Letters

Jargon and "The Juice"

I am writing regarding the editorial "Basic research: The need for lateral movement" (13 July, p. 149).

Once I got through the football jargon in the opening paragraph and understood the editorial's subject matter, I wholeheartedly agreed with its views. But since scientists are criticized so frequently for writing in laboratory jargon, unintelligible to the lay public, why are they expected to be familiar with the language of the locker room?

It's hard enough for a "university professor carrying out basic research" to keep up with his or her own jargon, without expecting knowledge about " 'The Juice,' who has taken his share of licks."

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Obstetrical Medication Study

There were a number of errors and a lack of clarity in the News and Comment article by Gina Bari Kolata (27 Apr., p. 391) covering the 19–20 March meeting of the Anesthetic and Life Support Drug Advisory Committee of the Food and Drug Administration (FDA). My affiliation is with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), not the National Institute of Mental Health. I made no announcement (nor promotion) "last fall" of findings from a study of obstetrical medication and infant development, of which Kolata should have been aware because she made several unsuccessful attempts to obtain informally from my office a preliminary draft of the report of this study. The earliest publicity was in two articles written by Kolata herself in *Science* (Research News, 17 Nov. 1978, p. 732) and in the Washington *Post* (19 November 1978). Sources cited were a University of Florida colloquium given by Yvonne Brackbill and testimony prepared by her for the subcommittee on health and scientific research of the U.S. Senate Committee on Human Resources.

The NINCDS Collaborative Perinatal Project (NCPP), source of the data under analysis in the obstetrical medication study, is incorrectly described as having been conducted in the "1950's." The obstetric phase of the NCPP was begun in 1959 and completed in 1966; follow-up of offspring to age 8 was completed in 1974.

John Bartko, a statistical consultant on the obstetrical medication study, also reviewed the manuscript by Brackbill and myself that reported on relationships between medication administered during labor and delivery and infant development in the first year of life. He indicated his approval of the scientific content by signing an NINCDS Manuscript Review and Clearance Form. This manuscript was not rejected for publication, as reported, but was returned to us for revision.

The quoted protests of Milton Alper that IQ scores are nowhere mentioned in the written report are puzzling. Before the meeting, he had received a copy of the report, which presented associations between obstetrical medication and indices of development through the period of infancy only. With regard to the methodological point raised of lack of a strict longitudinal approach in the analysis of the data, it should be noted that different aspects of development were assessed in the sample of infants at the three ages of primary interest (a pediatric examination at 4 months, a psychomotor examination at 8 months, and a pediatric-neurological examination at 12 months). For this reason, hypotheses related to change or stability over time are not readily formulated. However, efforts in this direction are being pursued as an additional analytic technique.

Emanuel Friedman correctly pointed out that the maternal hypertension variable developed by him for the NCPP (*1*) was not among the 13 complications of pregnancy for which women were excluded from the study sample. It has been determined that 186 of the women in the sample of 3416 were affected. Maternal hypertension has been included with other maternal and infant characteristics in multivariate analyses of examination items in the first year found to be associated with administration of obstetrical medication. In no instance was maternal hypertension significantly related to outcome.

Application of mid- or high forceps was among the labor and delivery complications for which women were excluded from the study sample. These cases were dropped after exclusions were made for incomplete obstetrical data, multiple births, pre- or postmaturity, pregnancy complications, and maternal age of under 16 or over 40 years. The number of women excluded for midforceps delivery was 606, and for high forceps delivery, one. Friedman's statement that midforceps deliveries could not have been excluded and so large a sample as 3416 white women retained is not supported by fact. In 1972, Niswander and Gordon (*2*) reported that 12.22 percent of the vaginal vertex deliveries among white women registering in the NCPP for the first time were accompanied by midforceps (head engaged but above the perineum) and 0.02 percent by high forceps (head not engaged). When these two groups are subtracted from the total sample of 16,446, 14,433 women remain. Similarly, in 1975, Broman, Nichols, and Kennedy (*3*) reported that 13.8 percent of the vaginal vertex deliveries among white, first-study registrants whose children were followed to age 4 (N = 10,927) were accompanied by midforceps, and that 0.03 percent were accompanied by high forceps. Obviously, even in this smaller white cohort, removing mid- and high forceps deliveries leaves many more than 3416 cases.

