Pulsatile Administration of Agents Using ALZET® Osmotic Pumps

ALZET pumps operate at constant rates, they can be adapted to deliver drugs at a time-varying schedule, such as a diurnal cycle of high-low delivery rates.

In this application, an ALZET pump filled with saline is attached to a length of catheter tubing which has been loaded with a predetermined series of drug infusions separated by an inert, spacer substance. The spacer substance can be any liquid in which the drug solution is not miscible (such as oil), or it can be sterile air (see P0639, below). Because the spacer substance and the drug solution are not miscible, in the loaded catheter the series of infusions appear as discrete segments along the length of the catheter.

When it begins pumping, the constant action of the ALZET pump pushes saline into one end of the catheter tubing, sequentially displacing the series of drug infusion and spacer substances from the opposite end. For more details about this technique, refer to the procedure on the following page, reference P0065, www.alzet.com , and the references listed below.

P0639 Mick, C.C.W. and Nicoll, C.S. Prolactin directly stimulates the liver in vivo to secrete a factor (synlactin) which acts synergistically with the hormone. Endocrinology 116(5), 2049-2053, 1985. Prolactin, ovine; Growth hormone, ovine IV (HEPATIC); IV (JUGULAR) PIGEON Combination: Glycerol; Citric acid; Control* 2001; 1 week comparison of agents effects; citric acid added to solvent for bacteriostatic effects; pulsed delivery of hormone or solvent (intermittent w/ air); peptides

P0065 Lynch, H.J., Rivest, R.W., and Wurtman, R.J. Artificial induction of melatonin rhythms by programmed microinfusion. Neuroendocrinology 31, 106-111, 1980. Melatonin SC RAT Phenolsulfonphthalein; Saline* replacement therapy (pinealectomy); pulsed delivery of agent (intermittent w/vehicle)

PREPARING THE LYNCH COIL FOR USE WITH THE ALZET® OSMOTIC PUMP

The Lynch coil method may be used for several purposes:

- Create a time-patterned delivery of an agent
- Deliver compounds and/or vehicles which are incompatible with the reservoir of the ALZET® Osmotic Pump
- Provide an initial period of no drug for surgical recovery
- Adapt a longer duration pump to a shorter period of drug infusion

Polyethylene tubing should be used because it is thermoformal, and can be formed into a permanent coil. The length of the tubing depends upon the size and duration of pump being used, and the duration of infusion desired from the solution in the coil. The pump itself is filled with saline, which is separated from the drug solution by a drop of mineral oil* or bubble of air placed in the polyethylene tubing at the end between the coil and the pump.

I. Fabricating a coil of polyethylene tubing:

a. Using closely spaced turns, wind the appropriate length of PE-60 tubing around a glass rod or syringe of the same outside diameter as the ALZET pump which will be used.

b. Submerge the rod and the tubing in boiling water for one minute.

c. Immediately immerse the tubing into cold water.

d. Basic reference on the pump and coil technique:
P0065 Lynch et al, Neuroendocrinology 31, 106-111, 1980.

The heat thermoforms the tubing into a tidy, permanent coil which provides a space-efficient auxiliary reservoir whose contents are pumped by the pump via displacement.

II. Catheter volumes:

To determine the appropriate length of catheter tubing, use the following length-volume conversion:

1 cm of PE-60 tubing contains 4.566 µl of solution

1 cm of PE-50 tubing contains 2.679 µl of solution

Following are nominal tubing lengths for coils which will last the entire duration of an ALZET pump. ALZET pumps vary in reservoir volume and release rate from one lot to the next, and therefore the duration will also vary slightly. To determine the length of time a specific pump lot will release, subtract 5% from the mean reservoir volume and divide by the mean release rate. (These means are given on the instruction sheet within each box of ALZET pumps.) The resulting number will be the number of hours over which a pump will release its contents.

Pump Volume	PE-60 Tubing Length	PE-50 Tubing Length
100 µl	22 cm	37.3 cm
200 µl	43.8 cm	74.7 cm
2000 µl (2 ml)	438 cm	746.5 cm

- Or some fluid immiscible with the fluid in the pump and the fluid in the tubing.

These conversions are calculated using the formula for a volume of a cylinder:

$$\pi R^2 \times \text{length} = \text{tubing volume}$$

In this equation, R is the radius of a cross-section of the tubing, or half of the inner diameter given above. The length is equal to the length of tubing being considered. Be sure to use the same units of measure throughout, and to convert the volume to µl to relate the final volume to the flow rate of the pumps, which is in µl/hr.

