dotoxin after a 40-min incubation and ~0.5 after 50 min. However, for the reaction mixture without ampicillin, the observed absorbance was ~0.95 for 0.6 ng/ml of endotoxin after 50 min.

From the calibration curve obtained in the presence of sodium ampicillin, the amount of endotoxin in the concentrated sample which was used in the rabbit pyrogen LAL tests was determined. It was revealed that 1 g (potency) of sodium ampicillin was contaminated with 6.4 ng of endotoxin (*E. coli* 0111-B4 endotoxin). Furthermore, the endotoxin in each vial was determined quantitatively without ultrafiltration by this chromogenic assay method using 40 vials (1 g/vial) of test samples. The results showed that the sodium ampicillin test samples were contaminated with an average of 4.73 ng of endotoxin (expressed as *E. coli* 0111-B4 endotoxin activity) per vial (gram) with a standard deviation (*SD*) of 1.75 ng/vial.

DISCUSSION

In the injectable sodium ampicillin test sample suspected of contamination, a trace amount of pyrogen (endotoxin) was detected by three methods. For each method, experiments were performed using a pyrogen-free sodium ampicillin preparation and as a control endotoxin derived from *E. coli*. The data indicate the following:

1. The presence of sodium ampicillin interferes with the detection of endotoxin, but sodium ampicillin could be separated from the endotoxin by ultrafiltration. Using ultrafiltration. it is possible not only to eliminate the coexistent drugs but also to concentrate the endotoxin. This makes it possible to detect the endotoxin in minute amounts.
2. The results obtained by the rabbit pyrogen test, LAL test, and chromogenic assay method indicated that the test samples of sodium ampicillin were contaminated with small amounts of endotoxin.
3. The endotoxin could be determined quantitatively in the presence of <20 mg/ml of sodium ampicillin. This study showed that the LAL test and the rabbit pyrogen test gave consistent results, suggesting that the *in vitro* method may become a useful method for the detection of pyrogens in drug preparations.

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Evaluation of the Teratogenicity of Morphine Sulfate Administered *Via* a Miniature Implantable Pump

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Received May 14, 1982, from the *Temple University, School of Pharmacy, Department of Pharmacology, Philadelphia, PA 19140.* Accepted for publication June 29, 1982.

Abstract □ A technique has been developed for the implantation of miniature infusion pumps in pregnant mice with minimal teratogenic and toxic side effects. In 7- to 10-day pregnant CF-1 mice receiving constant low doses of morphine sulfate *via* the infusion pump, the results, including fetal weight reduction and various skeletal and soft tissue abnormalities, were similar to those reported in previous investigations using single injections.

Keyphrases □ Delivery systems—implantable infusion pump, teratology studies □ Morphine sulfate—use of implantable infusion pumps for teratology studies, comparison with conventional techniques □ Infusion pump—delivery of test drug in teratology studies, comparison to conventional techniques

Teratology studies have often shown that drugs can affect the developing fetus, thereby dispelling the myth of a fully protective placental barrier. Many of these drugs have been administered to the pregnant animal in a single dose on a specific day of gestation allowing investigators to observe their teratogenic effects at different times of fetal development (1–3). However, with the introduction of a new type of drug dosing, the miniature infusion pump[1], a distinctly different approach can be used to study the possible teratogenic influence of drugs. This instrument is a constant-flow delivery system which allows the long-term steady-state effects of a drug on the developing fetus to be ascertained. Because there has been no reported use of this constant-flow delivery system for teratology studies, the feasibility of using the miniature infusion pump in such a study was investigated.

To determine if the use of the miniature infusion pump was a reasonable alternative to other types of drug dosing, a pilot study was undertaken comparing the fetal effects of saline administered *via* the pump and by hypodermic injection. The pump implantation procedure and the presence of the pump during pregnancy was observed to have a minimal effect on the fetus, thereby providing the

[1] Alzet mini-osmotic pump, Model 2001, Lot No. 07885, Alza Corp., Palo Alto, CA 94304.

