



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**

- 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)
ALZET Comments: Nerve growth factor; Methylene blue; BSA; CSF, artificial; CSF/CNS; Rat; 2002; 12 days; animal info (male, Wistar); functionality of mp verified by residual volume; ALZET brain infusion kit used; post op. care (SC injections of 0.9% saline (2ml)); pulsed delivery; used PE-60 tubing; used Lynch coil;
- Q3342:** K. K. Howell, *et al.* Inhibition of PKC disrupts addiction-related memory. *Frontiers in Behavioral Neuroscience* 2014;8(;):U1-U9
ALZET Comments: Peptide, zeta-inhibitory; chelerythrine; CSF, artificial; PBS; CSF/CNS (third ventricle); Mice; 1002; 2 days; 6 days; Controls received mp w/ vehicle; animal info (C57BL/6Jx129T2SvEms/J, adult); ALZET brain infusion kit 3 used; post op. care (buprenorphine injection); behavioral testing (locomotion, locomotor sensitization); pulsed delivery; dependence; peptides; zeta-inhibitory peptide aka ZIP; Lynch coil of ZIP administration for 14.5 hours; used mineral oil; Schematic of pump implantation pg.3 Fig 1A;
- Q3359:** S. C. Robins, *et al.* Extensive regenerative plasticity among adult NG2-glia populations is exclusively based on self-renewal. *Glia* 2013;61(10):1735-1747
ALZET Comments: Uridine, bromodioxo; Ara-C; CSF, artificial; CSF/CNS; Mice (transgenic); 7 days; 12 days; Animal info (male, NG2-CreER:tomato, 8-12 weeks old); pulsed delivery (delayed delivery 2 days with vehicle in catheter); brain tissue distribution; cyanoacrylate adhesive used to close catheter tubing; Plastics 1 cannula and catheter.
- Q3171:** P. A. Pereira, *et al.* Nerve growth factor retrieves neuropeptide Y and cholinergic immunoreactivity in the nucleus accumbens of old rats. *NEUROBIOLOGY OF AGING* 2013;34(8):1988-1995
ALZET Comments: Nerve growth factor; CSF, artificial; bovine serum albumin; CSF/CNS; SC; Rat; 2002; 12 days; Animal info (male, Wistar, 6-24 months old); functionality of BIK verified by methylene blue staining; ALZET brain infusion kit used; 0.1% Bovine Serum Albumin used; neurodegenerative (aging); post op. care (SC injections 2ml of 0.9% saline); pulsed delivery (used coiled Intramedic PE-60; 0.1% methylene blue with air-oil spacer at pump end with agent); peptides;
- Q3117:** C. B. Mantilla, *et al.* Motoneuron BDNF/TrkB signaling enhances functional recovery after cervical spinal cord injury. *Experimental Neurology* 2013;247(;):101-109
ALZET Comments: Brain-derived neurotrophic factor;; CSF/CNS (intrathecal); Rat; 2002; 14 days; Animal info (male, Sprague Dawley, adult); spinal cord injury; post op. care (Acetaminophen 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.
- Q2457:** A. M. Williams, *et al.* The effect of intermittent alcohol vapor or pulsed heroin on somatic and negative affective indices during spontaneous withdrawal in Wistar rats. *Psychopharmacology* 2012;223(1):75-88
ALZET Comments: Heroin; Saline; SC; Rat; 2ML4; 30 days; Control animals received mp w/ vehicle; animal info (Wistar, male, 70 days old); pulsed delivery; "By filling the pumps with saline and attaching polyethylene (PE60) tubing to the pump, based on the tubing inner diameter and pump flow rate characteristics, the volume needed for different infusion periods (e.g., 14- or 10-h periods) could be determined"; "the tubing was filled with alternating heroin solution and mineral oil"; pulsed delivery; good methods, pg 78; image of pump with connected Lynch coil; wound clips used; post op. care (Baytril); behavioral testing (elevated plus mazet forced swim test).



Q1822: J. P. Shaffery, *et al.* Brain-derived neurotrophic factor (BDNF) reverses the effects of rapid eye movement sleep deprivation (REMSD) on developmentally regulated, long-term potentiation (LTP) in visual cortex slices. *Neuroscience Letters* 2012;513(1):84-88

ALZET Comments: Brain-derived neurotrophic factor; PBS; BSA; CSF/CNS (visual cortex); Rat; 2002; 1007D; Controls received mp w/ saline; animal info (Long-Evans Hooded, P28; immature, P22-P25); pulsatile delivery; polyethylene tubing contained saline with an air bubble separator for a 5-day drug delay and recovery period; delayed delivery.