References on the Pulsatile Administration of Agents Using ALZET® Osmotic Pumps

Q7598: L. M. Hsu, *et al.* Intrinsic Insular-Frontal Networks Predict Future Nicotine Dependence Severity. J Neurosci 2019;39(25):5028-5037
Agents: Nicotine hydrogen tartrate salt **Vehicle:** Saline; **Route:** IP; **Species:** Rat; **Pump:** 2ML4; **Duration:** 14 days;
ALZET Comments: Dose (1.2, 4.8 mg/kg/day); saline pH adjusted to 7.2+/-0.5 used; Controls received mp w/ vehicle; animal info (male, Sprague-Dawley, 275-300g); behavioral testing (Precipitated withdrawal); pulsed delivery (Lynch coil 1hr-ON-1hr-OFF); dependence;

Q5177: P. A. Pereira, *et al.* Effects of chronic alcohol consumption, withdrawal and nerve growth factor on neuropeptide Y expression and cholinergic innervation of the rat dentate hilus. Neurotoxicology 2016;54(153-60
Agents: Nerve growth factor **Vehicle:** Methylene blue; BSA; CSF, artificial; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2002; **Duration:** 12 days;
ALZET Comments: animal info (male, Wistar); functionality of mp verified by residual volume; Pumps were pre-tested to confirm delivery rate; ALZET brain infusion kit used; post op. care (SC injections of 0.9% saline (2ml)); pulsed delivery; lynch coil; the cannulae were connected to methylene blue (0.01%) filled minipumps via sterile coiled PE-60 tubing. The tubing was filled with air–oil spacer at the pump end and with NGF (150 mg diluted in 150 ml of vehicle).

Q3117: C. B. Mantilla, *et al.* Motoneuron BDNF/TrkB signaling enhances functional recovery after cervical spinal cord injury. Experimental Neurology 2013;247(;):101-109
Agents: Brain-derived neurotrophic factor; **Vehicle:** Not Stated; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** 2002; **Duration:** 14 days;
ALZET Comments: Animal info (male, Sprague Dawley, adult); spinal cord injury; post op. care (Acetominophen orally and buprenorphine IM for 3 days); pulsed delivery (delayed delivery for 3 days - aCSF only in catheter); tissue perfusion (C4 segment of spine); peptides; "Mini-osmotic pumps were successfully implanted for intrathecal delivery at the C4 level and functioned properly throughout the 14 day duration of the experiment." pg 103 "Differences in survival rates across groups were likely unrelated to the possible additional morbidity associated with intrathecal catheter and miniosmotic pump implantation, as the survival rate was 70% (28 out of 40) compared to 84% (26 out of 31) in rats not implanted with an intrathecal pump (p = 0.17)." pg 103; PE-10 intrathecal cannula, 10 cm

R0352: A. A. Boulton. Animal Models of Dementia. Springer Protocols 2010;48(1-721
Agents: Amphetamine sulfate; Dopamine **Vehicle:** Propylene Glycol; **Route:** SC; CSF/CNS (nucleus accumbens); **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;
ALZET Comments: comparison of injections and sylastic pellet vs mp; pulsed delivery; PE tubing contained drug and a dye in short sections interspersed with a substance immiscible with drug, to allow 12 hour infusions of drug and l2-hour infusions of the inert substance (perfluorodecalin) throughout a 14 day infusion period.; pumps primed in a physiological saline solution at 37°C for 4 hours.

P5125: F. T. Sayer, *et al.* Neurotrophins reduce degeneration of injured ascending sensory and corticospinal motor axons in adult rat spinal cord. Experimental Neurology 2002;175(282-296
Agents: NT-3 **Vehicle:** PBS; Dye, toluidine blue; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** 2002; **Duration:** 7 days;
ALZET Comments: controls received mp w/ vehicle; comparison of IT injections vs. mp; pulsed delivery; peptides; pump partially coated w/ paraffin to reduce release rate to 0.2 ul/hr; Lynch coil used to separate agent from dye for verifying cannula patency (p. 285); diagram of pump, catheter and infusion location (p. 284); pump filled with dye vehicle, tubing filled with vehicle or NT-3, mineral oil spacer separated solution in pump from solution in catheter

