evidence whatever of an aggregate decrease in health care costs for the elderly as a result of research. The evidence, I believe, points in exactly the opposite direction.

The elderly have a powerful moral claim on health care, but not an unlimited claim. A primary goal of the health care system should be to help everyone have the chance to avoid a premature death and become an elderly person. That is a reasonable good. By contrast, an unlimited effort to extend the life of the elderly, regardless of cost and regardless of the burdens it can impose on the young, is not.

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1 de Lissovoy G. Medicare and heart transplants: will lightning strike twice? Health Aff (Millwood) 1988; 7(4):61-72.
2. Health Care Financing Administration. Special report: findings from the National Kidney Dialysis and Kidney Transplantation Study. Baltimore: Department of Health and Human Services, 1987.
3. Latta V, Keene RE. Leading inpatient surgical procedures for aged Medicare beneficiaries. Health Care Financ Rev 1989; 11:99-110.
4. Hosking MP, Warner MA, Lobdell CM, Offord KP, Melton LJ III. Outcomes of surgery in patients 90 years of age and older. JAMA 1989; 261:1909-15.
5. Office of Technology Assessment Task Force. Life-sustaining technologies and the elderly. Philadelphia: Science Information Resource Center, 1988: 400-18.

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The above letters were referred to the authors of the article and editorial in question, who offer the following replies:

*To the Editor:* In his book *Setting Limits*,[1] Daniel Callahan states that "severely ill, mentally alert patients who have lived out a full life span should receive care that is limited, as a rule, to general nursing care." He explicitly indicates that not only intensive care and advanced life support, but also general medical care such as antibiotic treatment, should be withheld from such patients. In the first point in his letter, Callahan appears to recommend only the limitation of "expensive high-technology medical care," whereas in his second point he returns to the broader prohibition in his book by recommending the limitation of "life-extending" care for the elderly. The use of penicillin is potentially life-extending for an older patient. I disagree with Callahan's contention that prohibiting the treatment of elderly patients with antibiotics or other general medical care is not a change in present policy.

As Callahan himself discusses in his book, the problem for those who wish to reduce health care costs by limiting care for the aged is that high expenditures for the elderly are due largely to the cost of regular medical care for chronic and severe acute illnesses. Only a small proportion of the high cost of medical care in the last year of elderly patients' lives, to which Dr. Hadorn refers, is for high-cost intensive care.[2,3] Contrary to Dr. Hadorn's statement, not only Callahan but also other thoughtful analysts have suggested limiting routine care for the elderly. Indeed, they must eliminate more than intensive care if they wish to reduce national health costs substantially by rationing health care to the elderly.

I do not share Dr. Callahan's pessimism about the economic effect of medical research. I see no reason why the major chronic degenerative diseases, such as osteoarthritis, osteoporosis, Parkinson's disease, and Alzheimer's disease, cannot be controlled or prevented. Decreases in dementia due to Alzheimer's and in hip fractures caused by osteoporosis will reduce national health care expenditures more than the ethically distasteful alternative of withholding beneficial care from the elderly. Beyond economics, success in such research will relieve suffering and improve the quality of life, goals on which we can all agree, however we feel about the "risk" that life may be extended as well.

In his editorial in the issue in which my article appeared, Dr. Relman stated that I "take no stand on rationing in general." Although my article focused on age as a criterion, I did state that "I am not persuaded that explicit rationing is necessary in the United States at this time." Dr. Relman himself, in two more recent editorials,[4,5] has cogently indicated why we should rationalize the U.S. health care system before we consider rationing beneficial care to anyone.

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1. Callahan D. Setting limits: medical goals in an aging society. New York: Simon and Schuster, 1987.
2. Lubitz J, Prihoda R. The use and costs of Medicare services in the last 2 years of life. Health Care Financ Rev 1984; 5(3):117-31.
3 Scitovsky AA. "The high cost of dying": what do the data show? Milbank Mem Fund Q Health Soc 1984; 62:591-608.
4. Relman AS. The trouble with rationing. N Engl J Med 1990; 323:911-3.
5. *Idem*. Reforming the health care system. N Engl J Med 1990; 323:991-2.