Q1737: S. Kudo, *et al.* Cartilaginous repair of full-thickness articular cartilage defects is induced by the intermittent activation of PTH/PTHrP signaling. *OSTEOARTHRITIS AND CARTILAGE* 2011;19(7):886-894

ALZET Comments: Parathyroid hormone (1-84), recomb. human; Saline, sterile; Knee (articular cavity); Rabbit; 2002; 14 days; Controls received mp w/ vehicle; animal info (male, white, adolescent, Japanese, 3-3.4 kg); pulsatile delivery; "The program consisted of alternating segments of 5 ul PTH (50 ug/ml) solution and 5 ul sterile saline interrupted by 1 ul air bubbles." pg 888.

Q0075: K. A. Stockwell, *et al.* Continuous rotigotine administration reduces dyskinesia resulting from pulsatile treatment with rotigotine or L-DOPA in MPTP-treated common marmosets. *Experimental Neurology* 2010;221(1):79-85

ALZET Comments: Rotigotine hydrochloride; DMSO; water, sterile; SC; Marmoset; 2004; 28 days; Comparison of SC injections or PO administration vs. SC mp; animal info (adult, common, male, female, 2-7 years old, 350-500); 50% DMSO used; "These data suggest that dyskinesia induced by pulsatile drug treatment may be improved by switching to continuous rotigotine delivery." pg. 79; "...this study highlights the potential benefits of continuous drug delivery." pg 84.

R0352: A. A. Boulton. *Animal Models of Dementia.* Springer Protocols 2010;48(1-721

ALZET Comments: Amphetamine sulfate; Dopamine; Propylene Glycol; SC; CSF/CNS (nucleus accumbens); Rat; 2ML2; 14 days; comparison of injections and systatic 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 12-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

ALZET Comments: NT-3; PBS; Dye, toluidine blue; CSF/CNS (intrathecal); Rat; 2002; 7 days; 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

ALZET Comments: Cocaine; pramipexole; Saline; SC; Rat; 2ML2; 14 days; 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

ALZET Comments: Oligodeoxynucleotide, antisense; Ringer's solution; CSF/CNS; Rat (lactating); 1007D; 4 days; 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

ALZET Comments: CART (42-89);; PBS;; CSF/CNS;; Rat;; 2001; 2002;; 7, 10 days;; 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;.

P4578: Y.-N. Sun, *et al.* A pharmacokinetic/pharmacodynamic model for recombinant human growth hormone effects on induction of insulin-like growth factor I in monkeys. *The Journal of Pharmacology and Experimental Therapeutics* 1999;289(3):1523-1532

ALZET Comments: Growth hormone, recomb. human; SC;; monkey;; 30 days;; comparison of SC injections vs. mp vs. microspheres; peptides; "Continuous rhGH input delivered by ProLease and osmotic pump is more effective than pulsatile injections in induction of IGF-I, especially when the delivery systems can maintain growth hormone concentration above the SC₅₀" (p. 1531).

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

ALZET Comments: Parathyroid hormone, human 1-34; NaCl; HCl; Serum, rat;; SC;; Rat;; 7 days;; 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

ALZET Comments: Luteinizing hormone, ovine;; Buffer, borate;; SC;; Rat;; 5 days;; 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

ALZET Comments: Morphine sulfate; MK-801; Saline, sterile; CSF/CNS (intrathecal); Rat; 2002; 8 days; 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

ALZET Comments: no duration posted; 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

ALZET Comments: Parathyroid hormone, human 1-34; NaCl; HCl; Serum, rat; Rat; 2001; 6 days; 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. Otolaryngology* 1995;16(3):304-309

ALZET Comments: Nerve growth factor; Neomycin; Saline; ear (cochlea); Guinea pig; 2 weeks; 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.

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



ALZET Comments: Growth hormone, human; Growth hormone, bovine; Growth hormone, rat; IV (jugular); IV (portal); Rat; 2001; 7 Days; 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

ALZET Comments: Liposomes; Eye (lens); rabbit; 2ML1; no duration posted; 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. *Biol. Reprod* 1993;48(512-514

ALZET Comments: Prolactin, ovine; Sodium azide; Sodium phosphate; Saline; Glycerol; IV (jugular); IV (hepatic portal); Rat; 2002; no duration posted; 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

ALZET Comments: Prolactin, ovine; IV (jugular); IV (hepatic portal); Rat; 2001; 5 days; 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).

R0105: T. L. Goldsworthy, *et al.* Concepts, labeling procedures, and design of cell proliferation studies relating to carcinogenesis. *Environ. Health Perspect* 1993;101(5):59-66

ALZET Comments: Uridine, bromodeoxy-; Rat;; no duration posted;; pump mentioned briefly on pg. 61-62 as method for continuous administration for cell proliferation labeling; some guidelines for using pumps in studies given, as well as how to decide between pump or pulsatile delivery; cancer;.