P5488: E. H. Ellinwood, *et al.* Effect of daily dosing duration of direct and indirect dopamine receptor agonists: cocaine cross-tolerance following chronic regimens. European Neuropsychopharmacology 2002;12(5):407-415
Agents: Cocaine; pramipexole **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2ML2; **Duration:** 14 days;
ALZET Comments: Functionality of mp verified by measuring residual volume; pulsed delivery - drugs administered either continuously or for 16 or 20 hrs per day (p. 409); study included behavioral testing; pramipexole is a direct dopamine agonist; microdialysis fiber attached to pump via catheter to minimize tissue necrosis caused by the cocaine (p. 408); intermittent delivery made possible by disconnecting and reconnecting an externalized catheter

P6184: I. D. Neumann. Antisense oligodeoxynucleotide effects on the hypothalamic-neurohypophysial system and the hypothalamic-pituitary-adrenal axis. METHODS 2000;22(3):227-237
Agents: Oligodeoxynucleotide, antisense **Vehicle:** Ringer's solution; **Route:** CSF/CNS; **Species:** Rat (lactating); **Pump:** 1007D; **Duration:** 4 days;
ALZET Comments: Tissue perfusion (various brain regions); comparison of ICV injections vs. mp; pulsed delivery (various ODN's, air bubble spacer); antisense; ODN's infused were antisense, mixed base, or 21-mer end capped phosphorothioated; the mp was filled with ringer's solution and PE tubing was filled w/ 50 ul of each agent solution. An air bubble was inserted between solutions; 25-g guide cannula and 27-g infusion cannula used together to allow concomitant icv injections

P4764: P. J. Larsen, *et al.* Chronic intracerebroventricular administration of recombinant CART (42-89) peptide inhibits food intake and causes weight loss in lean and obese Zucker (*fa/fa*) rats. Obesity Research 2000;8(8):590-596
Agents: CART (42-89) **Vehicle:** PBS; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; 2002; **Duration:** 7, 10 days;
ALZET Comments: Controls received mp w/ vehicle; dose-response (graph p. 592); pulsed delivery 24 hr. delay for recovery; stability verified by aspire 5 mL of pump contents, inject ICV into naive animals to verify biological activity; peptides; ALZET brain infusion kit used; recombinant CART (42-89) is a hypothalamic neuropeptide; CART (42-89) stands for cocaine-amphetamine-regulated transcript; low dose was 4.8 mg/day for 7 days, high dose was 12 mg/day for 10 days.; delayed delivery

P4421: R. T. Turner, *et al.* Programmed administration of parathyroid hormone increases bone formation and reduces bone loss in hindlimb-unloaded ovariectomized rats. Endocrinology 1998;139(4086-4091
Agents: Parathyroid hormone, human 1-34 **Vehicle:** NaCl; HCl; Serum, rat; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;
ALZET Comments: Controls received mp w/vehicle; replacement therapy (overiectomized); peptides; pulsed delivery; PTH during a daily 1-hour infusion for 7 days

P4407: F. W. Grzywacz, *et al.* Does age-associated reduced leydig cell testosterone production in brown Norway rats result from under-stimulation by luteinizing hormone? Journal of Andrology 1998;19(5):625-630
Agents: Luteinizing hormone, ovine **Vehicle:** Buffer, borate; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 5 days;
ALZET Comments: Controls received mp with peanut oil; pulsed delivery-LH was alternated with peanut oil;

P3958: S. A. Dunbar, *et al.* Repetitive opioid abstinence causes progressive hyperalgesia sensitive to n-methyl-d-aspartate receptor blockade in the rat. J. Pharmacol. Exp. Ther 1998;284(2):678-686
Agents: Morphine sulfate; MK-801 **Vehicle:** Saline, sterile; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** 2002; **Duration:** 8 days;
ALZET Comments: controls received mp w/ saline; functionality of mp verified by in vivo and in vitro assays; pulsed delivery (air used as spacer in Lynch coil); no stress (see pg. 681); good methods (pg. 679); tolerance

R0125: S. P. Vyas, *et al.* Circadian rhythm and drug delivery design. Pharmazie 1997;52(11):815-820
Agents: Not Stated **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Not Stated; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: Review on the advantages of providing drugs in a pulsed delivery fashion; mentions mp briefly, pg. 818

