experience the indications for discontinuing the drug after the acute signs and symptoms of infection subside depend upon the condition. We believe the practice of reducing the dosage when the acute phase has apparently been overcome will increase the incidence of recurrence, since organisms which develop a degree of resistance to penicillin will not be affected by the smaller dose.

In reply to Dr. Douglas, all our cesarean sections were of the low cervical type except one classical in a patient who had a history of a previous classical section. From the interesting work they are doing with penicillin in obstetrics, the remarks by Dr. Eastman and Dr. Plass are a real contribution. I wish to express my appreciation to them and to Dr. Otto Schwarz for their discussion.