THE YEAR BOOK *of* DRUG THERAPY 1971

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INTRODUCTION

Drug Therapy and Some Urgently Needed Reforms

There continues to be an ever-increasing interest in drug therapy. Each year brings some new and important development in the field. In 1970, perhaps the most important development was the release of L-dopa for the treatment of Parkinson's disease. There have recently appeared new and highly effective antibiotics which will exert an impact on the antibiotic field. Although the scientific developments have been great during the past year, there are many factors yet that remain to be explored which are not necessarily in themselves scientific in nature.

At present we are caught up in an era of great therapeutic progress. Numerous new and highly effective agents have been made available for the treatment of disease. Despite some increased difficulty in drug testing brought about by the panic created by the thalidomide episode, there continues to be an impressive search for new and more potent agents. As a result of the reforms initiated during the 1960s, the physician can now be reasonably certain that the drug he prescribes is indeed a potent substance which will exert the type of action claimed for it in the manufacturer's information bulletin.

Although this progress is highly commendable and has improved the situation a great deal over what existed a decade ago, there remain some glaring deficiencies which cause concern to any thinking individual interested in drug therapy. First, there is the problem of drug dating. Although for a long time antibiotics have been dated, with the physician returning outdated supplies for new ones, this has not been so for many other agents which are also subject to deterioration by the passage of time. For example, drugs such as nitroglycerin, tincture of belladonna, thyroid prepared from animal products and digitalis, to name a few, lose efficacy with aging and thus pose a hazard in the treatment of disease. Drugs such as nitroglycerin, which is known to be somewhat unstable, are sold by the manufacturer to the pharmacist in bulk amounts. The drug is then dispensed to the patient in smaller amounts over a period of months or perhaps even years. So far as I know, there is no dating by the manufacturer which indicates that the drug should be discarded after a certain period of time. Unquestionably, nitroglycerin that has been stored in various climates and opened to the air for different lengths of time must lose a certain portion of its potency or at times actually become impotent and, therefore, the patient does not receive benefit from the drug. There is no situation that requires a pharmacist to return a half-emptied bulk bottle of nitroglycerin although it may have been in his possession for months or even years. Furthermore, under the present method of handling drugs, he would have no real information as to whether the drug had deteriorated or not. The same could also be said of such agents as tincture of belladonna, which is known to deteriorate over a period of several months.

What is the situation for drugs such as various sedatives that are considered to have more stability? It would be altogether possible for

patients to receive drugs that might be 5, 10 or even 15 years old. The physician, the patient and the pharmacist have no information available as to the stability, the potency or the rate of deterioration or have any guidelines to follow as to when such a supply should be destroyed. Suffice to say, there should be established definite standards as to when drugs should be declared not suitable for human use. Certainly there should be established definite guidelines as to rate of deterioration in order to assure that those less stable agents are not prescribed to the unsuspecting patient.

Another concerning situation is the physician's lack of information as to the cost of the drugs he prescribes. It is exceedingly embarrassing to the physician to write a prescription for a drug and then face a somewhat unpleasant session with the patient who informs him that the prescribed drug cost a large sum of money or that the cost was so prohibitive the patient was forced to take a smaller amount or that the patient felt in some way he was being taken advantage of by the pharmacist. As the situation now exists, it is nearly impossible for the practicing physician to know the cost of the drug he prescribes. It is true that he could get copies of the pharmacist's *Red Book,* which might give him some guidance. However, most physicians are unaware of such a compendium and would find it tedious to look through the thousands of preparations in order to find the particular prescription item needed. It is shocking at times to discover how expensive certain items can be. When a prescribed preparation turns out to be highly expensive, the physician is inclined to think that the pharmacist is perhaps charging too much and thus taking advantage of the patient. It must be realized that certain drugs are definitely expensive. Usually, the costs are reasonable when one fully understands what has gone into the development of the drug and the fact that it may save the patient from a highly expensive and protracted illness. Unquestionably, certain items do seem to be overpriced, and physicians at times have a distinct feeling that the cost of certain items is out of proportion to their value and also to the effort that went into their discovery and manufacture. In order to correct some of this difficulty, it would be most helpful to the physician to have available the manufacturer's suggested price on a standard unit amount of each drug they manufacture. This could be put in the *Physicians' Desk Reference.* It is already being done in hospital formularies so that the physician may know in the beginning whether he was dealing with a highly expensive drug. If he knew the cost of that drug as sold to the pharmacist, he could then make a reasonably close estimate of the cost to the patient since the pharmacist should have a normal markup of approximately 60% on the product he sells to cover his operating expenses and services. The patient could thus be informed in advance approximately what the drug would cost him. Furthermore, such information would alert physicians to the necessity of checking carefully on the cost of drugs and selecting agents that are less expensive when such agents would cover the situation as well as the more expensive preparations. Much of this problem was discussed in an article by the editor which was published recently (Generic Terminology and the Cost of Drugs, J.A.M.A. 209:80, July 7, 1969).