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*Editor's reply:* As I have argued in two recent editorials,[1,2] I do not believe that rationing of beneficial services will be necessary in the United States if we develop a more rational and efficient health care system. Without substantial reform of our present system, rationing would be difficult to implement and, aside from its ethical problems, would probably not save any money in the aggregate.

Dr. Stoll's conviction that rationing is inevitable reflects the view from the United Kingdom, where there are centralized budgetary controls that limit total expenditures on health care to barely more than half the U.S. level. But here in the United States we have an open-ended health care system, based largely on fee-for-service and private practice; even if patients and physicians were prepared to accept it, I do not see how rationing could work very well under these conditions.

Dr. Harvey is quite right about the unequal effects of the proposed Oregon plan to ration health care to the poor. In my view, the proposal's chief virtue lies in the raising of public consciousness. Proponents have yet to come up with an acceptable and workable plan, which says something about the difficulties of explicitly rationing services in this country at this time.

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1. Relman AS. The trouble with rationing. N Engl J Med 1990; 323:911-3
2. *Idem*. Reforming the health care system. N Engl J Med 1990; 323:991-2.

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## ASBESTOS-RELATED DISEASES

*To the Editor:* Aware that more than 100,000 Americans will die of asbestos-related disease,[1,2] the public is understandably suspicious when we conclude that an occupational or environmental exposure is not the cause of a particular ailment. In assessing the importance of potentially hazardous exposures, full and painstaking disclosure is necessary. It was with much disappointment, then, that we read the *Journal* review article on asbestos-related diseases by Mossman and Gee.[3]

Mossman and Gee have emasculated much of the evidence that is at odds with their own position. In fact, the authors so emphatically articulate a legal position on nearly every issue that one questions just what purpose their article is to serve; contrary to their stated purpose, we find little effort "to elucidate the mechanisms of asbestos-related disease."

*Journal* readers seeking to balance their perspective are encouraged to look elsewhere for information on the relative pathogenicity of chrysotile asbestos[4,5] (and volume 14 of the *American Journal of Industrial Medicine*); the genetic and epigenetic changes involved in asbestos-induced lung cancer[6]; the linkage between exposure to asbestos and cancer of the gastrointestinal tract,[7] larynx,[8,9] and kidney[10-12]; pathological criteria[13,14] and radiographic sensitivity[15] in diagnosing asbestosis; and the likelihood that smoking habits are confounding any of the identified relations between asbestos and disease.[16,17]

Mossman and Gee, in discussing the radiographic progression of patients with asbestosis, refer only to an abstract[18] that reports on persons exposed to asbestos who did not necessarily have asbestosis. This is peculiar given the availability of published studies address-

ing this issue.[19-21] In a similar vein, the authors support a thesis with the findings of an epidemiologic study,[22] and then go on to report that the period of follow-up in the study was too short to demonstrate anything. Of importance to clinicians is the error the authors perpetuate in claiming that benign asbestos-related pleural effusions usually occur in the first 20 years after the initial exposure to asbestos. Hillerdal,[23] in the only population-based study of this condition, reports a mean latency of 30 years and the frequent finding of bloody pleural fluid.

In a field that is rife with scientific controversy, medicolegal combat, and intense public concern, a review article should identify controversial issues, objectively describe opposing positions, and cite relevant evidence. The article by Mossman and Gee fails to meet that standard. We believe that readers of the *Journal* should be aware of the large community of physicians and scientists who strongly disagree with many of the authors' conclusions. This letter, unanimously endorsed by all member clinics of the Association of Occupational and Environmental Clinics, evidences the depth of that sentiment. (The Association of Occupational and Environmental Clinics is an organization of 29 occupational health clinics based at or formally affiliated with schools of medicine or public health. The programs embody a deeply held commitment to preventive medicine and encompass a full range of clinical services, as well as research, physician training, and community education.)