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Table I—Mean Values of Treatment Groups

Treatment Group[a]	Maternal Weight Gain, g	Fetal Ratio[b]	Resorption Ratio[b]	Fetal Weight, g	Sex Ratio M/F	Abnormalities[c] Soft Tissue	Abnormalities[c] Skeletal
Untreated	23.2	5.8/3.3	0.3/0.8	1.34	5.5/3.6	0.6	1.6
Injection-saline-7	26.9	5.0/6.5[d]	0.8/0.3	1.17[d]	6.0/5.5[d]	0.5	4.3
Injection-saline-8	20.2	2.6[d]/5.1	1.1/1.6	1.18[d]	3.3[d]/4.5	0.6	5.0[d]
Injection-saline-9	25.3	6.1/4.0	0.1/1.0	1.21	5.5/4.6	0.6	3.0
Injection-saline-10	23.9	4.5/5.6	0.3/1.0	1.12[d]	5.6/4.8	0.5	5.5[d]
Pump-saline-7	25.4	5.5/3.6[e]	0.8/0.6	1.30[e]	4.6/4.5	0.3	2.8
Pump-saline-8	20.7	4.0/4.6	0.3/0.6	1.17	4.0/4.6	0.3	4.8
Pump-saline-9	17.6	4.6/4.0	0.5/0.8	1.11	4.3/4.3	1.6	4.6
Pump-saline-10	19.4[e]	4.8/4.8	0.6/0.3	1.14	4.8/5.0	0.6	4.3
Pump-4.0% morphine sulfate-7	21.2	4.6/5.5	0.8/0.5	1.15[f]	5.8/4.3	1.3	5.6
Pump-4.0% morphine sulfate-8	21.5	6.1[f]/4.3	0.5/0.6	1.24	5.6/4.8	2.0[f]	2.8
Pump-4.0% morphine sulfate-9	21.8	4.3/6.6[f]	0.3/0.5	1.20	5.3/5.6	2.1	4.3
Pump-4.0% morphine sulfate-10	19.6	5.0/4.1	0.5/0.8	1.21	5.3/3.8	1.8	3.5
Pump-0.4% morphine sulfate-7	23.6	5.8/4.5	0.3/0.1	1.24	5.6/4.6	1.3	4.5
Pump-0.4% morphine sulfate-8	19.7	3.5/5.3	0.5/1.1	1.17	4.5/4.3	0.8	6.0
Pump-0.4% morphine sulfate-9	22.3	7.1/4.6	0.5/0.3	1.08	6.1/5.6	0.6	10.1
Pump-0.4% morphine sulfate-10	22.5	5.3/5.1	0.5/0.6	1.14	5.1/5.3	1.0	7.5[l]
Pump-0.04% morphine sulfate-7	16.2[f]	4.0/4.6	0.8/0.6	0.96[f,g]	4.0/4.6	2.0	12.1[f,g]
Pump-0.04% morphine sulfate-8	21.6	5.1/5.8	0.5/1.0	1.15	5.0/6.0	2.6	9.8[h]
Pump-0.04% morphine sulfate-9	17.8	4.5/5.1	0.1/0.3	1.04[i]	4.8/4.8	3.6[k]	9.8[i]
Pump-0.04% morphine sulfate-10	17.8	5.5/4.0	0.1/0.6	1.04	4.5/5.0	3.0	14.3[f,j]

[a] Designated as method of delivery-solution administered-gestation day of dosing. The saline dosage was 0.3 ml sc; the volume released by the infusion pump was 0.17 ml. [b] Right horn/left horn of the uterus. [c] Average per litter. [d] Significantly different ($p < 0.05$) compared with the untreated control. [e] Significantly different ($p < 0.05$) compared with the subcutaneously delivered saline control. [f] Significantly different ($p < 0.05$) compared with the pump-delivered saline control. [g] Significantly different ($p < 0.05$) compared with the pump-4.0% morphine sulfate-7 and pump-0.4% morphine sulfate-7 groups. [h] Significantly different ($p < 0.05$) compared with the pump-4.0% morphine sulfate-8 group. [i] Significantly different ($p < 0.05$) compared with the pump-4.0% morphine sulfate-9 group. [j] Significantly different ($p < 0.05$) compared with the pump-4.0% morphine sulfate-10 group. [k] Significantly different ($p < 0.05$) compared with the pump-0.4% morphine sulfate-9 group. [l] Significantly different ($p < 0.05$) compared with the pump-4.0% morphine sulfate-10 group.

rationale for a full investigation of the long-term steady-state effects of a drug on the developing fetus. Because this laboratory has conducted several studies with morphine sulfate and elucidated its teratogenic effects, this drug was selected for the test system. The reproductive effects of low constant doses of morphine sulfate administered *via* the miniature infusion pump throughout specific critical days of gestation are reported herein.