There has been a great deal of discussion concerning the use of so-called generic terminology in the prescription for drugs. The use of generic terminology in medical centers where the Formulary System is employed and where there is an experienced pharmacist and his staff to select the drugs that are authorized for the Formulary is of great service and has widespread acceptance. Because of the success of this approach, many teachers and younger members who are well acquainted with the Formulary System believe that the use of the generic terminology approach should be universal and that all prescriptions should be written in the generic form. The proponents of this approach are certain that there would be considerable savings to the patient, and there would be no difference in the therapeutic result. It is tempting to follow this line of reasoning, and a great many people have done so without looking at all the consequences of such an approach. If an ideal situation existed where every drug that is available for prescription use was equally effective therapeutically irrespective of the manufacturer, then this situation could be embarked upon with confidence by the physician. However, there are many aspects that worry the thinking physician with the situation being as it is at present. It must be remembered that once the physician writes a prescription in generic terminology, he then delegates the responsibility of selecting the drug to be dispensed to the pharmacist. Most pharmacists are conscientious individuals who select the best drugs they can, usually from manufacturers of reliable reputation. Because they have no way of evaluating the drugs themselves, they feel that this is the best course and they make a determined effort to see that their customers get a drug that will do what it is supposed to do. These pharmacists dispense to the patient a drug which is prepared by a highly experienced manufacturer and, although the prescription has been written in generic terminology, a well-known trade name item is dispensed to the patient, and he is charged accordingly. As things are now, it is to the advantage of the pharmacist, even though he may be highly conscientious, to see that the patient gets a high-quality drug which may even be more expensive than another high-quality drug because he gets a markup of at least 60% on each prescription item sold. Therefore, since he is a business man as well as a professional man, he may be inclined to dispense the more expensive item for the added profit that his operation would receive. I doubt that this is a major factor in the decision of a pharmacist in dispensing a drug, but the situation can exist. As a consequence, many pharmacists and others have advocated that a pharmacist be paid a set fee for his services and then charge the cost of the drug, avoiding any markup on the sale itself. Finally, the pharmacist may not be a conscientious individual. He may buy the cheapest drugs he can get without any consideration of the manufacturer or have no real knowledge as to the ability of the firm which supplies the drugs. He may not even know from where the original supply of drugs came. This individual may or may not, as a result of this policy, carry potent agents and may at times carry agents that are inactive.

There is also another aspect to this question that is of concern. Every thinking physician and pharmacist knows that many factors enter into

the manufacture of the finished product that is accepted by the FDA and then marketed. These items are naturally protected by copyrights and patents so that for many years they cannot be sold except by that manufacturer or licensed individuals. Therefore, no matter what terminology is written, the same product is dispensed at the same cost. However, once the patent rights expire, many manufacturers can enter the field and put the product on the market under the generic term. Although most of these manufacturers are capable and do put out good products, some operations are questionable. It is impossible for the FDA to police adequately the numerous manufacturing plants in the United States. However, as public pressure builds and the FDA becomes more active in this field, many careless or inept manufacturers will be apprehended and forced to change their ways or go out of business.

Finally, until recently, it has been thought that, if a preparation contained the required amount of chemical, it would be as effective as any other agent containing the same amount of the chemical ingredient. However, we now know that this is not so, that elements that go into the manufacturing of the drug can rather profoundly influence the degree of availability of the chemical to the cells of the patient. Therefore, a preparation that has been thoroughly investigated and found to be clinically effective and put on the market by the manufacturer who developed it represents all the technics of manufacture and such that went into it in such a way that the drug ends up as an effective product. Another manufacturer, using the same amount of chemical but not knowing the exact process of manufacturing, may end up with a product that is not as effective because it is not available to the cells in the same amount. Therefore, it seems to me that the item that has been proved to be effective clinically and has been in use for a long time should be the standard with which all other preparations of this particular chemical substance should be compared. It should be demonstrated that the new manufacturer's product is capable of giving the same blood levels and presumably the same absorption and excretion curves as were already known for the standard product.