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1. Nicholson WJ, Perkel G, Selikoff IJ. Occupational exposure to asbestos: population at risk and projected mortality — 1980-2030. Am J Ind Med 1982; 3:259-311.
2. Walker AM, Loughlin JE, Friedlander ER, Rothman KJ, Dreyer NA. Projections of asbestos-related disease 1980-2009. J Occup Med 1983; 25:409-25.
3. Mossman BT, Gee JBL. Asbestos-related diseases. N Engl J Med 1989; 320:1721-30.
4. Churg A, Green FHY, eds. Pathology of occupational lung disease. New York: Igaku-Shoin, 1988:223-4, 253, 279-82.
5. Cullen MR. Controversies in asbestos-related lung cancer. Occup Med 1987; 2:259-72.
6. Barrett JC, ed. Mechanisms of environmental carcinogenesis. Vol. 1. Role of genetic and epigenetic changes. Boca Raton, Fla.: CRC Press, 1987:
7. Frumkin H, Berlin J. Asbestos exposure and gastrointestinal malignancy: review and meta-analysis. Am J Ind Med 1988; 14:79-95 [Erratum, Am J Ind Med 1988; 14:493.]
8. Doll R, Peto J. Other asbestos-related neoplasms. In: Antman K, Aisner J, eds. Asbestos-related malignancy. Orlando, Fla.: Grune & Stratton, 1987:81-96.
9. Smith AH, Handley MA, Wood R. Epidemiological evidence indicates asbestos causes laryngeal cancer. J Occup Med 1990; 32:499-507.
10. Smith AH, Shearn VI, Wood R. Asbestos and kidney cancer: the evidence supports a causal association. Am J Ind Med 1989; 16:159-66.
11. Maclure M, Poole C. Asbestos and kidney cancer. Am J Ind Med 1990; 17:647-8
12. Enterline PE, Henderson V. Asbestos and kidney cancer. Am J Ind Med 1990; 17:645-6.
13. Warnock ML, Wolery G. Asbestos bodies or fibers and the diagnosis of asbestosis. Environ Res 1987; 44:29-44.
14. Roggli VL, Pratt PC. Number of asbestos bodies on iron-stained tissue sections in relation to asbestos body counts in lung tissue digests. Hum Pathol 1983; 14:355-61.
15. Kipen HM, Lilis R, Suzuki Y, Valciukas JA, Selikoff IJ. Pulmonary fibrosis in asbestos insulation workers with lung cancer: a radiological and histopathological evaluation. Br J Ind Med 1987; 44:96-100.
16. Axelson O. Confounding from smoking in occupational epidemiology. Br J Ind Med 1989; 46:505-7.
17. Blair A, Steenland K, eds. Smoking and occupation in epidemiologic studies. Am J Ind Med 1988; 13:3-190.
18. Gaensler EA, Jederlinic PJ, McLoud TC. Progression of asbestosis. Chest 1987; 91:305 abstract.
19. Suoranta H, Huuskonen MS, Zitting A, Juntunen J. Radiographic progression of asbestosis. Am J Ind Med 1982; 3:67-74.
20. Berry G. Mortality of workers certified by pneumoconiosis medical panels as having asbestosis. Br J Ind Med 1981; 38:130-7.
21. Cookson W, De Klerk N, Musk AW, Glancy JJ, Armstrong B, Hobbs M. The natural history of asbestosis in former crocidolite workers of Wittenoom Gorge. Am Rev Respir Dis 1986; 133:994-8.
22. Hodgson JT, Jones RD. Mortality of asbestos workers in England and Wales 1971-81. Br J Ind Med 1986; 43:158-64.
23. Hillerdal G. Non-malignant asbestos pleural disease. Thorax 1981; 36:669-75.