P3802: H. Dobnig, *et al.* The effects of programmed administration of human parathyroid hormone fragment (1-34) on bone histomorphometry and serum chemistry in rats. Endocrinology 1997;138(11):4607-4612
Agents: Parathyroid hormone, human 1-34 **Vehicle:** NaCl; HCl; Serum, rat; **Route:** Not Stated; **Species:** Rat; **Pump:** 2001; **Duration:** 6 days;
ALZET Comments: controls received mp w/vehicle; comparison of sc injections vs mp; pulsed delivery, sesame oil used in lynch coil; no stress (see pg. 4609); stress/adverse reaction: high PTH dose lethal for 3/7 rats in first group; good methods (pg. 4608)

P4101: R. A. Schindler, *et al.* Enhanced preservation of the auditory nerve following cochlear perfusion with nerve growth factor. Am. J. Otology 1995;16(3):304-309
Agents: Nerve growth factor; Neomycin **Vehicle:** Saline; **Route:** ear (cochlea); **Species:** Guinea pig; **Pump:** Not Stated; **Duration:** 2 weeks;
ALZET Comments: controls received mp w/vehicle; tissue perfusion (scala tympani); pulsed delivery; cannula/catheter filled with neomycin which was infused for the first 24 h; pump was filled with NGF; peptides

P3098: T. Wells, *et al.* The sensitivity of hepatic CYP2C gene expression to baseline growth hormone (GH) bioactivity in dwarf rats: effects of GH-binding protein in vivo. Endocrinology 1994;134(5):2135-2141
Agents: Growth hormone, recomb. human **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 6 days;
ALZET Comments: Replacement therapy (dwarf rats used); comparison of pulsed infusion pump vs. mp; peptides

P3226: S. C. Low, *et al.* Sexual dimorphism of hepatic 11B-hydroxysteroid dehydrogenase in the rat: the role of growth hormone patterns. J. Endocrinol 1994;143(541-548
Agents: Growth hormone, human **Vehicle:** Not Stated; **Route:** SC; **Species:** Not Stated; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: Replacement therapy (GH-deficient dwarf rats used + hypophysectomized normal rats); comparison of pulsed iv injections vs. mp; peptides

P2944: N. L. Schlechter, *et al.* Physiological evaluation of the role of the liver as a mediator of the growth-promoting action of somatotrophin. Zoological Science 1993;10(235-244
Agents: Growth hormone, human; Growth hormone, bovine; Growth hormone, rat **Vehicle:** Not Stated; **Route:** IV (jugular); IV (portal); **Species:** Rat; **Pump:** 2001; **Duration:** 7 Days;
ALZET Comments: controls received mp with solvent or sham operation; replacement therapy (hypophysectomy); pulsed delivery; catheter contained heparin

P1978: S. Lerman, *et al.* Miniosmotic pumps for liposomal drug delivery. Liposome Technol 1993;1(429-438
Agents: Liposomes **Vehicle:** Not Stated; **Route:** Eye (lens); **Species:** Rabbit; **Pump:** 2ML1; **Duration:** Not Stated;
ALZET Comments: Pulsed delivery described; detailed surgical methods

P2456: L. S. Katz, *et al.* Evidence for a role of the liver in the luteotropic action of prolactin in rats. Biology of Reproduction 1993;48(512-514
Agents: Prolactin, ovine **Vehicle:** Sodium azide; Sodium phosphate; Saline; Glycerol; **Route:** IV (jugular); IV (hepatic portal); **Species:** Rat; **Pump:** 2002; **Duration:** Not Stated;
ALZET Comments: Pulsed delivery; peptides; air used in lynch coil

P2312: N. J. Hebert, *et al.* Restoration of lactation in bromocriptine-treated rats by prolactin replacement: comparison of constant versus pulsatile infusion and intrahepatic versus intrajugular routes of delivery. J. Endocrinol. Invest 1993;16(29-35
Agents: Prolactin, ovine **Vehicle:** Not Stated; **Route:** IV (jugular); IV (hepatic portal); **Species:** Rat; **Pump:** 2001; **Duration:** 5 days;
ALZET Comments: controls received mp w/ solvent; functionality of mp verified by in vitro dye testing of pulsatile release; comparison of pulsed delivery w/ mp vs. continuous infusion w/ mp; pulsed delivery; "Constant infusion of oPRL. . . was, overall, more effective at restoring lactation. . . than was giving pulses, regardless of the site of delivery." (pg. 29)

