(4) R. R. Ellison, J. F. Holland, M. Weil, C. Jacquillat, M. Boiron, J. Bernard, A. Sawitsky, F. Rosner, B. Gussoff, R. T. Silver, A. Karanas, J. Cuttner, C. L. Spurr, D. M. Hayes, J. Blom, L. A. Leone, F. Haurani, R. Kyle, J. L. Hutchison, R. J. Forcier, and J. H. Moon, *Blood*, **32**, 507 (1968).

(5) B. D. Clarkson, M. D. Dowling, T. S. Gee, I. B. Cunningham, and J. H. Burchenal, *Cancer*, **36**, 775 (1975).

(6) F. Maley, in "Cancer, A Comprehensive Treatise," vol. 5, F. F. Becker, Ed., Plenum, New York, N.Y., 1977, chap. 12.

(7) A. W. Chow, J. Foerster, and W. Hryniuk, in "Antimicrobial Agents and Chemotherapy–1970," G. L. Hobby, Ed., American Society for Microbiology, Bethesda, Md., 1971, pp. 214–217.

(8) Y. F. Shealy and C. A. O'Dell, *J. Heterocycl. Chem.*, **13**, 1353 (1976).

(9) R. W. Brockman, J. W. Carpenter, C. A. O'Dell, Y. F. Shealy, and L. L. Bennett, Jr., *Fed. Proc.*, **37**, 234 (1978).

(10) K. Kikugawa and M. Ichino, *Tetrahedron Lett.*, **1970**, 867.

(11) R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3**, 1 (1972).

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Received December 21, 1978.
Accepted for publication February 14, 1979.
Supported by the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Contract NO1-CM-43762, and by Southern Research Institute.
Testing against L-1210 leukemia was performed in this Institute under the supervision of Dr. F. M. Schabel, Jr., and Dr. W. R. Laster, Jr., and was supported by Contract NO1-CM-43756 with the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.
Mass spectra were determined by M. C. Kirk; NMR spectra were determined by Martha C. Thorpe.

Absorption of Insulin Delivered to Rabbit Trachea Using Aerosol Dosage Form

Keyphrases □ Insulin—aerosol dosage forms, tracheal administration, absorption, rabbits □ Dosage forms, aerosol—insulin, tracheal administration, absorption, rabbits □ Proteins—aerosol dosage forms, insulin, tracheal administration, absorption, rabbits

To the Editor:

Insulin, an endogenous hormone used in treatment of diabetes mellitus, has been administered parenterally rather than orally because it readily decomposes in the GI tract. However, some effective approaches have been developed for oral (1–3), nasal (4), and rectal and aerosol (5, 6) dosage forms. The aerosol dosage form has been receiving much attention because it can be used by diabetic patients with little difficulty.

Wigley *et al.* (5) reported that insulin delivered to patients and volunteers by aerosol inhalation using a nebulizer was absorbed through the respiratory tract epithelium and was an effective therapeutic form for diabetes mellitus (5). However, little has been mentioned about the pharmaceutical factor that governs insulin absorption from aerosol dosage forms.

The present study was undertaken to investigate the bioavailability of powdered aerosol insulin when administered intratracheally to rabbits.

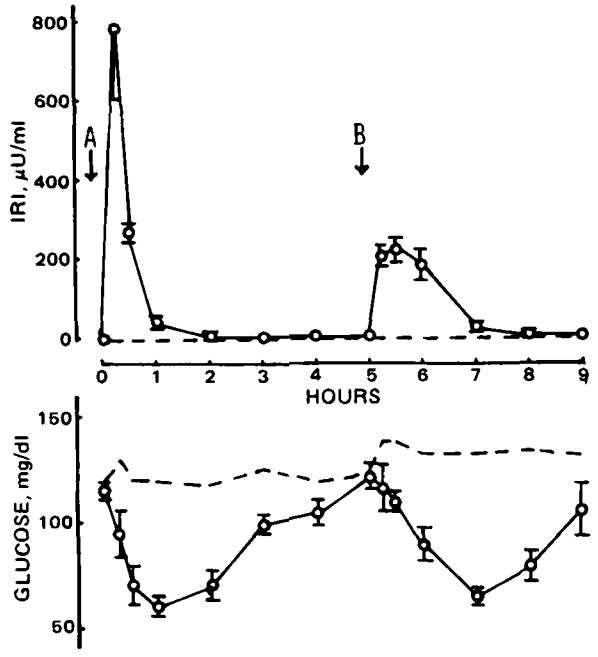

Figure 1—*Plasma concentration profiles of immunoreactive insulin (IRI) and glucose after intravenous (A, 1 U/kg) or intratracheal (B, 2.5 U/kg) insulin administration. Each point represents the mean ± SEM of three experiments. Broken lines denote immunoreactive insulin and glucose levels in sham-operated rabbits.*

