Health Service, reveals a steady fall in the past few years in the percentage of children immunized against both poliomyelitis and measles, particularly among the urban poor.[4] The explanation for these unfortunate trends undoubtedly involves many factors, including the expiration in 1968 of the federal Vaccination Assistance Act, which had provided funds to state and local health departments for the purchase of vaccines. Of greatest importance with respect to poliomyelitis, however, is the declining awareness of the disease as a potential threat, and the consequent relaxation of efforts to immunize *all* young children. Part of the difficulty is that the preschool population, by far the most important one with respect to both poliomyelitis and measles immunization, is the most difficult to identify and to reach. A decade ago, when the memory of paralytic poliomyelitis was fresh in the minds of parents, the task was easier. Beginning in 1962, community-wide immunization programs were mounted throughout the country, and by 1964, it is estimated that approximately 85 per cent of children had received adequate protection against poliomyelitis. Since then, with the remarkable drop in the annual number of cases of the disease, a certain amount of complacency has replaced concern, the result being a steady fall in the immunization rate. Only intensified efforts directed particularly at reaching young children in inner-city and other poverty areas can reverse the trend. Education, persistence and provision of funds to health departments are required to achieve this end. It would be sad indeed if a serious outbreak of poliomyelitis were necessary to provide the impetus to correct the lagging immunity of American children.

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REFERENCES

1. Lamb GA, Feldman HA: Rubella vaccine responses and other viral antibodies in Syracuse children. Am J Dis Child 122:117-121, 1971
2. Melnick JL, Burkhardt M, Taber LH, et al: Developing gap in immunity to poliomyelitis in an urban area. JAMA 209:1181-1185, 1969
3. Center for Disease Control. Neurotropic Diseases Surveillance: Annual poliomyelitis summary – 1970. Atlanta, Georgia, The Center, September 30, 1971
4. *Idem:* United States Immunization Survey – 1970. Atlanta, Georgia, The Center, April, 1971

BIOAVAILABILITY OF DIGOXIN

A VARIABLE or poor response to a therapeutic agent may not have its origin in the patient; it may be due to a formulation defect in the drug product administered. The most commonly recognized formulation defect in a dosage form such as a tablet is a deficiency or excess of the active ingredient. The fact that difficulties of this type were occurring with certain lots of digoxin and digitoxin tablets on the market was discovered by the Food and Drug Administration through a systematic testing program inaugurated in April, 1970, by the Bureau of Drugs with the testing done at the National Center for Drug Analysis (NCDA). This program also revealed that the analysis of a number of individual tablets from the same lot was necessary to appraise the problem properly, since lots were found in which a pooled sample of 10 tablets met USP standards of potency in spite of wide variation in digoxin content among individual tablets. In October, 1970, the FDA instituted, through the co-ordinated efforts of the Office of Compliance and the Office of Pharmaceutical Research and Testing in the Bureau of Drugs, a voluntary certification program for digoxin and digitoxin to ensure uniform quality among the drug products on the market. The systematic testing and voluntary certification programs have resulted in 79 recall actions involving digoxin tablets and 15 involving digitoxin from April to November, 1970. The programs on digoxin and digitoxin request voluntary embargo on the part of the manufacturer on all batches until assay results are received from NCDA. Firms that do not comply with these voluntary programs are covered through FDA compliance activities, which include legal sanctions or recalls or both.

Lindenbaum et al.[1] present in a recent issue of this journal an example of another way in which a formulation may fail as an effective drug-delivery system: the drug in the formulation may be incompletely absorbed in relation to its absorption from another, similar formulation, even though both meet USP standards of potency, disintegration time and dissolution rate. In the jargon of the day, the poorer performing formulation is said to lack comparable bioavailability. Lindenbaum et al.[1] measured in the same four normal subjects the serum levels of digoxin produced by tablets from four different lots of digoxin, including two produced by the same manufacturer. Of two lots from the same manufacturer, tablets from one gave peak levels only 1/5 as high as the other, and as little as 1/7 as high as the highest peak obtained from the other lots. The importance of these values becomes apparent when one considers that in one study[2] nontoxic patients with normal renal function receiving daily maintenance doses of digoxin had mean serum concentrations of 1.1 to 1.4 ng per milliliter, whereas similarly treated patients with cardiac arrhythmias attributed to digoxin toxicity had a mean serum level of 3.3 ng per milliliter, with little overlap between the values of the two groups. The toxic and nontoxic levels were separated by a factor of about three. Patient needs cannot be served by digoxin products that generate serum levels of drug differing by a factor of 5 to 7 as observed in the present study.