EXPERIMENTAL

Animals—CF-1 albino mice[2], weighing at least 25 g, were used in all of the procedures. All females were placed in aggregate cages, each containing 10 animals. They were allowed to acclimatize for 2 weeks. Following this period, those females weighing at least 25 g were allowed to mate. The male mice were housed in individual cages measuring 12.5 × 15 × 10 cm, each with a wire mesh front and floor[3]. Food[4] and tap water were offered *ad libitum;* artificial light was supplied with a 12-hr light/dark cycle.

Drugs and Solutions—Normal saline[5] was used as the vehicle for the morphine sulfate[6] solutions (40, 4.0, and 0.4 mg/ml); fresh solutions were prepared weekly. In addition, normal saline was administered to all vehicle controls including subcutaneous injection and infusion pump groups. All injections were given subcutaneously with a 1-ml glass syringe equipped with a 0.5-cm 26-gauge needle. All pumps were filled with filtered solutions[7] using a specially designed blunt-tipped 26-gauge steel needle[8]. The injection volume was 0.3 ml; the pump release was 0.17 ml of solution.

The bone-staining solution and decalcifying Bouin's solution were prepared according to previously published reports (2).

Breeding, Group Selection, and Treatment—The breeding procedure has been described previously (4). Gravid females were randomly assigned to the 21 experimental groups. The controls consisted of one untreated group and four groups given single subcutaneous saline injections on day 7, 8, 9, or 10 of gestation. There were 16 treatment groups; infusion pumps containing either saline or a 4.0% (40 mg/ml), 0.4% (4.0 mg/ml), or 0.04% (0.4 mg/ml) solution of morphine sulfate were implanted in each mouse on day 7, 8, 9 or 10 of gestation.

Surgical Procedure—On the day of treatment, the body hair of the animals in the dorsal-scapular area was sheared with scissors, and the mice were anesthetized with ether[9]. A small skin incision (1–1.5 cm) was made perpendicular to the backbone in the dorsal-scapular area. The infusion pump was inserted into a subcutaneous pouch made by separating the skin from the underlying muscle and secured by the closure of the incision with three or more interrupted sutures. The anesthesia duration was ~3 min, and an antiseptic solution[10] was used as a postoperative wound dressing. All animals, regardless of the treatment, were allowed to recover undisturbed.

Examination of Fetuses—On day 18 (1 day prior to full term), each mouse was weighed; the terminal maternal weight was adjusted for pump weight if necessary. Each mouse was then sacrificed by cervical dislocation, at which time the number and position of the fetuses and resorption sites (metrial glands) were recorded. The fetuses were blotted dry and checked for viability by reflex movement on stimulation with a blunt probe. Further examination consisted of the observation of each fetus under a dissecting microscope[11] for gross defects and sex; the weight of each fetus was recorded to the nearest hundredth of a gram on a torsion balance[12]. One-half of the fetuses were then randomly selected for preparation in a bone-staining solution for skeletal examination by the method of Staples and Schnell (5). The remaining fetuses were prepared in Bouin's solution for soft tissue examination by the method of Wilson (6). The statistical significance of the observations was determined using Student's t test and the uncorrected chi-square test for a binomial population.

RESULTS AND DISCUSSION

Effects of Pumps Implantation—*Maternal Effects*—Two deaths occurred during the pump implantation procedures; both were attributed to an overdose of the ether anesthesia and not to surgical trauma. There were no maternal deaths due to drug toxicity or postsurgical complications observed in any treatment group.

Most animals became fully conscious within minutes following the pump implantation procedure, although spontaneous activity was suppressed for several hours. This was judged to be the result of the proce-

[2] Charles River Breeding Laboratories, Wilmington, Mass.
[3] Norwich Wire Works, Norwich, N.Y.
[4] Purina Laboratory Chow, Ralston-Purina Co., St. Louis, Mo.
[5] 0.9% Sodium Chloride Injection USP, Lot No. 92-166-DE-7 exp. 9/1/82, Abbott Laboratories, North Chicago, IL 60064.
[6] Morphine Sulfate, Lot No. 4455, Merck & Co., Rahway, N.J.
[7] Millex H-A Filters, 45 μm, Lot No. SLHA02505, Millipore Corp., Bedford, MA 01730.
[8] Alza Corp., Palo Alto, CA 94304.
[9] Ether, ethyl ether, Lot No. 413759, J. T. Baker Chemical Co., Phillipsburg, NJ 08865.
[10] Betadine solution, Purdue Frederick Co., Norwalk, CT 06856.
[11] Binocular dissecting microscope, Bausch & Lomb, Lot. ASZ3012.
[12] Torsion Balance Co., Model PL-800, 500820, Ireland.