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The above letter was referred to the authors of the article in question, who offer the following reply:

*To the Editor:* Kern and associates criticize our account of laryngeal cancer even though we cited opposing opinions, including one mentioned in their letter. Worse still, while citing one new paper supporting their views on asbestos and laryngeal cancer,[1] they ignore two other recent contrary opinions[2,3] and the rejection of this association by the British Advisory Council.[4] Furthermore, the paper they cite[1] uses enhanced standard mortality ratios for lung cancer as a surrogate for measures of exposure to asbestos — a questionable approach. Are we biased when we cite the position of the American Thoracic Society on benign asbestos-related disorders together with "a response thereto"? In criticizing our account of the potential progression of asbestosis, they ignore an entire paragraph in our review describing the classic clinical course. They also criticize us on the issue of radiologic sensitivity in diagnosing asbestosis, citing one of the signatories' papers.[5] We quoted this paper. We also discussed the issue in a paragraph indicating that pathologic processes can precede radiologic manifestations. Surely the issue in 1991 is the role of high-resolution CT scanning in the diagnosis of lung fibrosis.

They also criticize our comments on the confounding effects of smoking on standard mortality ratios for lung and laryngeal cancer, citing Axelson,[6] who in fact estimates confounding errors from smoking in standard mortality ratios of up to 1.6 — close to our earlier suggested value of about 2.0 in a paper coauthored by an ex-president of the Association of Occupational and Environmental Clinics.[7] An Austrian study of cement workers[8] also indicates that "deaths from lung cancer in asbestos workers were higher (SMR [standard mortality ratio], 1.7) but after adjustment for age and sex specific smoking habits, this was not significant (SMR, 1.04)." They use outdated risk estimates of deplorable mortality among asbestos workers and ignore the seven more recent estimates of risk discussed

in our review. However, the most serious omission is their failure to cite three recent international scientific symposia, all of which report mesothelioma to be due largely to amphiboles rather than chrysotile.[9-11] As recently as September 1990, an editorial espoused the same views.[12] Further accounts of the importance of amphiboles can be found in studies of occupational and paraoccupational cases of mesothelioma.[13] This view was also espoused by Dr. Churg, whose textbook they cite.[14]

Before publication of our article, some sections on the mechanisms of asbestos-related disease were deleted because of space limitations. We therefore refer readers to our recent article[15] and a book[16] on current research developments in this field.

It is unfortunate that labor unions and the plaintiff bar so often depend on the advice of members of the Association of Occupational and Environmental Clinics, which we believe is frequently neither correct nor contemporary. Society deserves better.

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1. Smith AH, Handley MA, Wood R. Epidemiological evidence indicates asbestos causes laryngeal cancer. J Occup Med 1990; 32:499-507.
2. Edelman DA. Laryngeal cancer and occupational exposure to asbestos. Int Arch Occup Environ Health 1989; 61:223-7.
3. Liddell FDK. Laryngeal cancer and asbestos. Br J Ind Med 1990; 47:289-91.
4. Industrial Injuries Advisory Council. Report on cancer of the larynx. London: Her Majesty's Stationery Office, 1989.
5. Kipen HM, Lilis R, Suzuki Y, Valciukas JA, Selikoff IJ. Pulmonary fibrosis in asbestos insulation workers with lung cancer: a radiological and histopathological evaluation. Br J Ind Med 1987; 44:96-100.
6. Axelson O. Confounding from smoking in occupational epidemiology. Br J Ind Med 1989; 46:505-7.
7. Welch L, Hertz J, Cullen MR, Gee JBL. Current pulmonology. In: Simmons DA, ed. Occupational lung disease. Chicago: Year Book Medical, 1985:155.
8. Neuberger M, Kundi M. Individual asbestos exposure: smoking and mortality — a cohort study in the asbestos cement industry. Br J Ind Med 1990; 47:615-20.
9. Doll R. Mineral fibres in the nonoccupational environment: concluding remarks. In: Bignon J, Peto J, Saracci R, eds. Non-occupational exposure to mineral fibres. Lyon, France: International Agency for Research on Cancer, 1989. (IARC scientific publications no. 90.)
10. Spengler JD, Ozkaynak H, McCarthy JF, Lee H. Summary of symposium on health aspects of exposure to asbestos in buildings. Cambridge, Mass.: Energy and Environmental Policy Center, Harvard University, 1989.
11. World Health Organization report on occupational exposure limit for asbestos, Oxford, United Kingdom, April 10–11, 1989. Geneva: World Health Organization, 1989.
12. Gibbs AR. Role of asbestos and other fibres in the development of diffuse malignant mesothelioma. Thorax 1990; 45:649-54.
13. Gibbs AR, Griffiths DM, Pooley FC, Jones JSP. Comparison of fibre types and size distributions in lung tissues of paraoccupational and occupational cases of malignant mesothelioma. Br J Occup Med 1990; 4:621-6.
14. Churg A, Green FHY, eds. Pathology of occupational lung disease. Tokyo: Igaku-Shoin, 1988.
15. Mossman BT, Bignon J, Corn M, Seaton A, Gee JBL. Asbestos: scientific developments and implications for public policy. Science 1990; 247:294-301.
16. Mossman BT, Begin RO, eds. Effects of mineral dusts on cells. Vol. 30 of NATO ASI series H: cell biology. Berlin, Germany: Springer-Verlag, 1989.

