Drug Therapy for Patients With Type 2 Diabetes

To the Editor: In his Scientific Review article about treatment of type 2 diabetes, Dr Inzucchi[1] advocates achieving glycemic control by using any available antihyperglycemic therapy. He bases this recommendation on decreased rates of microvascular complications observed in the Diabetes Control and Complications Trial (DCCT)[2] and the United Kingdom Prospective Diabetes Study (UKPDS).[3]

An ancillary study of the DCCT, however, showed that intensive drug treatment of patients with type 1 diabetes resulted in greater weight gain than conventional treatment.[4] With intensive treatment, subjects in the highest quartile of weight gain had the highest body mass index, blood pressure, and levels of triglycerides, total cholesterol, and low-density lipoprotein cholesterol. In addition, this group had a higher waist-to-hip ratio, a higher percentage of their cholesterol as very low-density lipoprotein and dense low-density lipoprotein fractions, and lower high-density lipoprotein cholesterol compared with those in the first quartile.

These findings suggest that changes in lipid levels and blood pressure that occur with excessive weight gain during intensive therapy may increase the risk of coronary artery disease in patients who have type 1 diabetes, who are not usually considered at risk for macrovascular complications. The majority of deaths in type 2 diabetes are due to macrovascular complications.[5] Although there was significant weight gain in the intensive therapy group in the UKPDS,[3] a follow-up study to assess the cardiac risk profile of individuals who gained weight was not done. It is imperative to know whether weight gain associated with antihyperglycemic therapy contributes to increased macrovascular complications and death before advocating glycemic control as the primary objective of therapy in patients with type 2 diabetes.

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To the Editor: I have several concerns about Dr Inzucchi's review[1] of oral antihyperglycemic therapy. First, he described the effects of various agents only in terms of comparison with placebo rather than with baseline values. This way of presenting the data can be misleading. In diabetes clinical trials, glycemic control frequently deteriorates in the placebo group, which amplifies the efficacy of active therapy.

It is equally important to consider the comparison with baseline levels in head-to-head trials. For instance, in one study mentioned in Table 2, mean glycohemoglobin levels increased by 0.58% in the repaglinide group and by 0.45% in the glyburide group after 12 months of treatment compared with baseline values.[2] Inzucchi stated that the 2 drugs had "equivalent efficacy," while in reality neither was effective. The same observation applies to a study comparing troglitazone and glyburide[3] presented in the same table.

Second, I disagree with Inzucchi's claim that there are no long-term data regarding α-glucosidase inhibitors, as indicated in Table 3. In fact, acarbose was evaluated for 3 years in a large subpopulation of patients who had diabetes (n=1946) and were previously enrolled in the UKPDS.[4] Patients were randomized to receive acarbose or placebo in addition to their assigned antidiabetic therapy. Glycemic control worsened in both groups throughout the duration of follow-up. However, by intent-to-treat analysis, there was a significant difference of 0.2% in median glycohemoglobin levels in favor of the acarbose group. No differences in any diabetes-related end point or microvascular disease were found between the acarbose and placebo groups.[4]

Third, Inzucchi recommended that nonsulfonylurea secretagogues be used with caution in patients with impaired renal function. In fact, the metabolites of repaglinide are excreted via the bile; only 8% of a given dose of the drug is excreted renally. In patients with diabetes and mild to moderate renal dysfunction (creatinine clearance, 40-79 mL/min), no change in the pharmacokinetics of repaglinide was found. However, its terminal half-life was prolonged in those with severe renal failure (creatinine clearance, 20-39 mL/min).[5] Preliminary data on nateglinide, published in abstract forms, were similar.[6] Thus, this class of antidiabetic agents could be appropriate for patients who have mild to

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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

moderate renal impairment and cannot receive metformin or sulfonylureas.

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1. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA*. 2002;287:360-372.
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In Reply: The ancillary DCCT study that Dr Poothullil cites does not present a strong argument against achieving tight glycemic control in diabetic patients when it is associated with weight gain. Although the subjects who gained the most weight did indeed demonstrate higher lipid and blood pressure levels, intensive control in the DCCT was still associated with a trend toward improved cardiovascular outcomes.[1] Similarly, sulfonylurea and insulin therapy in the more applicable UKPDS resulted in both weight gain and a modest trend toward decreased macrovascular events.[2] Unfortunately, weight gain frequently accompanies the achievement of glycemic control with many therapeutic agents, including sulfonylureas, insulin, and thiazolidinediones. Interestingly, the weight gain associated with the latter appears to be relegated to the more metabolically quiescent peripheral sites, while sparing visceral adipose stores,[3] and overall, thiazolidinedione therapy appears to improve cardiovascular risk profiles.[4] Thus, I maintain that normalization or near-normalization of blood glucose concentrations should be a primary goal of therapy for most individuals with type 2 diabetes, although admittedly its benefits have been easier to demonstrate for microvascular end points. Weight gain should not dissuade this effort.