Before these findings are misinterpreted as suggesting a widespread problem with the bioavailability of digoxin products, a note of caution should be added. The lot of digoxin tablets from Firm B show-

ing the poorest performance in the study (formulation B_2) had been assayed at the FDA's National Center for Drug Analysis. Ten tablets selected at random from this lot assayed 76.2 to 158.2 per cent of declared potency by the standard USP method, with six of these 10 tablets being outside USP XVIII limits of 92 to 108 per cent. The product was out of compliance and subject to recall. The one lot of digoxin tablets from Firm C (formulation C) was not available for assay. Both these products were marketed in 1969 before the voluntary certification program. The low serum levels of digoxin produced by these drugs may have been due not only to poor bioavailability but also to low potency, and today such preparations would not reach the market.

On the other hand, the second lot of digoxin from Firm B (formulation B_1) and the lot from Firm A (formulation A) both met USP assay specifications, and both lots were marketed in late 1970 after going through the certification program. One may therefore legitimately attribute the ⅓ lower serum levels of digoxin obtained with the former to a reduced bioavailability of drug from this particular preparation.

These findings, as well as those reporting the bioavailability of certain other drugs, raise several questions of importance to physicians, to the pharmaceutical industry, and to us at the FDA: Is a difference in bioavailability between two formulations of the same drug an uncommon event, or does it occur frequently with certain types or classes of drugs? To what extent can two preparations differ in bioavailability and still be considered therapeutically equivalent? Would the systematic testing of important drugs for bioavailability substantially improve the quality of drugs in this country, or would it simply dissipate funds and clinical research facilities and increase the cost of drugs with little practical gain? The FDA does not presume to have final answers to these questions at present, since their resolution must await much more information than is currently available. We encourage additional studies of the type reported by Lindenbaum et al., and seek the co-operation of clinical investigators and practitioners in bringing such information to the attention of the Food and Drug Administration.

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REFERENCES

1. Lindenbaum J, Mellow MH, Blackstone MO, et al: Variation in biologic availability of digoxin from four preparations. N Engl J Med 285:1344-1347, 1971
2. Smith TW, Butler VP Jr, Haber E: Determination of the therapeutic and toxic serum digoxin concentrations by radioimmunoassay. N Engl J Med 281:1212-1216, 1969

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DEATHS

BLUMERFIELD — Israel Michael Blumerfield, M.D., of Boston, died on September 26. He was in his 78th year.

Dr. Blumerfield received his degree from Middlesex University School of Medicine, Waltham, in 1920. He was a member of the dermatologic staff at New England Medical Center and of the staffs of the Beth Israel Hospital, Boston City Hospital, Parker Hill Medical Center, Brooks Hospital and Lahey Clinic. He was a member of the American Medical Association.

Dr. Blumerfield is survived by his widow, a daughter, a brother, a sister and four grandchildren.

BRADLEY — John Francis Bradley, M.D., of Peabody, died on October 12. He was in his 78th year.

Dr. Bradley received his degree from Middlesex University School of Medicine, Waltham, in 1921. He was a member of the staffs of the J. B. Thomas Hospital in Peabody and Union Hospital in Lynn. He was a member of the American Medical Association.

Dr. Bradley is survived by his widow, two sons, two daughters, 14 grandchildren, a sister, nieces and nephews.

CHURCH — Charles N. Church, M.D., of Millbury, died on January 17. He was in his 78th year.

Dr. Church received his degree from the University of Vermont College of Medicine, Burlington, in 1918. He was a member of the American Medical Association and a 50-year member of the Massachusetts Medical Society.

Dr. Church is survived by a son.

CHUTE — James Lemuel Chute, M.D., of Osterville, died on October 1. He was in his 75th year.

Dr. Chute received his degree from Tufts College Medical School in 1923. He was a member of the American Medical Association and the American College of Surgeons.

Dr. Chute is survived by his widow, one daughter, two sons and four grandchildren.

DOUGLAS — Archibald John Douglas, M.D., of Westfield, died on August 30. He was in his 92d year.

Dr. Douglas received his degree from Albany Medical School in 1903. He was formerly a member of the medical staff at Noble Hospital serving as president, chief of surgery, and chief of staff. He also served as consultant physician for