## LACK OF EFFICACY OF HYDERGINE IN ALZHEIMER'S DISEASE

*To the Editor:* Thompson et al. (Aug. 16 issue)[1] suggest that Hydergine (Sandoz brand of ergoloid mesylates) is ineffective in treating Alzheimer's disease and may in fact "cause cognitive dysfunction, perhaps through a direct toxic effect or by accelerating the progression of Alzheimer's disease." Such speculation seems unsupported by the data presented and may cause unwarranted concern among patients, their families, and their physicians.

Hydergine has been studied in dozens of clinical trials during the past 20 years,[2-7] and although evidence of efficacy is equivocal, no suggestion of adverse cognitive effects has emerged. The speculation about such effects by Thompson et al. is not supported by their findings. The authors report that the patients treated with Hydergine for 24 weeks had greater deterioration on a standard test of psychomotor speed, the Wechsler Adult Intelligence Scale (WAIS) Digit Symbol Substitution Task, than did the patients given placebo. One must question whether the test was properly administered. The mean base-line scores for both groups would place the study subjects high among normal subjects of the same age, suggesting the test was improperly administered or has little relevance in Alzheimer's disease. Beyond that, the scores of the drug-treated group actually improved between weeks 12 and 24 of the study, making it hard to understand how Hydergine could have toxic effects or speed the deterioration due to Alzheimer's disease. The results of the only test of cognitive function, the Wechsler Memory Scale, showed no change with Hydergine treatment.

Analysis of the data is open to question. In view of the base-line difference between the drug and placebo groups on the WAIS Digit Symbol Substitution Task and the different results reported for this test and for the Geriatric Evaluation by Relatives Rating Instrument at 12 and 24 weeks, the appropriate analysis of treatment effects would seem to be a repeated-measures analysis of covariance, with base-line performance entered as a covariate.

The most disturbing aspect of this paper is that a study of few patients for a short time with questionably analyzed data and mysterious base-line scores on the only cognitive test to show a change resulted in headlines in the popular press and unsupported speculation about the toxic effects of a widely prescribed drug. If Hydergine is useless or toxic, we need to know about it, but this study has not answered those questions.