Finally, Kolata reports that the FDA "critics" support the joint recommendations of the American Academy of Pediatrics Committee on Drugs and the American College of Obstetricians and Gynecologists, which she paraphrases. These recommendations are quoted in full in the discussion section of the manuscript that was under review (*4*) at the FDA hearings.

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2. K. R. Niswander and M. Gordon, *The Women and Their Pregnancies* (Saunders, Philadelphia, 1972).
3. S. H. Broman, P. L. Nichols, W. A. Kennedy, *Preschool IQ: Prenatal and Early Developmental Correlates* (Erlbaum, Hillsdale, N.J., 1975).
4. Y. Brackbill and S. H. Broman, in preparation.

It is true that Broman did not announce her findings to the press. However, Brackbill did, speaking for herself and Broman. I first became aware of the findings of Brackbill and Broman when Brackbill dropped in at *Science* and left a copy of her Senate testimony.

Bartko stands by his statement that he disassociates himself from the manuscript by Brackbill and Broman. As for whether it was rejected, Brackbill and Broman received a letter from the Society for Research in Child Development, where they submitted their paper, saying "the manuscript as it presently stands is not acceptable for publication." I mentioned in my article that they are revising their paper prior to resubmission.

Finally, whether or not Broman and Brackbill quoted the joint recommendation of the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists appears to me to be beside the point. This recommendation is to avoid using drugs with adverse side effects, to use minimal effective doses of drugs, and to discuss the drugs with women before they go into labor.—GINA BARI KOLATA

The FDA's Anesthetic and Life Support Drug Advisory Committee met for the first time on 19–20 March. Its task is to decide whether data from some 40 studies showing adverse neurobehavioral effects of obstetrical drugs on infants and children are sufficiently compelling to warrant changes in prescribing information.

Kolata's report of the meeting contains many mistakes. It also fails to convey accurately the gist of the proceedings, which was as follows.

Although FDA procedures require proof of safety and efficacy before a new drug is cleared for clinical use, most drugs used for childbirth have not been approved for that purpose on any grounds; nor has any drug approval been based on tests that measure early neurobehavioral effects on infants or predict later central nervous system dysfunction (*1*).

Scientists' fears that neurobehavioral effects may result from even brief exposure to toxic substances are grounded on several lines of empirical evidence. One concerns the infant's structural and functional immaturity at birth. As Kolata has noted (Research News, 17 Nov. 1978, p. 732), "Important areas of the newborn's brain, particularly the hippocampus and the cerebellum, are not fully developed at birth and are particularly vulnerable to damage. Obstetrical medication crosses the placenta rapidly, easily reaches the fetus's brain because the blood-brain barrier is immature, and is only slowly cleared from the newborn's body because the baby's liver and kidneys are functioning immaturely at birth."

A second line of worrisome evidence relates to the wide variety of substances, including inhalant anesthetics, that have been shown to cause neuroanatomical changes (cell death, cell malformation, and aberrant cell migration) after short- or long-term exposure in young animals (*2*).

A third line of evidence consists of actual studies of neurobehavioral changes in human infants that were observed after administration of anesthetic and preanesthetic agents to their mothers during labor and delivery. There are at least 40 of these to date. None has shown that drugs enhance or improve behavioral functioning in infants (*3*). All have shown some degree of adverse behavioral effects, generally related to obstetrical drug dosage, in their otherwise clinically normal subjects. The effects are most frequently seen in habituation (*4–8*); auditory responses (*4–9*); temperament (*10*); electroencephalograms (*11*); feeding, sucking, and rooting (*7, 12–14*); heart rate (*7, 10*); language (*10*); mother-infant interaction (*13*); motor development (*4, 13*); scores on standardized pediatric-neurological-behavioral tests (*4–8, 10–13, 15–20*); state (alertness, sleep) (*5, 15, 17, 21*); visual responses (*8*); and cognitive development (*10*).