White male rabbits, 2.8–3.1 kg, were anesthetized with pentobarbital sodium and maintained under anesthesia for the entire experiment. After the animal was secured in a supine position, insulin solution (1.0 U/kg) or physiological saline (as the control) was injected into the ear vein.

Blood samples were collected from the femoral vein at timed intervals to monitor immunoreactive insulin and glucose levels in plasma. Four hours after intravenous insulin injection, the rabbit trachea was exposed and polyethylene tubing was inserted through a tracheal incision. Insulin aerosol was sprayed into the trachea 1 hr after surgical treatment, and the appearance of immunoreactive insulin and the blood glucose level then were determined at timed intervals.

The insulin aerosol formulation was composed of: monocomponent porcine insulin[1], 5 mg; lactose, 75 mg; acetylglycerin monostearate, 50 mg; dichlorodifluoromethane, 3.6 g; and dichlorotetrafluoroethane, 2.4 g. A metered aerosol valve was designed to release 0.058 mg (1.5 U) of insulin/delivery. The plasma glucose level was measured by the method of Hyvärinen and Nikkilä (7), and immunoreactive insulin in plasma was determined by the method of Desbuquois and Aurbach (8).

Figure 1 shows the time courses of immunoreactive insulin and glucose concentrations in plasma after intravenous injection and after intratracheal aerosol insulin administration. After intravenous administration, there was a sharp increase in plasma immunoreactive insulin and a decrease in plasma glucose. The decline in plasma glucose continued for about 3 hr, although the plasma immuno-

[1] Crystals, lot S 837301 (biological potency 26.6 I.U./mg), Novo Industry Co., Copenhagen, Denmark.

0022-3549/79/0500-0670$01.00/0

reactive insulin was almost completely cleared within 1 hr. After intratracheal insulin administered by aerosol, the circulating plasma immunoreactive insulin showed a significant rise and there was a sustained decline in the plasma glucose level.

The bioavailability calculated from the area under the plasma immunoreactive insulin curves after intratracheal aerosol administration of about 2.5 U of insulin/kg was almost the same as that after intravenous injection of 1 U/kg. Wigley *et al.* (5) reported that the plasma immunoreactive insulin area with aerosol delivery of about 3 U/kg was 7–16% of that after intravenous injection of 0.2 U/kg. This low bioavailability might depend on many factors such as adherence to the glass nebulizer, the mouth, and the throat. Our results indicated that most of the insulin (~40%) delivered directly into the trachea in an aerosol formulation is absorbed into the bloodstream through the epithelial layer of the respiratory tract. Accordingly, if an aerosol formulation could be administered directly into the trachea, it could be an effective tool for clinical applications of proteins and peptides.

(1) R. H. Engel, S. J. Riggi, and M. J. Fahrenbach, *Nature*, **219**, 8561 (1968).

(2) C. W. Crane, M. C. Path, and G. R. W. N. Luntz, *Diabetes*, **17**, 625 (1968).

(3) H. M. Patel and B. E. Ryman, *FEBS Lett.*, **62**, 60 (1976).

(4) S. Hirai, T. Ikenaga, and T. Matsuzawa, *Diabetes*, **27**, 296 (1978).

(5) F. M. Wigley, J. H. Londono, S. H. Wood, J. C. Shipp, and R. H. Waldman, *ibid.*, **20**, 552 (1971).

(6) S. Lee and J. J. Sciarra, *J. Pharm. Sci.*, **65**, 567 (1976).

(7) A. Hyvärinen and E. A. Nikkilä, *Clin. Chim. Acta*, **7**, 140 (1962).

(8) B. Desbuquois and G. D. Aurbach, *J. Clin. Endocrinol. Metab.*, **33**, 732 (1971).