Table II—Fetal Anomalies Occurring in Significant Numbers in the Pump-Administered Morphine Sulfate Groups

Anomaly	Group[a] 4.0% Morphine Sulfate 7 8 9 10	0.4% Morphine Sulfate 7 8 9 10	0.04% Morphine Sulfate 7 8 9 10
Exencephaly	— — — —	— — — —	L — — —
Hydronephrosis	— B — F	— — — —	B B — F
Intestinal hemorrhage	— — — —	— — — —	— B B B
Split supraoccipital	— — — —	— — B —	B — — F
Malformed sternebrae	L L B —	— — B F	B — L F
Malformed xiphoid	— — — —	— — — —	B — B B

[a] Based on six litters per group. Key: significantly different ($p < 0.05$) from the pump saline control on a litter basis (L), a fetal basis (F), or both (B).

dure and not a drug effect, because similar observations were noted for the saline groups and, also, several hours are needed for the pump to reach full capacity. Observation of the spontaneous activity of the animals on subsequent days showed little difference between the treatment (pump-implanted) groups and the untreated controls. On sacrifice of the animals, the pumps were excised and the pouch area examined. In no case was there any evidence of gross infection or any type of inflammation present in or around the pouch area.

The only maternal variable measured during this experiment was the maternal weight gain. There were no significant differences between the untreated controls and any treatment group. However, when the pump-saline-10[13] group was compared with the injection-saline-10 group (Table I), there was a significant decrease in maternal weight gain observed, obviously a direct consequence of the pump implantation procedure.

Fetal Effects—A crucial point in this study was to determine the feasibility of the pump implantation procedure for use in a teratology study. The fetal effects resulting from the pump implantation procedure were determined by the statistical comparison of saline administered *via* the infusion pump *versus* subcutaneous injection. Only one group (pump-saline-7) showed any significant differences: an increase in mean fetal weight and a reduction in the number of fetuses in the left uterine horn. Because the number of fetal resorptions was not significantly different, these effects are possibly due to an increased uterine blood supply and not the pump implantation procedure (which is performed after uterine implantation of the ova). Therefore, there does not appear to be any major difference in the fetal effects of saline administered *via* subcutaneous injection or the pump implantation procedure.

Effects of Morphine Sulfate—The doses used in this study were only a fraction of the morphine sulfate doses administered in previous studies (7–9). The exact dose administered is a function of the animal body weight as the drug concentration and release rate is the same in all cases.

Maternal Effects—Observation of the animals implanted with a pump containing morphine sulfate showed the discernable effects of the drug to be quite minimal. The maternal weight gain significantly decreased in only one group (pump-0.04% morphine sulfate-7), which is in general agreement with previous reports (7–9).

Fetal Effects—A significant reduction in mean fetal weight was noted which agreed with previous data (7–9). Significant fetal resorptions, which were noted in one of the previous studies (7), did not occur in the present investigation.

Three groups (pump-4.0% morphine sulfate-8, pump-0.04% morphine sulfate-7, and pump-0.04% morphine sulfate-10) showed significant increases in the total number of soft tissue and/or skeletal defects when compared with the pump saline controls. A trend in the mean values of the total number of soft tissue/skeletal abnormalities and fetal weights is evident. With the exception of the soft tissue anomalies of the pump-morphine sulfate-8 groups, the lowest doses of morphine sulfate (0.04%) have nearly twice the number of abnormalities and much lower mean fetal weights compared with the corresponding gestation day for the highest doses (4.0%). This trend is supported statistically, as significance was noted for dose comparisons involving the mean fetal weight and total number of soft tissue and/or skeletal abnormalities (Table I), with the greatest difference appearing between the highest (4.0%) and lowest doses (0.04%) of morphine sulfate.