Most of the studies were cross-sectional and were carried out on infants under the age of 1 month; in a few, older infants were studied. Of these long-term studies, one is under particular scrutiny because it is more long-term than the others, is longitudinal in design, and includes a very large sample of subjects. This is the NINCDS Collaborative Perinatal Project (NCPP), a study of more than 53,000 babies born between 1959 and 1966 in 12 collaborating teaching hospitals across the United States and given a variety of pediatric/neurological and behavioral examinations at birth, 4 months, 8 months, 12 months, 4 years, and 7 years. Using subject selection criteria agreed upon in 1966 by a National Institutes of Health task force on obstetrical medication, Sarah Broman and I drew from the larger sample a cohort of 3400 full-term, singleton, white infants born to healthy mothers with low-risk pregnancies and uneventful, vertex position, vaginal deliveries. As in other studies of obstetrical medication effects, the logic underlying subject selection criteria was to eliminate disease states or abnormal conditions whose effects might otherwise be confounded with the effects of obstetrical medication.

Although statistical analyses of the NCPP data are not yet complete, both the preliminary univariate analysis and the first of two multivariate analyses show drug effects at all ages tested, with the strongest associations between deficient or abnormal behaviors and the perinatal use of inhalant anesthetics.

Four statisticians employed by the FDA reviewed the NCPP univariate analysis along with analyses in 30 of the 40 published studies. Statisticians Johnson, Pledger, and Dubey concluded that, while there was "little evidence" that obstetrical drugs have long-term effects on children, the findings of short-term studies, particularly in terms of the consistency of their results (*22*)

> . . . lend evidence that obstetrical medications (especially high dosages of barbiturates and epidural anesthetics) have a significant association with depressed neurobehavioral response in infants up to four or five days following birth.

Statistician D'Agostino concluded (*22*),

> The analyses do demonstrate statistical significance, and the investigators' interpretations may be correct. However, the investigators have not presented enough material in their reports, nor have they performed sufficient statistical analyses, to warrant at this time an unequivocal acceptance of their conclusions. Given the importance of the problem under investigation, it appears essential to have a more detailed presentation of the data and to perform a more elaborate and sensitive statistical analysis.

During the discussion concerning the merits of the 40 obstetrical drug studies, I reminded the committee that it is the responsibility of the FDA to provide proof of drug safety and efficacy for infants and children before the drugs are released for clinical use and that it is *not* the responsibility of individual research scientists to test those drugs for adverse effects. If the FDA discredits the present body of research as insufficiently definitive to answer questions of long-term safety, then it is the responsibility of drug manufacturers or the FDA to carry out whatever research is necessary to provide such definitive answers.

Although the committee did unanimously concede that obstetrical drugs produce short-term effects in infants, it did not agree to pass this information along to clinicians or to parents of the 3.5 million infants who are annually affected by the drugs. Committee members and guest speakers raised several issues concerning the rights of patient-consumers to receive drug information and the re-

sponsibilities of the FDA, drug manufacturers, and clinicians to provide the drug information.

One issue raised concerns the possible impact of information on consumers' peace of mind. Committee member Jacobi stated that, if effects are only short term, there is no need to put anything "scary" into the package insert. Committee member Sugioka disagreed, noting that informed parents are less alarmed than uninformed parents when adverse effects do appear.

I then noted that, when an approved drug is used for a nonapproved purpose, its status reverts to "investigational," that is, the drug is being used experimentally. For example, mepivacaine (Carbocaine) is a relatively new local anesthetic agent frequently used in obstetrics, but it is unapproved for that purpose. When it is used for anesthesia during childbirth, that birth literally becomes an experiment, and the mother and infant become experimental subjects. Under current Department of Health, Education, and Welfare guidelines for protection of the rights of human subjects, the physician-experimenter is required to disclose all information that bears upon the mother's giving informed consent for her own participation and proxy consent for her unborn child's participation (*23*). Thus, the mother is entitled to drug information both on moral and on legal grounds.