P2542: O. Torring, *et al.* Inhibition by human interleukin-1a of parathyroid hormone-related peptide effects on renal calcium and phosphorus metabolism in the rat. Endocrinology 1992;131(1):5-13
Agents: Parathyroid hormone-related peptide; Interleukin-1, alpha **Vehicle:** Albumin, mouse serum; Cysteine HCl; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 14 days;
ALZET Comments: controls received mp w/ vehicle; comparison of injections vs. mp; pulsed delivery (pg. 10); pumps replaced after 7 days; no stress (see pg. 11); stability of IL-1a verified by ELISA (see pg. 6); peptides; agents given concomitantly in some cases; cysteine prevented degradation of PTHrP.

P2396: V. Hollt, *et al.* Effect of nicotine on mRNA levels encoding opioid peptides, vasopressin and a-3 nicotinic receptor subunit in the rat. Clin. Investig 1992;70(224-231
Agents: Nicotine **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 4, 7, 14 days;
ALZET Comments: controls received mp w/ saline; pulsed delivery of nicotine w/ sesame oil; sesame oil superior to air; Dose (0.4 mg/kg)

R0130: F. Theeuwes, *et al.* Systems for triggered, pulsed, and programmed drug delivery. Annals of the New York Academy of Sciences 1991;618(428-440
Agents: Melatonin **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;
ALZET Comments: review of programmed drug delivery systems; pulsed delivery

P2032: J. N. Petitte, *et al.* Daily infusion of corticosterone and reproductive function in the domestic hen (Gallus domesticus). Gen. Comp. Endocrinol 1991;83(3):397-405
Agents: Corticosterone **Vehicle:** PEG 400; **Route:** SC; **Species:** Bird (chicken); **Pump:** 2ML2; 2ML4; **Duration:** 14 days;
ALZET Comments: Dose-response; pulsed delivery achieved by externalizing PE-60 catheter from pump. Catheter could be disconnected at will for intermittent delivery: 10 hr on/14 hr off, 4 hr on/20 hr off, 24 hr on/0 hr off (pg 398-399)

P2029: N. A. Pampori, *et al.* Renaturalizing the sexually dimorphic profiles of circulating growth hormone in hypophysectomized rats. European Journal of Endocrinology 1991;124(3):283-289
Agents: Growth hormone **Vehicle:** Albumin; Bicarbonate; Glycerol; **Route:** IP; **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;
ALZET Comments: functionality of mp verified by serum GH RIA; replacement therapy (hypophysectomy); comparison of sc injections and intermittent external pump vs mp; pulsed delivery attempted; peptides

R0092: V. H. L. Lee. Problems and solutions in peptide and protein drug delivery. Pharmacokinetics and Pharmacodynamics 1991;3(80-92
Agents: Not Stated **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Not Stated; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: Pulsed delivery, brief mention

P4166: Y. Sun, *et al.* The use of an ALZET osmotic pump as a "carryable" external infusion pump for small animal studies. Proceed. Intern. Symp. Control. Rel. Bioact. Mater 1990;17(371-372
Agents: Insulin **Vehicle:** Not Stated; **Route:** IV (jugular); **Species:** Rat; **Pump:** 2ML1; 2ML2; **Duration:** Not Stated;
ALZET Comments: External pump application; the pumping rate was adjusted by greatly varying the osmolality of the medium in the fluid chamber in which the pump was placed; pulsed delivery: air used as spacer in Lynch coil; peptides; manufacturer's note: pumps need to be primed at 37 degrees rather than 23 degrees C, and the pumps cannot be reused

P1253: V. C. Rayner, *et al.* Chronic intracerebroventricular morphine and lactation in rats: dependence and tolerance in relation to oxytocin neurones. Journal of Physiology 1988;396(319-348
Agents: Morphine sulfate; Radio-isotopes **Vehicle:** 3H tracer; Water; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; **Duration:** 5, 6, 7 days;
ALZET Comments: controls received mp w/ water; mp connected to cannula in ICV; mp primed overnight in saline; mp used in 4 of 5 exp.; labeled morphine used in only 1 exp.; functionality of mp verified by compression of mp to obtain contents; pulsed delivery (increasing dose)