I agree with Dr Mikhail that the standard presentation of antihyperglycemic efficacy as the difference between the glycohemoglobin change in treatment and placebo groups can be misleading. Certainly, the glycohemoglobin change from baseline provides more useful information to the clinician. However, displaying data in this fashion remains most appropriate when study subjects are not drug-naive at baseline. Most placebo-controlled trials of antidiabetic drugs have included relatively brief washout periods of prior antihyperglycemic therapy. Usually, these are long enough to allow fasting glucose levels to rise to a new pretreatment baseline but not long enough to allow glycohemoglobin to reach a similar steady state. Accordingly, many drugs appear to be less effective on the basis of glycohemoglobin when the majority of trial participants were treated with other agents before study enrollment. Thus, the current preference to present data vs the results of placebo therapy is understandable, although imperfect. Clearly, head-to-head trials provide the best data to compare drugs. This discussion may soon be a historical footnote, however, since new antidiabetic agents will probably be compared with the best current therapy as opposed to placebo because of ethical concerns of the deleterious effects of untreated hyperglycemia.[5]

Mikhail also cites a trial of acarbose involving previous UKPDS participants as an example of a study of long-term effectiveness of α-glucosidase inhibitors. This investigation was really one of glycemic efficacy and did not have enough power to show any effect of acarbose on chronic complications. As pointed out, no such effect was observed, but this is not surprising, since the influence of acarbose on glycemia was minimal.

Finally, Mikhail raises concerns as to the precise metabolic fate of the nonsulfonylurea secretagogues. The current package insert of repaglinide,[6] but not that of nateglinide,[7] recommends caution during use in patients with advanced renal failure. I agree that these agents are, in general, safer in this patient population than the longer-acting sulfonylureas. Caution, however, seems reasonable when any insulin secretagogue is used in a patient with renal insufficiency, since these individuals are predisposed to hypoglycemia not only because of altered drug metabolism, but also because of reduced insulin clearance.[8]

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Treatment Decisions for Type 2 Diabetes

To the Editor: I disagree with 3 of the assertions that Dr Holmboe makes in his Clinical Applications article[1] about treatment of type 2 diabetes. First, he describes a patient with a ran-

dom plasma glucose concentration of 480 mg/dL (27 mmol/L) and states that such a patient would require insulin. I believe that this patient would almost certainly respond to high doses of a sulfonylurea agent. I have treated more than 100 symptomatic patients with glucose levels of this magnitude, many of whom have had ketosis, a few with slightly lowered bicarbonate levels (down to 16 meq/L), and a fair number with significant weight loss. More than 90% of them do not require insulin. After 4 months, 6 of 55 patients[2] were lost to follow-up (4 patients had lost their health maintenance organization insurance and 2 would not comply with the recommended follow-up). Of the remaining 49 patients, 6 continued taking a maximal dose of glyburide, 29 were taking a submaximal dose, 11 were treated with diet alone, and 3 were taking insulin. The insulin was started several weeks to several months later, when goal levels of glycemia were unmet, not as an emergency to treat the initial hyperglycemia. At the time this study was carried out, no other oral antidiabetes drugs were available in the United States. It is likely that the addition of another oral drug would have avoided the need for these 3 patients to take insulin during the 4 months of the study. Thus, one can spare the patient the rigors of immediate insulin therapy to see if he or she will respond to a high dose of a sulfonylurea agent.

Second, I disagree with Holmboe that this patient may eventually need 2 oral agents because of the degree of her hyperglycemia. As shown in the UK Prospective Diabetes Study,[3] type 2 diabetes is diagnosed when approximately 50% of beta cell function is left and there is a progressive decrease, regardless of what therapy is used. Therefore, almost all patients will eventually require more than 1 oral agent, but not initially. It is well recognized that most patients newly diagnosed with type 2 diabetes will respond well to whatever pharmacological therapy is initially chosen.[4]

Third, Holmboe claimed that the data of Stenman et al[5] showed that glipizide doses above 10 mg were ineffective, based on averaging the glucose responses of the entire group. Thus, patients who did not respond would mask those who did. If one looks at the responses in individual patients whose dose of glyburide was increased from 10 mg to 20 mg, the fasting plasma glucose concentration decreased by at least 10% in half of them.[6] One might not achieve glycemic goals in many of the patients, but maximizing the dose of one agent before exposing patients to the potential adverse effects of a second one seems prudent.