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1. Thompson TL II, Filley CM, Mitchell WD, Culig KM, LoVerde M, Byyny RL. Lack of efficacy of Hydergine in patients with Alzheimer's disease. N Engl J Med 1990; 323:445-8.
2. Rouy JM, Douillon AM, Compan AM, Wolmark Y Ergoloid mesylates ('Hydergine') in the treatment of mental deterioration in the elderly: a 6-month double-blind, placebo-controlled trial. Curr Med Res Opin 1989; 11:380-9.
3. Thienhaus OJ, Wheeler BG, Simon S, Zelman FP, Hartford JT. A controlled double-blind study of high-dose dihydroergotoxine mesylate (Hydergine) in mild dementia. J Am Geriatr Soc 1987; 35:219-23.
4. Chierichetti S, Cucinotta D, Santini V. Implications of long-term study of Hydergine in elderly patients with chronic senile cerebral insufficiency. Biomed Issues 1985; 1:377-93.
5. Lazzari R, Franzese A, Chierichetti S, et al. Multicenter double-blind placebo-controlled long-term clinical trial of Hydergine in chronic senile cerebral insufficiency: an interim report. Ageing 1983; 23:347.
6. Loew DM, Weil C. Hydergine in senile mental impairment. Gerontology 1982; 28:54-74.
7. McDonald RJ. Hydergine: a review of 26 clinical studies. Pharmakopsychiatr Neuropsychopharmakol 1979; 12:407-22.

The above letter was referred to the authors of the article in question, who offer the following reply:

*To the Editor:* We welcome the opportunity to respond to Dr. Posner and Ms. Landsberg. First, the writers take issue with the speculation that Hydergine may have a detrimental effect in Alzheimer's disease. They base their criticism on the fact that the base-line scores on the WAIS Digit Symbol Substitution Task were quite high for patients with Alzheimer's disease, and that the treated group had a lower mean score at 12 than at 24 weeks. The scores were indeed high, and in reviewing our methods, we have found that we inadvertently allowed the patients 3 minutes to complete the task instead of the standard 90 seconds. Although this variation does preclude comparison with other studies using the WAIS Digit Symbol Substitution Task, the internal validity of our study is fully

intact, and the detrimental effect of the drug is still evident. With regard to the lower mean score at 12 than at 24 weeks, this difference (−9.96 vs. −8.85) was not significant. The data certainly support our speculation about a possible harmful effect; unexpected results are often critically important in science, and we would be remiss in ignoring them. Readers will note that we drew no conclusion regarding this issue.

Next, on the question of whether a repeated-measures analysis of variance would have been a more appropriate statistical test, we find no compelling reason to agree. We think that the test we used — a one-way analysis of covariance — is appropriate and simple and that the more complicated repeated-measures analysis is unnecessary.

Finally, why the dissatisfaction with the appearance of reports of our study in the popular media? Our study was not, as compared with most earlier studies of Hydergine, a small one with a "few patients," nor was it conducted "for a short time." We appreciate the careful detection of what may have been confusing the Digit Symbol Substitution Task base-line scores, but still find the more important change in scores valid. The central conclusion, that there was no hint of a beneficial effect of Hydergine in these patients with Alzheimer's disease, remains unchallenged. Information of this sort is understandably sought by a nation increasingly preoccupied with the problems of Alzheimer's disease and other dementias. We did not solicit media attention, but when approached, we thought it was appropriate to describe our findings in a reasonable manner. It is our belief that we did so.

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## TRANSPLACENTAL PASSAGE OF INSULIN

*To the Editor:* Menon et al. (Aug. 2 issue)[1] make the interesting observation that animal insulin, mainly in the form of insulin-antibody complexes, can be detected in the cord serum of some infants born to mothers with insulin-dependent diabetes mellitus treated with animal insulin. The authors conclude that the higher rate of macrosomia in infants of such mothers is partly due to the stimulatory effect of the transplacentally transferred insulin.[1] We disagree with this conclusion.

If the animal insulin transferred from the mother to the fetus contributed to fetal macrosomia, one would expect a lower rate of macrosomia in the 17 infants of the series studied by Menon et al. in whom no animal insulin could be detected in the cord serum. In this group, however, there was an even higher rate of macrosomia (in 9 of 17 vs. 12 of 28 infants). We do not disagree that transferred animal insulin could be a growth factor in the fetus. Its effect might be balanced, however, through the inhibition of insulin secretion in the fetus, which supposedly would occur if fetal blood glucose levels were lowered by transferred insulin.