P1557: M. T. Martin-Iverson, *et al.* Chronic administration of a selective dopamine D-2 agonist: factors determining behavioral tolerance and sensitization. Psychopharmacology 1988;95(534-539
Agents: Hydroxynaphthoxacine, 4-propyl-9- **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 11, 15 days;
ALZET Comments: 12 hours (intermittently); comparison of injections vs. mp infusion; functionality of mp verified in vitro; pulsed delivery using coiled tubing, intermittent inert placebo, 12h 'on' and 12h 'off'; PHNO is dopamine D-2 receptor agonist

P1218: R. J. Bicknell, *et al.* Naloxone excites oxytocin neurones in the supraoptic nucleus of lactating rats after chronic morphine treatment. Journal of Physiology 1988;396(297-317
Agents: Morphine sulfate **Vehicle:** Water; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; **Duration:** 168 days;
ALZET Comments: controls received mp w/ water; pulsed delivery (cannula and tubing filled w/ increasing doses of morphine separated by 1.0 ul of air); mp connected to cannula; long-term study

R0077: N. Ray, *et al.* Implantable osmotically powered drug delivery systems. In 'Drug Delivery Systems: Fundamentals and Techniques,' P. Johnson and J. G. Lloyd-Jones (eds.), Ellis Horwood Ltd. , Chichester, England and VCH Verlasgesellschaft mbH, Weinheim, Federal Republic of Germany 1987;Ch. 7):120-138
Agents: Antipyrine; bleomycin; dopamine HCl; melatonin; methotrexate, sodium; nicotine; prednisolone; radio-isotopes; valproic acid **Vehicle:** ^{14}C tracer; ^{3}H tracer; **Route:** IA; IP; SC; **Species:** Mice; Rabbit; Rat; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: ALZA-authored; synoptic review of mp; post op. care (antibiotic); comparison of sc injections vs. mp infusion; pulsed delivery

P1399: J. A. Phillips, *et al.* Modification of reproductive rhythm in lizards via GnRH therapy. Annals of the New York Academy of Sciences 1987;519(128-136
Agents: Luteinizing HRH analog, chicken **Vehicle:** Peanut oil; **Route:** IP; **Species:** Iguana; **Pump:** 2ML2; **Duration:** 10 days;
ALZET Comments: Coiled catheter; continuous versus pulsed delivery both by mp; pulsed delivery; peptides

P1048: J. A. Phillips, *et al.* Exogenous GnRH overrides the endogenous annual reproductive rhythm in green iguanas, iguana iguana. Journal of Experimental Zoology 1987;241(227-236
Agents: Luteinizing HRH **Vehicle:** Peanut oil; **Route:** IP; **Species:** Iguana; **Pump:** 2ML2; **Duration:** 14 days;
ALZET Comments: controls received mp w/vehicle; peptides; pumps primed in saline before implantation; pulsed delivery; chicken & mammal LHRH used

R0075: A. A. Amkraut, *et al.* Delivery of therapeutic agents by osmotic pumps. In 'The Pharmacology and Toxicology of Proteins,' UCLA Symposia on Molecular and Cellular Biology, New Series, Alan R. Liss, Inc. , New York 1987;131-148
Agents: Not Stated **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Not Stated; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: ALZA-authored; general description of mp and its uses; comparison of routes of administration; replacement therapy; stability; pulsed delivery; peptides

P0771: N. L. Schlechter, *et al.* A direct growth effect of growth hormone in rat hindlimb shown by arterial infusion. American Journal of Physiology Endocrinology and Metabolism 1986;250(American Journal of Physiology Endocrinology and Metabolism):E231-E235
Agents: Growth hormone, rat; Prolactin, ovine **Vehicle:** Glycerol; Sodium azide; **Route:** IA (superior vesicle); **Species:** Rat;
Pump: 2001; **Duration:** 7 days;
ALZET Comments: replacement therapy (hypophysectomy); mp connected to catheter in superior vesicle artery; detailed description and diagram of catheter apparatus; constant and pulsed delivery of GH; peptides

P0902: M. C. Ruiz de Elvira, *et al.* A backpack system for long-term osmotic minipump infusions into unrestrained marmoset monkeys. Laboratory Animals 1986;20(329-334
Agents: Luteinizing HRH **Vehicle:** Not Stated; **Route:** SC; **Species:** Monkey; **Pump:** 2001; **Duration:** Up to 22 days;
ALZET Comments: mp conn. to cannula, external pump application; pumps replaced every 10 days; mp cont. in saline filled vial attached to backpack; sys. used for long-term inf. up to 3 mths; pulsed delivery of LHRH using backpack system; peptides