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1. Holmboe ES. Oral antihyperglycemic therapy for type 2 diabetes: clinical applications. *JAMA*. 2002;287:373-376.
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In Reply: Dr Davidson argues that patient 1 does not need insulin and would most likely respond to a high-dose sulfonylurea agent. I agree that a sulfonylurea drug is an appropriate option for the initial and long-term care of this patient, as I stated in the article. However, the question is whether this patient should start therapy with insulin before switching to an oral agent. It was not my intention to suggest that initiating a short course of insulin therapy in a patient who has newly diagnosed diabetes and significant hyperglycemic symptoms was necessarily an emergency, but rather one option to help selected patients achieve more rapid control of hyperglycemic symptoms.[1] Furthermore, insulin may potentially improve response to oral agents by reducing glucose toxicity.[2] From an evidence-based point of view, insulin is still one of several appropriate therapeutic choices for this patient.[3,4]

Admittedly, starting with insulin does require access to a care system that is able to educate the patient on using insulin effectively and safely. Not all patients have this type of care readily available. The patient will also require immediate education on the use of a home glucose monitor, avoidance, recognition, and treatment of hypoglycemia, close follow-up to assess progress, and dietary changes. However, these later requirements apply to all patients with type 2 diabetes, regardless of initial therapy. Finally, I do agree that patient preferences are crucial in choosing the initial therapy.[5]

On his second point, Davidson and I seem to agree that this patient will eventually require more than 1 agent to control her diabetes. Given that the average absolute reduction in glycosylated hemoglobin (HbA_{1C}) for each of the 3 main classes of oral agents is 2% to 3%, this patient's baseline HbA_{1C} would most likely need to be less than 10% to achieve the goal HbA_{1C} of 6.5% to 7.0%. If the patient also is successful with lifestyle changes and weight reduction, then it is quite possible she will not need a second agent in the near future.

Finally, the decision about whether to maximize the dose of a sulfonylurea should be based on the patient's glycemic control and preferences. However, it is unlikely that the additional 10% benefit from maximizing the dose of glyburide will help achieve optimal glycemic control for the 57-year-old man who is mentioned in the article and is receiving 10 mg of glyburide with an HbA_{1C} level of 8.5%. Again, I agree that the decision should include a careful consideration of the risks and benefits of each therapeutic option.[5]

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1. Leahy JL. Type 2 diabetes mellitus. In: Leahy JL, Clark NG, Cefalu WT, eds. *Medical Management of Diabetes Mellitus*. New York, NY: Marcel Dekker; 2000: 131, 270.

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The Costs of Making Practice More Cost-effective

To the Editor: Dr Mason and colleagues[1] derived an economic model, based on England's National Healthcare System (NHS), for determining when it might be cost-effective to try to change physician behavior. Although health care is not nationalized in the United States, some health care services for eligible elderly and disabled patients are federally funded through Medicare. Three differences between the NHS and Medicare must be recognized before the model of Mason et al[1] can be applied to Medicare policy.

First, under Medicare, physicians incur costs when changing their practices. In the NHS, it may be reasonable to assume no costs associated with practice change; physicians are salaried and apparently have an allocation of time dedicated to such pursuits. For US physicians who are obtaining Medicare reimbursement for services, time spent away from patient care represents lost income. Although the low Medicare reimbursement rates may mitigate the effect somewhat, this financial disincentive may decrease the intervention's effectiveness. The combination of higher costs and lower effectiveness increases the loading costs substantially.

Second, medications are not liabilities in the Medicare system. In the model of Mason et al,[1] the primary direct costs to the NHS are medication costs; downstream reductions in health care service utilization associated with their use are excluded.[2] Medicare does not pay for medications and, therefore, incurs no direct pharmacy costs. Patients may rationally choose to purchase more expensive medications if they are also more effective or have fewer adverse effects. To the extent that patients' use of health care services decrease because of privately funded medication use—fewer visits because of fewer adverse effects or fewer hospitalizations because of more effective treatment—Medicare obtains a windfall.

Finally, in the model of Mason et al, benefits that accrue to NHS would be liabilities for Medicare. Additional life-years gained represent an extension of Medicare's liability for health care services funding for patients and US medical costs are increasing more rapidly than the 5% discount rate used in the model.[2] Therefore, in the United States, additional life-years do not represent benefits, but more, and more costly, health care services payments.

These considerations do not diminish the model's utility. On the contrary, they offer insight into why cost-effectiveness analyses may not be very informative in the United States. Within the US health care system, physicians' self-interest is frequently financially, not socially, driven. Only by addressing those incentives can leaders of health care systems motivate physicians to change.

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1. Mason J, Freemantle N, Nazareth I, Eccles M, Haines A, Drummond M. When is it cost-effective to change the behavior of health professionals? *JAMA*. 2001; 286:2988-2992.