In view of the type of dosing and since it is well known that constant morphine administration induces tolerance to many of its physiological effects, a logical explanation for these trends might be the induction of microsomal liver enzymes. However, the induction of microsomal liver enzymes does not explain the increase in fetal defects at the lowest dose of morphine as compared with the high dose; the enzymatic *N*-demethylation of morphine is reduced with chronic administration (10–12). This reduction of the *N*-demethylation of morphine can be partially reversed by nalorphine (10). Because of the similar substrate stereospecificity between the liver enzymes and the opiate receptors, Axelrod (10) suggested that the depression of enzymatic activity may be related to a similar depression of receptor activity, seen physiologically as the development of tolerance. To further elucidate the similarity of the stereospecificity between the enzyme, *N*-demethylase, and the opiate receptor, Mannering and Takemori (11) used the steric isomers of 3-hydroxy-*N*-methylmorphinan (dextrorphan and levorphan) in chronic doses and measured the *N*-demethylase enzyme activity in response to a test dose of morphine. Dextrorphan is known to lack most morphine-like properties, while levorphan produces many morphine-like effects. Mannering and Takemori (11) reported that the rate of enzymatic *N*-demethylation of morphine was inhibited with chronic administration of levorphan, while dextrorphan was observed to be relatively noneffective.

If the teratogenic effects of morphine are expressed through the opiate receptor activity, the inhibition of the receptor by chronic administration of morphine may result in a lower incidence of fetal anomalies at higher doses (4.0%). There is a possibility that constant administration at the lowest dose of morphine (0.04%) may not be sufficient to inhibit the receptor but is large enough to cause fetal abnormalities. With morphine *N*-demethylation inhibited at higher doses, the production of the end product (formaldehyde) is also inhibited; with constant administration of low doses of morphine, tissue levels of formaldehyde, a secondary teratogenic agent, may build up. However, the development of tolerance and the induction of fetal defects by morphine are probably not due to a single cause, but to multiple and presently unknown factors.

The fetal abnormalities produced in significant numbers as a result of morphine sulfate administration *via* the infusion pump have been listed in Table II. Specifically, those malformations include exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital bone, (malformed, crankshaft, fused, poly, and split) sternebrae, and malformed (butterfly and split) xiphoid bone. In addition, various soft tissue anomalies were also observed in this study, although their incidence was not significant. These defects included: cleft palate, cryptorchidism, ectopic ovary or testis, hydrocephaly, microphthalmia, missing lens, skin bumps, abnormal tail, and polydactyly. There were also numerous skeletal defects observed in significant numbers, including: brachygnathia; delayed ossification of the ribs, skull, sternebrae, and xiphoid; split ribs; malformed basiphenoid, xiphoid, and centrum; and missing sternebrae and supraoccipital bone.

It is known that the specific fetal malformation is related to the fetal organs most susceptible to injury at the time of drug challenge (7–9). Therefore, one would expect that litters from dams with the morphine-containing pump implanted on day 7 of gestation should show all the defects observed in the litters from dams implanted on subsequent days because of the continually present drug levels. However, the data does not show such a trend. Possibly, the teratogenic insult is greatest on the first day of drug administration (and on the organs developing at that time) and lessens thereafter.

In conclusion, this study has proven that the infusion pump is a feasible dosage form in teratology studies. The methodology necessary for future studies of this type has been developed. In administering morphine sulfate *via* the implantable pump, this study has shown fetal abnormalities similar to those observed in previous (injection) studies.

[13] Each group was designated by method of delivery—solution administered-gestation day of dosing.

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Pharmacokinetics and Bioavailability of Intravenous and Topical Nitroglycerin in the Rhesus Monkey: Estimate of Percutaneous First-Pass Metabolism

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Abstract □ [^{14}C]Nitroglycerin was administered intravenously and topically to three rhesus monkeys and the pharmacokinetics were determined. The rhesus monkey is an animal model for which percutaneous absorption is similar to that in the human. After intravenous administration the decline in plasma nitroglycerin concentration was biexponential with an initial half-life of 0.8 min (2–5 min postadministration) and a terminal half-life of 18 min (5–60 min postadministration). After topical application in an ointment, plasma concentrations of unchanged nitroglycerin were first detectable at 0.25 hr postapplication. Peak plasma nitroglycerin concentrations occurred between 4–6 hr, and nitroglycerin was still detectable at 24 hr postapplication. Plasma levels fit a biexponential curve with an α-phase half-life of 3.0 hr, a β-phase half-life of 4.3 hr, and a lag time of 0.5 hr. The absolute bioavailability of topical nitroglycerin was 56.6 ± 5.8%. The differences in bioavailability estimates between unchanged nitroglycerin and total carbon-14 is considered to be the amount of nitroglycerin which is metabolized as it is absorbed through the skin (percutaneous first-pass effect). This value for topical nitroglycerin was quite small, only 16–21% depending on the method of comparison.