Until all of these above factors can be resolved, the physician should be hesitant about writing generic terminology for drugs that may have a critical role in the treatment of his patient.

Generic terminology can be used to advantage in certain situations, e.g., the physician writes for the medicine in generic terminology and then designates a manufacturer whom he knows to be reliable and who has made his product available at a more reasonable price than other manufacturers. Considerable saving can be passed on to the patient in this way, provided the pharmacist who dispenses the drug will see to it that this saving is actually realized by the patient. Some examples of this type of savings were given in an article by the editor and his colleagues (Generic Drugs and Therapeutic Equivalance, J.A.M.A. 206: 1785, Nov. 18, 1968). (Editorial)

The *Modern Drug Encyclopedia* lists some 12,000 items available for prescription by the physician. The *Physicians' Desk Reference* lists approximately 5,000 preparations. The *United States Pharmacopeia,*

which has a select group of experts, finds that approximately 600-700 items are all that is necessary for the practice of the highest type of medical therapeutics. Therefore, it must be obvious that there are many items which actually are of limited use or are very seldom used and certainly have no compelling role in the management of patients. Since the average practicing physician is not an expert on drug therapy, it is most difficult for him to be selective in the use of such a plethora of drugs. Frequently, it results in many of these much less effective or sometimes nearly ineffective agents being used widely because of a lack of real informed sources to guide the physician. Many years ago, the author recommended a national prescription formulary be prepared by a select group of individuals who would go through the many thousands of agents available and select the essential core needed in the practice of medicine. It should have enough variety to cover the needs of various regions of the United States and various therapeutic customs and a wide enough range to give the physician an adequate choice of agents in each category. It is estimated that such a formulary would contain perhaps 1,000-1,500 items. The formulary should be prepared in a format such as would be readily available to the physician for prescription purposes. It would list the drug, the generic terminology, the usual dose, the daily dose, a few words about the most common and dangerous toxic effects, a code to classify it as to degree of cost and, finally, the amount recommended for prescription. If such a compendium were prepared by a group such as that of the *US Pharmacopeia,* the Council of Drugs of the AMA or various government services or a combination of these, it would have the same type of use as the hospital formulary has to the hospital staff. The drugs selected for inclusion in this formulary would be passed on by an expert committee, and therefore items would be expected to be therapeutically effective provided they were properly manufactured as compared with the standards of each particular category. Such a formulary should be made available to every physician, actually as a part of his dues to the AMA or his local society. Such a formulary, supported by the profession and prepared by knowledgeable individuals, would have the confidence of the physician and unquestionably would contribute considerably to an improvement in prescription habits of the practicing physician.

In conclusion, it is apparent that there are certain badly needed reforms in drug therapy despite the great advances that have been made. The FDA should devote a great deal more attention to the problem of seeing that the patient gets effective agents through proper dating. The physician should be in a position to guide his patient as to drug costs, and there should be a much more sensible discussion of generic prescribing than has been evident so far. Finally, we all should work together to improve the ability of the physician to prescribe effective agents at the least cost to his patient.

D. G. F.

Abortion

Therapeutic Abortion Using Prostaglandin $F_{2\alpha}$. Prostaglandins are efficient as oxytocics and have been used to induce labor in women at or near term. S. M. M. Karim (Makerere Univ. Med. School, Kampala, Uganda) and G. M. Filshie[1] (King's College Hosp., London) describe the