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Received January 22, 1979.
Accepted for publication February 14, 1979.

BOOKS

REVIEWS

Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry. Vol. 1: Respiratory Gases, Volatile Anesthetics, Ethyl Alcohol, and Related Toxicological Materials; Vol. 2: Hypnotics, Anticonvulsants, and Sedatives; Vol. 3: Antipsychotic, Antiemetic, and Antidepressant Drugs; Vol. 4: Central Nervous System Stimulants; Vol. 5: Analgesics, Local Anesthetics, and Antibiotics. By BENJAMIN J. GUDZINOWICZ and MICHAEL J. GUDZINOWICZ. Dekker, 270 Madison Avenue, New York, NY 10016, Vol. 1: 1977, 223 pp., 15 × 23 cm, Price $23.75; Vol. 2: 1977, 493 pp., 15 × 23 cm, Price $45.00; Vol. 3: 1977, 268 pp., 15 × 23 cm, Price $29.75; Vol. 4: 1978, 458 pp., 15 × 23 cm, Price $45.00; Vol. 5: 1978, 541 pp., 15 × 23 cm, Price $55.00.

The above titles are the first five volumes in what the publisher promises to be a continuing series. Indeed, the flyleaf of Volume 5 states that Volume 6 will cover cardiovascular, antihypertensive, hypoglycemic, and thyroid-related agents. The stated purposes of this series are: to provide a chronological literature compilation of the GLC and GLC–mass spectrometry procedures for the analysis of specific drugs and their metabolites; to provide qualitative and quantitative procedures in such detail that they might be reproduced "faithfully" in the reader's laboratory; to present the results, precision, accuracy, and limits of detection achieved by a given procedure; and to indicate, wherever possible, the procedure's applicability to pharmacokinetic studies.

Each volume has a separate author and subject index. These indexes are not cumulative, but that is not necessary since each volume is self-contained. The authors assume that the reader is familiar with GLC and GLC–mass spectrometry. No pages are wasted on cursory introductory chapters, although the authors do include a few sketches of special instrument modifications such as sampling traps and injection ports. Where appropriate, the chemistry of a chemical class is described in an expanded discussion, which usually contains the structures and sometimes the biotransformations. Each chapter contains representative GLC tracings and tabulated retention data. Some mass spectra or printouts of mass fragment values are presented.

A logical question is: Does this series duplicate or overlap *Analytical Profiles*? To a limited extent, the answer is yes, only because GLC and mass spectra analyses are found in *Analytical Profiles*. Whereas the latter deals more with the pure drug, *Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry* emphasizes the analysis of mixtures that include the specific drugs under discussion. The two series complement each other, and the volumes covered in this review discuss a much larger group of compounds.

Volume 1 consists of two chapters of about equal length. The first chapter discusses respiratory gases, volatile anesthetics, and related toxicological materials. The second includes sterilizing agents, common organic solvents found in blood, and riot-control aerosol irritants. The second chapter also features ethanol and volatile trace components in breath, body fluids, and body tissues. The term "volatile" may be a little misleading, because the discussion on urine includes screening of urinary steroids and acids plus other chemicals.

The topics become more pharmaceutically oriented in the remaining volumes. About half of Volume 2 is devoted to barbiturates. One-third of the volume is a chapter that includes chloral derivatives, tertiary acetylenic alcohols, cyclic ethers, carbamates and ureides, piperdinediones, quinazalones, benzodiazepines, and carbamazepine. The third and final chapter makes up about 20 percent of the book and covers the traditional anticonvulsants including hydantoins, succinimides, primidone, paramethadione and trimethadione, and some miscellaneous anticonvulsants.

Volume 3 has two chapters of about equal length. Chapter 1 covers phenothazines, butyrophenones, and thioxanthines; Chapter 2 includes a moderate discussion on monoamine oxidase inhibitors and a rather complete coverage of the tricyclic antidepressants.

Volume 4 also contains two chapters of about equal length. Most of Chapter 1 is devoted to the amphetamines and related compounds, with the remainder including the xanthines and pentylenetetrazol. Chapter 2 mainly covers the phenylethylamine-related compounds, with the balance devoted to tryptamine- and propranolol-related compounds.