What could cause the significant correlation between transferred animal insulin and the macrosomia rate? Potentially, transferred maternal antibodies could neutralize fetal insulin, causing fetal hyperglycemia and thus beta-cell hyperplasia. The results of measurements of C peptide in cord serum do not support this possibility, however.[2]

The macrosomia rate of 47 percent in the population studied by the authors is higher than the rate of 10 to 25 percent in recently published studies and in our own population with insulin-dependent diabetes mellitus[3] and unpublished data). One could hypothesize that the higher rate of macrosomia in the patients of Menon et al. was due to somewhat poorer glycemic control in some patients treated in the early 1980s, when, for example, blood glucose monitoring at home was not widespread. Poor glycemic control might then coincide with higher doses of animal insulin, because the use of highly immunogenic insulins was more common. It would be interesting if the authors could stratify their patients according to the year in which they were pregnant.

Their method of assessing glycemic control — i.e., measurement of glycosylated hemoglobin with the minicolumn assay — may not be well suited to detecting small differences in glycemia within the nearly normoglycemic range.[4] Thus, although the authors found no difference in glycemic control as determined by the percentage of glycosylated hemoglobin, there could have been higher blood glucose levels in the mothers of the infants with macrosomia.

We agree with the authors that immunogenic insulins should not be used in pregnant women. The influence of insulin antibodies on insulin pharmacokinetics and their possible role in prolonging fetal hypoglycemia are reasons enough not to use them.[5] The use of pure insulins will not reduce rates of macrosomia in diabetic women, however, unless metabolic control as close as possible to that of pregnant nondiabetic women is maintained throughout pregnancy.[3]

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1. Menon RK, Cohen RM, Sperling MA, Cutfield WS, Mimouni F, Khoury JC. Transplacental passage of insulin in pregnant women with insulin-dependent diabetes mellitus: its role in fetal macrosomia. N Engl J Med 1990; 323:309-15.
2. Mylvaganam R, Stowers JM, Steel JM, Wallace J, MacHendry JC, Wright AD. Insulin immunogenicity in pregnancy: maternal and fetal studies. Diabetologia 1983; 24:19-25.
3. Gabbe SG, Quilligan EJ. General obstetric management of the diabetic pregnancy. Clin Obstet Gynecol 1981; 24:91-105.
4. Kaplan LA, Cline D, Gartside P, Burstein S, Sperling M, Stein EA. Hemoglobin A1 in hemolysates from healthy and insulin-dependent diabetic children, as determined with a temperature-controlled mini-column assay. Clin Chem 1982; 28:13-8.
5. Knip M, Lautala P, Leppäluoto J, Akerblom HK, Kouvalainen K. Relation of entroinsular hormones at birth to macrosomia and neonatal hypoglycemia in infants of diabetic mothers. J Pediatr 1983; 103:603-11.

*To the Editor:* In their report on exogenous insulin found in the cord serum of neonates born to mothers with insulin-dependent diabetes mellitus, Menon et al. do not discuss one very interesting finding. In the infants without exogenous insulin in cord serum, the mean level of endogenous insulin was only 16 percent of that in the infants with exogenous insulin in cord serum. Furthermore, the level of endogenous insulin in the infants without exogenous insulin was only 39 percent of that in the subgroup of infants without macrosomia who had detectable exogenous insulin. Since birth weight correlated with levels of endogenous insulin in all the infants, it is possible that the remarkable increase in endogenous insulin levels contributed to the promotion of growth in addition to the exogenous insulin. Indeed, the mean excess of exogenous insulin in cord serum in the group with macrosomia, as compared with the group without macrosomia, was only 711 pmol per liter (1113 − 402), whereas the corresponding excess of endogenous insulin was 1818 pmol per liter (2726 − 908).

We conjecture that the increase in the level of endogenous fetal insulin associated with maternal anti-insulin antibody, more than transplacentally transferred exogenous insulin, underlies the fetal macrosomia.

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