DETAILS OF CASES OF THERAPEUTIC ABORTION INDUCED BY INFUSION OF 50 μG. PROSTAGLANDIN $F_{2\alpha}$ PER MINUTE

No.	Age	Nationality	Para	Gravida	Gestation (wk.)	Induction-abortion interval	Interval between the delivery of the fetus and placenta	Remarks
1	21	British	1	1	16	12 hr. 15 min.	0 min.	..
2	16	West Indian	0	1	17	24 hr. 30 min.	0 min.	Previous hysterotomy
3	29	British	6	7	14	6 hr.	3 hr.	..
4	20	Nigerian	3	3	14	10 hr.	0 min.	Diarrhœa
5	28	Nigerian	5	6	19	6 hr. 20 min.	0 min.	Diarrhœa and vomiting
6	22	British	0	0	14	17 hr.	0 min.	Diarrhœa and vomiting
7	17	West Indian	1	1	16	4 hr. 20 min.	0 min.	Diarrhœa
8	27	British	4	4	12	8 hr. 15 min.	..	Evacuation of retained products of conception; diarrhœa
9	35	West Indian	4	7	15	9 hr.	7 hr.	Diarrhœa
10	20	British	3	3	9	12 hr. 40 min.	7 hr.	..
11	24	West Indian	2	3	22	17 hr. 47 min.	0 min.	..
12	36	British	5	5	12	11 hr. 30 min.	0 min.	..
13	31	British	0	0	16	Failed*	..	..
14	18	British	0	0	12	8 hr.	0 min.	Diarrhœa and vomiting
15	22	West Indian	4	4	16	27 hr. 15 min.	0 min.	..

*Failed induction after 48 hours' infusion.

(1) Lancet 1:157-159, Jan. 24, 1970.

effects of intravenous infusion of prostaglandin $F_{2\alpha}$ on the early and midpregnant uterus and its usefulness for therapeutic abortion in the 1st and 2d trimesters. Fifteen patients recommended for therapeutic abortion were infused with prostaglandin $F_{2\alpha}$. The gestation age was 9-22 weeks. Uterine activity was recorded before and during the infusion, which was continued until the abortion was complete.

With intravenous infusion of 50 μg. prostaglandin $F_{2\alpha}$ per minute, stimulation of uterine activity was observed in all 15 women. The initial response, which appeared after a latent period of 1-3 minutes, consisted of an increase in tone of 20-50 mm. Hg, which lasted 10-15 minutes. During this period, small and irregular contractions were superimposed on hypertonus. As the hypertonus began to disappear, the uterus began to contract regularly and rhythmically with an increase in frequency and amplitude of contractions. The contractions became stronger, frequency increased and abortion ensued in 14 of the 15 women. In 10 women, the fetus and placenta were expelled simultaneously, and in 3 cases the placenta was expelled after a delay of 3-7 hours. There was 1 case of retained (but detached) placenta which was removed by an evacuation procedure. Detailed results are shown in the table. In 1 patient, prostaglandin $F_{2\alpha}$ failed to produce an abortion after 48 hours of infusion despite strong frequent contractions. Pregnancy was later successfully terminated with intra-amniotic injection of sodium chloride solution.

The only side effect of prostaglandin $F_{2\alpha}$ was diarrhea in 7 women, 3 of whom also vomited. The side effects were not severe and responded to symptomatic treatment. No changes in pulse rate or blood pressure were observed.

The study shows that prostaglandin $F_{2\alpha}$ stimulates the uterus before term and is effective for therapeutic abortion. This technic eliminates the risk of exposing the fetus to possible trauma from operative procedures and minimizes the risk of infection. It has a high incidence of complete abortion and seems equally effective in both the 1st and 2d trimesters of pregnancy.

► [Certainly, the use of prostaglandin is highly effective and much less hazardous than many other procedures used. In view of the widespread revival of interest in abortions, it is hoped this biochemical procedure will prove to be as safe and effective as present studies indicate.—Ed.]

Acne

Inhibition of Pancreatic Lipase by Tetracyclines. Improvement in acne with tetracyclines has been attributed to reduced free fatty acid formation in the pilosebaceous canal. Corynebacterium acnes has lipolytic activity and is sensitive to tetracycline in vitro and it is reduced on the skin surface during treatment. Its sensitivity to penicillin does not affect the acidity of human sebum. Inhibition of pancreatic lipase by chlortetracycline has been reported.

Alan R. Shalita and Victor Wheatley[2] (New York Univ.) attempted to verify this and compared the action of several tetracyclines with other antibiotics on this enzyme system. The rate of hydrolysis of an emulsion

(2) J. Invest. Dermat. 54:413-415, May, 1970.

of olive oil was determined by potentiometric titration, using an enzyme solution prepared from purified hog pancreatic lipase. Drugs were added to substrate solution just before the addition of enzyme, with adjustment of the pH to 8.1 in all experiments.

