livery systems, five at Genentech, John Patton determined that the pulmonary system has the greatest advantages for macromolecular delivery—one of the least explored alternatives to the needle. Genentech's hesitancy to pursue this path forced an amiable parting of the ways, says Patton, who left to form Inhale (Palo Alto, CA).To prove his point., Patton cites human and animal studies demonstrating 10-25 percent absolute bioavailability of inhaled peptides and proteins.

Insulin experiments in the 1920s suggested that macromolecules pass easily through the lung into the blood[6]. Subsequent work in the 60s and 70s confirmed this notion. But, successes with potent peptides of molecular weights less than 1200 Da. (vasopressin [and its analogue dDAVP], oxytocin, and LHRH [and its analogue buserelin]) through the nasal route refocused pharmaceutical attention on the nose.

When it became apparent that higher MW proteins such as calcitonin (3400 Da), insulin (5700 Da) or growth hormone (22000 Da) gave low bioavailability and required "enhancers"—which severely irritated nasal membranes—[7] pharmaceutical companies realized they would face regulatory problems. The safety and long term effects of an enhancer conjugated to a protein would chart new areas for FDA approval—a voyage no one is anxious to take.

Delivery through the lung is largely a question of technology brought to bear on physiology. The deep lung has a surface area of about 143 m^2 in adults—larger than most New York city apartments. Permeability is thought to be the highest in the alveolar region but getting a uniform, reproducible dose of the right protein into the room, today, is like trying to spray paint the floor through the keyhole.

A particle entering the lung encounters a branching system of airways (bronchi and bronchioles) covered with thick columnar epithelium similar to that which lines the nose and the G.I. tract—a relatively impermeable absorptive barrier. This branching serves as a highly efficient impaction filter. Particle size, therefore, is the critical determinant for absorption—two to four micrometers is optimal.

Christopher Graeme-Barber of The Technology Partnership (Melbourn Royston, U.K.), says the company has developed electronic atomization technology with Bespak (King's Lynn, U.K.) which is ideally suited to overcome pulmonary delivery problems. Fitting in the user's pocket, the system employs low-frequency ultra-sound to nebulize protein into an appropriately-sized aqueous based droplet. Low velocity spray—instead of the normal pressurized CFC propellant—delivers the peptide to the alveoli. The company claims that the integration of a breath sensor enables high repeatability, minimizing patient variation at a level superior to conventional metered-dose inhalation (MDI) systems.

Delivery to the alveoli eliminates many of the problems associated with oral systems. Peptides are absorbed quickly and directly into the blood stream. There are few proteases to degrade the protein, a less hydrophilic environment to denature it, and no first pass metabolism to contend with. These factors combined with the large, naturally absorptive surface area recommend it highly as an alternative to the needle.

But Ian Kellaway, from the University of Wales (Cardiff, U.K.), while agreeing that it's an extremely attractive system, sees problems which still must be ironed out if it is to fulfill its potential. Proteins may shear in the process of atomization. Drug not immediately absorbed in the alveoli is whisked away on a continuously moving mucosal lining or phagocytosed by macrophages. And, the biotech drug's topical effects on the lung remain unknown.

A Golden Age For Physiology

With so little of the basic physiology for biotech drug delivery understood, what emerges is the need for a multidisciplined research effort to explore the mechanisms of uptake and metabolism. Most biopharmaceutical companies realize that their future commercial opportunities may be limited by the degree they don't pioneer this research.

In response to this situation, pharmaceutical companies have developed proprietary analytical methods—as closely guarded as their drugs under development. "You can't deliver it unless you can measure it," Mark Eickhoff repeatedly admonishes his staff. As Sterling Research Group's (Paoli, PA) principal scientist, Eickhoff develops mathematical models for comparing tradeoffs between such factors as drug cost, metabolic loss, rate of degradation, and rate of absorption. His group also develops *in vitro* systems to project bioavailability of drugs *in vivo*.

The European Commission (EC) recognizes the critical importance of such efforts to enhance the competitiveness of biotech companies there. The EC awarded a $2.8 million grant to Danbiosyst (Nottingham, U.K.) and its partners Pharmatec (Italy) and Gent University (Belgium) for a four-year study on systemic delivery of polypeptides via the large intestines.

More funding of this kind is needed to study the tractability of other drug delivery systems such as the pulmonary, ocular, buccal, vaginal, rectal, and iontophoretic (transdermal), if biotech drugs are to make the transition to chronic care. Although the problems appear at first glance insurmountable, the entrepreneurial spirit which attracts researchers to this area is the strongest argument that biotech will make this transition. When Enzytech's Tom Beck was questioned about the wisdom of tackling such a difficult area, especially after his considerable experience in pharmaceuticals, he was quick to reply, "Oh no, this field isn't that impossible. Some of my buddies from pharmaceutical days took on something much harder—gene therapy."

References

1. Pharm. Manufact. Ass.. 1991. Products in the pipeline. *Bio/Technology.* **9**:947-949.
2. Singh, B. and P. Wise. 1991. Detection of glibenclamide in oral insulin capsules. *Lancet.* **338**:308, Aug. 3.
3. Cho, Y.W. and Flynn, M. 1989. Oral delivery of insulin. *Lancet* **ii**:1518-1519., Dec. 23.
4. Smith, P.L., Wall, D.A., Gochoco, C.H., and Wilson, G. 1991. Oral absorption of peptides and proteins. *Adv. Drug Delivery Reviews. in press.*
5. Russel-Jones, G.J., and H.J. de Aizpurua. 1988. Vitamin B12: a novel carrier for orally presented antigens. *Proceed. Intern. Symp. Control Release Bioact. Mater.* **15**:142-143.
6. Gansslen, M. 1925. Uber inhalation von insulin. *Klin. Wochenschr.* **4**:71.
7. Patton, J.S. and G.A.Keller,1991. Alternatives to injections:pulmonary delivery of peptides and proteins. *in press.*.

HOW THE BIG BOYS SEE IT

"Any product manager will tell you—put it in a pill or a tablet and you'll blow the competition away," says Sterling Research Group scientist Mark Eickhof. But he, and other top pharmaceutical scientists, see the real excitement for peptide delivery as parenteral and occurring in-house—through medicinal chemistry—not through formulation. Ask for examples and you get tight-lipped allusions to peptide structures mimicked by heterocyclic molecules to get them across membranes, making them more protease resistant, and extending the half life. Research managers say that in two to three years some of these molecules, primarily small hormones and peptides, will be making news.

To overcome the need for multiple injections, many peptide drug makers are turning to polymers for controlled release. The technology allows injected encapsulated peptides to leach out over time as the capsule gradually biodegrades. Danny Lewis, president of Medisorb Technology International (Cincinnati, OH), says biopharmaceutical licensing contracts have grown so numerous that the company is building a 100 million doses per year, GMP, aseptic processing facility scheduled to open in 1992. While the licensees names remain confidential, Lewis does say that recombinant interleukins, hGH, and colony stimulating factors are among the projects Medisorb is working on.

As for the academics, and their companies, many pharmaceutical executives suggest that the systems they propose are not relevant, not practical, and will never work for proteins, especially when it comes to oral delivery. "Systems looking for a drug," one scientist called them. "Desirability and feasibility are on the opposite ends of the scale," said another.