P0701: J. A. Phillips, *et al.* Stimulating male sexual behavior with repetitive pulses of GnRH in female green iguanas, Iguana iguana. Journal of Experimental Zoology 1985;234(3):481-484
Agents: Luteinizing HRH **Vehicle:** Acetic acid; **Route:** IP; **Species:** Iguana; **Pump:** 2ML2; **Duration:** 4 weeks;
ALZET Comments: No stress (see pg. 483); pulsed delivery of LHRH (intermittent w/peanut oil); mp primed in saline prior to implant; peptides; chicken LHRH used

P0639: C. C. W. Mick, *et al.* Prolactin directly stimulates the liver in vivo to secrete a factor (synlactin) which acts synergistically with the hormone. Endocrinology 1985;116(5):2049-2053
Agents: Growth hormone, ovine; Prolactin, ovine **Vehicle:** Citric acid; Glycerol; **Route:** IV (hepatic portal); IV (jugular); **Species:** Bird (pigeon); **Pump:** 2001; **Duration:** 1 week;
ALZET Comments: Comparison of agents effects; citric acid added to solvent for bacteriostatic effects; pulsed delivery of hormone or solvent (intermittent w/ air); peptides; tissue perfusion

P0843: D. Lindburg, *et al.* Induced estrus in the cheetah. AZA Conference Proceedings 1985;560-563
Agents: Luteinizing HRH **Vehicle:** Not Stated; **Route:** SC; **Species:** Cat (cheetah); **Pump:** Not Stated; **Duration:** 10 days;
ALZET Comments: mp model not stated; pulsed delivery of GnRH to induce estrus; peptides

P0661: T. Cronan, *et al.* Effects of chronically administered nicotine and saline on motor activity in rats. Pharmacology Biochemistry and Behavior 1985;22(5):897-899
Agents: Nicotine **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 8 days;
ALZET Comments: pulsed delivery of nicotine and saline (intermittent w/air, 16 hrs. on, 8 hrs. off); pumps primed in saline; stress/adverse reaction (tissue growth over mp, preventing release of drug)

P0761: B. L. Lasley, *et al.* Stimulating ovarian function in exotic carnivores with pulses of GnRH. Presented at the Annual Meeting of the American Association of Zoo Veterinarians, Oct. 24-27, Tampa, FL 1983;14-15
Agents: Luteinizing HRH **Vehicle:** Not Stated; **Route:** SC; **Species:** Cat (cheetah); Cat (golden cat); Cat (leopard); **Pump:** 2ML2; 2ML4; **Duration:** 9, 11 days;
ALZET Comments: Pulsed delivery of LHRH and peanut oil; mp primed in saline for 8 hrs. prior to implant; peptides; stress/adverse reaction (fibrous tissue adhering to silastic coils connected to mp in the golden cat)

P0322: L. L. Ewing, *et al.* Effect of luteinizing hormone on Leydig cell structure and testosterone secretion. Endocrinology 1983;112(5):1763-1769
Agents: Follicle stimulating hormone; Growth hormone, ovine; Luteinizing hormone; Prolactin, ovine; Thyroid-stimulating hormone **Vehicle:** Borate; Peanut oil; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 5 days;
ALZET Comments: Replacement therapy (hypophysectomy); simultaneous infusion of testosterone & estradiol implants w/ mp infusion of polypeptides; pulsed delivery of agents (intermittent w/ vehicle); peptides; ovine LH used

P0065: H. J. Lynch, *et al.* Artificial induction of melatonin rhythms by programmed microinfusion. Neuroendocrinology 1980;31(106-111
Agents: Melatonin **Vehicle:** Phenolsulfonphthalein; Saline; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: Replacement therapy (pinealectomy); pulsed delivery of agent (intermittent w/vehicle)

P0067: H. J. Lynch, *et al.* Control of rhythms in the secretion of pineal hormones in humans and experimental animals. In 'Biological Rhythms and their Central Mechanism,' M. Suda, O. Hayaishi, and H. Nakagawa (eds.), Elsevier/N. Holland, Biomedical Press 1979;117-131
Agents: Melatonin **Vehicle:** Phenolsulfonphthalein; Saline; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** Not Stated;
ALZET Comments: Replacement therapy (pinealectomy); pulsed delivery of agent (intermittent w/vehicle); comparison of human vs. animal data