Hog pancreatic lipase was inhibited by the tetracyclines tested; maximal inhibition occurred with 0.625 mg. tetracycline per ml., 0.937 mg. demethylchlortetracycline per ml. and 1.562 mg. doxycycline per ml. No other antibiotics tested had a significant effect on the lipase system even in concentrations up to 10 times that of tetracycline. They included penicillin G, oxacillin, ampicillin, streptomycin, several erythromycins, chloramphenicol, sulfasoxazole and sulfamethoxazole.

Possibly erythromycin acts solely by its bacteriostatic action or affects the specific lipases present in comedones without affecting pancreatic lipase. The other drugs tested have no known effects on free fatty acid formation within the follicle.

► [Tetracyclines are helpful in acne and it is possible that lipase inhibition may be the basis of their action. If so, it should also be true of lincomycin, which is also active. If it can be specifically shown that only those drugs inhibiting lipase are active, a better understanding of how drugs act in acne will have been achieved.—Ed.]

Actinomycosis

Actinomycosis Treated with Lincomycin. Penicillin is the drug of choice in treatment of actinomycosis, but patients allergic to penicillin constitute a treatment problem. Erythromycin, tetracyclines, chloramphenicol, streptomycin and isoniazid have given varying beneficial results in such cases, but the initial response may be slower than with penicillin, and prolonged treatment is more likely to have untoward effects. John A. Mohr, Everett R. Rhoades and Harold G. Muchmore[3] (Univ. of Oklahoma) report results of lincomycin therapy in 4 patients with actinomycosis who were allergic to penicillin. This is believed to be the first report of actinomycosis treated with lincomycin.

Man, 21, had swelling in the lower left jaw 2 months after removal of a wisdom tooth from that area. The swelling progressed despite treatment with numerous antibiotics, excluding penicillin. About a year after the extraction, he was admitted to this center. He could not open his mouth and had lost weight. Swelling obscured the entire left masseter muscle; it contained a central fluctuant area. X-rays of the jaw showed a lytic defect of the ascending ramus of the left mandible. The fluctuant area was aspirated; cultures of the pus yielded Actinomyces israelii, susceptible to penicillin G, erythromycin, tetracycline and lincomycin. Lincomycin was given in a dosage of 600 mg. intramuscularly every 12 hours and 500 mg. orally every 8 hours. The swelling decreased and, in about 6 weeks, disappeared; the jaw lesion sclerosed. Masticatory movements became normal. The patient was continued on oral lincomycin for 6 months and has remained asymptomatic.

Two of these patients had pulmonary and 2 cervicofacial actinomycosis. All responded favorably to lincomycin, the responses being comparable to those seen with penicillin therapy. Side effects were minimal. The minimal inhibitory concentration of lincomycin reported for several strains of A. israelii is below 0.2 μg./ml. The rapid ap-

(3) J.A.M.A. 212:2260-2262, June 29, 1970.

pearance of lincomycin in bony tissue may partly explain the rapid clinical responses seen in the present patients.

► [Here is another infection that is susceptible to lincomycin. It is surprising the side effects were so minimal in view of the gastrointestinal effect seen so often with lincomycin.—Ed.]

Addiction

Changes in Personality and Subjective Experience Associated with Chronic Administration and Withdrawal of Opiates were investigated by Charles A. Haertzen and Nall T. Hooks, Jr.[4] (Addiction Res. Center, Lexington, Ky.) in 15 physically healthy prisoner opiate addicts. The subjects were tested with the Minnesota Multiphasic Personality Inventory, Addiction Research Center Inventory, Lexington Personality Inventory and an appetite rating scale before drug administration and after an average of 3.5 months of chronic administration of 240 mg. morphine or 95 mg. heroin, intravenously, per day, as well as on the 10th day of dose reduction.

Euphoria was increased after an acute dose of morphine and was reduced to predrug levels during chronic administration; tolerance to such symptoms as a lowered motivation for activity, constipation, dryness of the skin and an appetite for the opiate drug used in the experiment failed to develop completely. Hypochondriasis increased during the chronic phase but was not evident after a single dose of morphine. Over-all, an acute dose of morphine produced only slight changes on items which differentiate the chronic dose condition from the nondrug condition. Psychopathic traits, believed by many to be exaggerated by opiates, were not increased during acute, chronic or withdrawal phases of the addiction cycle. Many other traits, such as acceptability for psychotherapy, were not altered.