Keyphrases □ Nitroglycerin—percutaneous absorption pharmacokinetics in the rhesus monkey, comparison of intravenous and topical administration bioavailability □ Pharmacokinetics—nitroglycerin in the rhesus monkey, comparison of intravenous and topical administration bioavailability □ Bioavailability—topical nitroglycerin in the rhesus monkey, comparison with intravenous administration, pharmacokinetics □ Percutaneous absorption—topical nitroglycerin, determination of first-pass effect

Nitroglycerin is a drug shown to be effective in angina pectoris (1–4) which may be effective in other cardiac diseases (5). The usual dosage form is a sublingual tablet, which has the disadvantage of a short duration of action. Nitroglycerin is also administered orally; however, first-pass metabolism during absorption is estimated to be large (6, 7). A third route of administration is transdermal delivery. Transdermal administration results in a longer duration of action than sublingual administration and may bypass the first-pass metabolism seen with oral administration. The result is a dosage form that delivers nitroglycerin over an extended time period. Recent publications attest to the clinical effectiveness of topically applied nitroglycerin (4, 5). Thus, it is important to determine the pharmacokinetic parameters of nitroglycerin after topical administration. This information can help in understanding the effectiveness of the drug and perhaps can be used to improve nitroglycerin therapy.

The animal model chosen for the study of the transdermal delivery of nitroglycerin was the rhesus monkey. Percutaneous absorption of several compounds in the rhesus monkey have been shown to be similar to that in the human (8–11).

EXPERIMENTAL

Female rhesus monkeys weighing ~4–6 kg were used. The monkeys were lightly anesthetized with 50–100 mg ketamine[1] for placement in the metabolism chairs. The monkeys were restrained in the metabolism chairs for 24 hr after drug administration (length of topical application) and then returned to metabolism cages for continued blood and urine collection. The monkeys had free access to food and water in the metabolism cages; they were hand fed and watered while confined to the metabolism chairs. In the topical application studies, the wrists of the monkey were taped to the sides of the chair to prevent the monkey from removing the applied dose. Each animal had an indwelling catheter in the saphenous vein for blood collection; a saline drip was connected to the cathether while blood samples were not being collected.

[^{14}C]Nitroglycerin was prepared from uniformly labeled glycerol and had a specific activity of 128 μCi/mg. The synthetic material was purified by chromatography on silica gel (toluene) followed by further purification using high-performance liquid chromatography (HPLC) on a μ-Bondapack C-18 column (water–methanol, 60:40) at a flow rate of 2 ml/min. The chemical and radiochemical purity, as determined by HPLC and TLC, was 99%.

The intravenous dosage form was 1.92 mg of labeled nitroglycerin with a specific activity of 250 μCi in 0.5 ml of ethanol. Administration was by bolus injection in the saphenous vein of the noncatheterized leg. The topical dosage form was 2% nitroglycerin ointment[2] containing 19.0 mg of labeled nitroglycerin (specific activity 210 μCi) spread over a 50-cm^2 area of skin. [^{14}C]Nitroglycerin was added to the ointment using the procedure of Lindsay *et al.* (12). Topical administration was to the inner upper arm. The area was lightly clipper shaved, which does not affect percutaneous absorption in the rhesus monkey (8). [The application site also has been determined not to affect the percutaneous absorption of nitroglycerin in the rhesus monkey (13).] The topical application was occluded with aluminum foil and adhesive tape. The ointment was left in place for 24 hr, and then the site was washed with soap and water. There was a 1-week period between drug administrations.

At each sampling time, ~3 ml of blood was drawn and placed in a

[1] Ketaset; Bristol Laboratories, Syracuse, N.Y.
[2] Nitro-BID; Marion Laboratories, Kansas City, Mo.

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