Committee member Matanoski raised the issue of fiduciary trust and consumer information. She pointed out that, in the absence of information, patients assume the drugs they receive are nonexperimental and risk-free. She drew the committee's attention to the fact that its motion disclaiming long-term effects does not mean they don't exist, but rather that current data on long-term effects are insufficient. She stressed the importance of adding such a statement to drug labels so that consumers will not assume that the absence of information means the drug is safe (*24*).

It was also pointed out that increasing demands by patient-consumers for drug information (*25*) and participation in decision-making (*26*) is reflected in recently passed and pending legislation and in recent judicial decisions. For example, the state of New York passed a law, effective 1 September 1978, requiring physicians and nurse-midwives to inform pregnant women of all drugs to be used during pregnancy and delivery and of their effects on mother and child. Currently pending New York State legislation specifies 13 separate points of information to be given pregnant women. Legislation is also pending before the U.S. Senate (S. 865) and House of Representatives (H.R. 3444) that ensures the right of individuals to obtain copies of their medical care facility records. The state of California is considering adoption of a regulation requiring that certain categories of over-the-counter drugs carry labels encouraging caution in use of the drug by pregnant and nursing women. In the state of New York, two recent Court of Appeals decisions (*27*) found physicians negligent in failing to advise, or advise accurately, the pregnant women who consulted them to obtain such information.

In connection with lawsuits, I reminded the committee that providing patients with information is the clinician's best defense against litigation, since the extent to which the patient herself accepts responsibility in deciding to consume drugs is the extent to which the physician is relieved of that responsibility and is therefore less vulnerable to suits for malpractice, negligence in providing information, and failure to obtain informed consent for experimentation.

Despite its agreement that short-term drug effects have been demonstrated in infants, the committee was not persuaded by the arguments in favor of providing consumers with this information. Chairperson Burnell R. Brown, Jr., created a subcommittee to study the matter.

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References and Notes

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3. Notwithstanding the implication of R. E. Myers and S. E. Myers [*Am. J. Obstet. Gynecol.* **133**, 83 (1979)], based on histological and post-strangulation survival time in wild rhesus monkeys, that barbiturates are good for human mothers and babies (see also R. E. Kron and Y. Brackbill, unpublished manuscript), and the assertion of D. H. Ralston and S. M. Shnider [*Anesthesiology* **48**, 53 (1978)], based on Canadian data as yet unanalyzed epidemiologically or statistically [Ontario Perinatal Mortality Study Committee, *Second Report of the Perinatal Mortality Study in Ten University Teaching Hospitals* (Department of Health, Toronto, 1967)] that obstetrical anesthesia reduces maternal mortality.
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24. Current examples of approved drugs used for unapproved purposes during labor are adrenergic beta receptor agonists [for example, isoxsuprine HCl (Vasodilan)] when administered to inhibit labor and adrenal cortex steroids [for example, dexamethasone (Decadron)] when administered to accelerate surfacant-producing systems in the lungs of preterm fetuses. [For a more detailed discussion, see Y. Brackbill, in *Pre-term and Post-term Births: Relevance to Optimal Psychological Development*, S. L. Friedman and M. Sigman, Eds. (Academic Press, New York, in press).]
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27. Becker *vs.* Schwartz, **46** *N.Y. 2nd Ser.*, 401 (1979); Park *vs.* Chessin, *ibid.*

Erratum: In the article "Nuclear risks: Still uncertain" (News and Comment, 18 May, p. 714), in the fourth paragraph, the sentence, "If one assumes that 40 gigawatts are produced a year, as was the case in 1975 . . ., then the nuclear industry is causing *two* cancer deaths a year," should have read, "*20* cancer deaths a year."