P2542: O. Topping, *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

ALZET Comments: Parathyroid hormone-related peptide; Interleukin-1, alpha; Albumin, mouse serum; Cysteine HCl; SC; Rat; 2001; 14 days; 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

ALZET Comments: Nicotine; SC; Rat; 4, 7, 14 days; 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. *Ann. N. Y. Acad. Sci* 1991;618(428-440

ALZET Comments: Melatonin; Rat; 7 days; review of programmed drug delivery systems; pulsed delivery.

P2032: J. N. Petite, *et al.* Daily infusion of corticosterone and reproductive function in the domestic hen (*Gallus domesticus*). *Gen. Comp. Endocrinol* 1991;83(3):397-405

ALZET Comments: Corticosterone; PEG 400; SC; bird (chicken); 2ML2; 2ML4; 14 days; 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. *Acta Endocrinol. (Copenh)* 1991;124(3):283-289



ALZET Comments: Growth hormone; Albumin; Bicarbonate; Glycerol; IP; Rat; 7 days; 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)

ALZET Comments: no duration posted; 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)

ALZET Comments: Insulin; IV (jugular); Rat; 2ML1; 2ML2; no duration posted; 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.

P1832: D. E. English, *et al.* Evidence for a role of the liver in the mammatrophic action of prolactin. *Endocrinology* 1990;126(5):2252-2256

ALZET Comments: Prolactin, ovine; Glycerol; Sodium azide; IV (jugular); IV (hepatic portal); Rat; 2 weeks; pulse delivery; peptides.

P1253: V. C. Rayner, *et al.* Chronic intracerebroventricular morphine and lactation in rats: dependence and tolerance in relation to oxytocin neurones. *J. Physiol* 1988;396(319-348)

ALZET Comments: Morphine sulfate; Radio-isotopes; 3H tracer; Water; CSF/CNS; Rat; 2001; 5, 6, 7 days; 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)

ALZET Comments: Hydroxynaphthoxacine, 4-propyl-9-; SC; Rat; 2002; 11-15 days; 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. *J. Physiol* 1988;396(297-317)

ALZET Comments: Morphine sulfate; Water; CSF/CNS; Rat; 2001; 168 days; 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 Verlagsgesellschaft mbH, Weinheim, Federal Republic of Germany 1987;Ch. 7):120-138

ALZET Comments: Antipyrine; bleomycin; dopamine HCl; melatonin; methotrexate, sodium; nicotine; prednisolone; radio-isotopes; valproic acid; ¹⁴C tracer; ³H tracer; IA; IP; SC; Mice, rabbit, Rat; no duration posted; 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. *Ann. N. Y. Acad. Sci* 1987;519(128-136)

ALZET Comments: Luteinizing HRH analog, chicken; Peanut oil; IP; iguana; 2ML2; 10 days; 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. *J. Exp. Zool* 1987;241(227-236)



ALZET Comments: Luteinizing HRH; Peanut oil; IP; iguana; 2ML2; 14 days; 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

ALZET Comments: no duration posted; 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. *Am. J. Physiol* 1986;250(E231-E235)

ALZET Comments: Growth hormone, rat; Prolactin, ovine; Glycerol; Sodium azide; IA (superior vesicle); Rat; 2001; 7 days; 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. *Lab. Anim* 1986;20(329-334)

ALZET Comments: Luteinizing HRH; SC; monkey; 2001; up to 22 days; 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. *J. Exp. Zool* 1985;234(3):481-484

ALZET Comments: Luteinizing HRH; Acetic acid; IP; iguana; 2ML2; 4 weeks; 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

ALZET Comments: Growth hormone, ovine; Prolactin, ovine; Citric acid; Glycerol; IV (hepatic portal); IV (jugular); bird (pigeon); 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; tissue perfusion.

P0843: D. Lindburg, *et al.* Induced estrus in the cheetah. *Ann. Proc. AAZPA* 1985;560-563

ALZET Comments: Luteinizing HRH; SC; cat (cheetah); 10 days; 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. *Pharmacol. Biochem. Behav* 1985;22(5):897-899

ALZET Comments: Nicotine; Saline; SC; Rat; 2002; 8 days; 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

ALZET Comments: Luteinizing HRH; SC; cat (cheetah); cat (golden cat); cat (leopard); 2ML2; 2ML4; 9-11 days; 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

ALZET Comments: Follicle stimulating hormone; Growth hormone, ovine; Luteinizing hormone; Prolactin, ovine; Thyroid-stimulating hormone; Borate; Peanut oil; SC; Rat; 5 days; 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)

ALZET Comments: Melatonin; Phenolsulfonphthalein; Saline; SC; Rat; no duration posted; 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

ALZET Comments: Melatonin; Phenolsulfonphthalein; Saline; SC; Rat; no duration posted; replacement therapy (pinealectomy); pulsed delivery of agent (intermittent w/vehicle); comparison of human vs. animal data.