During withdrawal, neurotic traits such as depression, hypochondriasis, anxiety and feelings of weakness, sickness and irritability, as well as classically defined withdrawal symptoms, were markedly increased. The immediate subjective feeling of the usefulness of morphine or heroin for settling symptoms was more highly correlated with the intensity of the opiate withdrawal symptoms than with psychopathic traits.

► [As has been suspected for a long time, the narcotic addict had his type of personality in the beginning. When the drug is withdrawn, this personality becomes evident again. Recent experience with young heroin addicts who are addicted as a result of experimenting with the drug can often be completely rehabilitated when off the drug. Although the amount of exposure and dose in these addicts is often less than that in the hard-core addict, undoubtedly an important element in successful withdrawal is that these youths often are better motivated, have less personality hang-up and are able to adjust to society once they get going.—Ed.]

Comparison of Acetylmethadol and Methadone in the Treatment of Long-Term Heroin Users: Pilot Study is reported by Jerome H. Jaffe, Charles R. Schuster, Beth B. Smith and Paul H. Blachley.[5] High-dose oral methadone therapy facilitates the social rehabilitation of long-term compulsive heroin users, but the duration of action of methadone poses

(4) J. Nerv. & Ment. Dis. 148:606-614, June, 1969.
(5) J.A.M.A. 211:1834-1836, Mar. 16, 1970.

problems. The drug must be taken at least once a day to avoid withdrawal symptoms. Giving patients a complete supply creates the possibility of illegal redistribution and a risk of accidental ingestion by nonpatients.

Fraser and Isbell (1952) reported that α-dl-acetylmethadol, a synthetic congener of methadone, can prevent withdrawal symptoms for over 72 hours. The drugs were compared in 21 volunteer patients from the Illinois Department of Mental Health Drug Abuse Program who had been stabilized on 20-90 mg. methadone daily and who were judged to have good potential for rehabilitation. After a baseline period, 12 patients received α-dl-acetylmethadol, initially in a dose of 1.2 times the daily methadone dose. These patients received placebo medication matched for taste on intervening days. The average dose of methadone in the final 3-week period was 37 mg. daily and that of α-dl-acetylmethadol, 50 mg. 3 days a week. Placebo was then given to 6 patients in each group.

Four study patients were dropped because of anxiety and nervousness, and 1 control patient reported abdominal pain. The groups were similar initially on an opiate withdrawal subscale and a withdrawal symptom check list. Two methadone patients took emergency medication 36 hours after placebo substitution because of intense withdrawal symptoms. All 4 patients who completed 48 hours of deprivation without extra medication had dramatic increases in symptom intensity. Symptoms in the study group increased slightly at 72 hours and markedly at 96 hours. Criminal records and illicit drug use were comparable in the two groups of subjects.

These findings indicate that α-dl-acetylmethadol can effectively suppress opiate withdrawal symptoms for up to 72 hours. Former compulsive heroin users who had adjusted socially on methadone maintenance continued to do well while using α-dl-acetylmethadol only 3 times each week. The α-dl-acetylmethadols may have practical therapeutic advantages over methadone in the treatment of heroin addicts.

► [An exciting study. There is a definite need for a drug which can be given once a week or less to patients on a maintenance program. The daily taking of methadone at a center under controlled conditions, which is absolutely necessary at present, works a hardship on patients who are trying to live a normal life. I look forward to the time when perhaps an injection once a month will be able to control the chronic narcotics user.—Ed.]

Pregnancy in Narcotics Addicts Treated by Medical Withdrawal: Methadone Detoxification Program. George Blinick, Robert C. Wallach and Eulogio Jerez[6] (Beth Israel Med. Center, New York) followed the outcome of pregnancy in 100 of 300 female addicts, who were pregnant on admission to the Bernstein Institute for narcotic withdrawal.

The patients received methadone in decreasing doses for 10 days. Then they had a 2-4 weeks' stay for psychiatric and rehabilitative care. Prior to readmission for labor, 40% of the women were again taking heroin and 10% admitted taking a "fix" for labor pains immediately before admission. Labor was conducted in the same manner as for nonaddicts.

There were 2 twin deliveries, a stillbirth at 24 weeks' gestation and 97

(6) Am. J. Obst. & Gynec. 105:997-1003, Dec. 1, 1969.