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To the Editor: Dr Mason and colleagues[1] provide a useful framework for assessing the cost-effectiveness of quality improvement efforts. However, this model has several potential limitations as a tool for decision-making policy.

Many interventions, such as academic detailing and drug utilization review, may result in greater improvements than Mason et al estimated.[2,3] More importantly, quality improvement interventions may have benefits that are not immediately quantifiable. By promoting a culture of quality improvement, interventions in one area may contribute to better care in other domains. Moreover, this framework does not account for individual and social benefits that are not easily measured in monetary value. These may include the effects of disease treatment on quality-of-life, the spread and resistance of communicable pathogens, and the social value that is placed on certain diseases. Explicit evaluations of cost-effectiveness are important, but are only one of several factors needed to make rational and compassionate policy decisions.

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1. Mason J, Freemantle N, Nazareth I, Eccles M, Haines A, Drummond M. When is it cost-effective to change the behavior of health professionals? *JAMA*. 2001; 286:2988-2992.

2. Avorn J, Soumerai SB. Improving drug-therapy decisions through educational outreach: a randomized controlled trial of academically based "detailing." *N Engl J Med*. 1983;308:1457-1463.

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To the Editor: Dr Mason and colleagues[1] assert that "newer classes of antidepressants have achieved widespread first-line use without demonstrating added value." In a recent study, however, Kroenke et al[2] stated that "compared with tricyclic antidepressants, selective serotonin reuptake inhibitors have a more favorable adverse effect profile, simpler dosing, and less toxic effects in the event of an overdose," while demonstrating ef-

fectiveness equal to tricyclic antidepressants. The contrast between assumptions of these 2 articles raises questions about the kind of evidence that should be considered in making these judgments.

Although both assertions are based on clinical evidence, they appear to begin from different starting assumptions about which evidence is worth considering in making a choice about treatment. These implicit biases relate not to the method of answering a clinical question, but rather to the process of formulating a question in the first place. Primary care physicians, whether in England or the United States, generally consider patients' point of view on adverse effects, suicide potential, and convenience in discussions of value. By contrast, a narrower question that considers only objective symptoms might lead to opposite conclusions. I would hope that physicians would be sensitive to patients' definition of outcomes and would have the good sense not to base a change in prescribing habits on the right answer to the wrong question.

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1. Mason J, Freemantle N, Nazareth I, Eccles M, Haines A, Drummond M. When is it cost-effective to change the behavior of health professionals? *JAMA*. 2001; 286:2988-2992.
2. Kroenke K, West SL, Swindle R, et al. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. *JAMA*. 2001;286:2947-2955.

To the Editor: Dr Mason and colleagues[1] need look no further than the high cost of antepartum fetal surveillance to find an example of "suboptimal" health care. Despite costly, intensive monitoring of pregnancies at risk for stillbirth, up to one half of all fetal deaths have no identifiable risk factors.[2] Furthermore, although several inexpensive methods to predict stillbirth have been known for several years, they have yet to receive widespread adoption by physicians.

For instance, in 1989, Moore and Piacquadio[2] reported a significant reduction in fetal mortality following the introduction of a count-to-10 fetal movement-screening program. In 1991, Whitty et al[3] reported their experience with women who were instructed to call for less than 4 movements per hour for 2 consecutive hours. Although the low-risk nontested women had higher rates of intrauterine growth retardation, the control group had no fetal deaths and the study group experienced only 5 fetal deaths of 4727 patients monitored, a lower incidence than other authors have reported. In 1987, Ahn et al[4] reported that women seen for decreased fetal movement were 3.7 times more likely to have oligohydramnios than those with other indications for nonstress testing. The study group was small and fetal mortality was not improved by nonstress testing. Finally, the most current Practice Bulletin (October 1999) of the American College of Obstetrics and Gynecology could not endorse a formal program of fetal movement assessment.[5]

Although the best US study used a historical comparison group and was not randomized, the effect was large. During the last 7 months of a 14-month trial, fetal mortality decreased from 8.7 to 2.2 per 1000 births following the introduction of a fetal movement screening program.[2] The incremental costs of identifying an additional 50% of gestations at risk for fetal death has not been calculated and may be substantial. Moore and Piacquadio[2] noted a 13% increase in the total number of tests ordered, a higher proportion of labor inductions, and more cesarean deliveries. However, the dollar value saved by failing to identify those pregnancies at risk for stillbirth may be incalculable and perhaps indefensible because all monitoring is by the patient.

Although we closely monitor high-risk gestations with advanced world-class technology in the United States, we have failed to implement a simple program of universal fetal movement monitoring for the healthy-risk pregnancy. The healthy mother instructed to report decreased fetal activity is at worst identifying a pregnancy at risk and is at best preventing stillbirth of the fetus.

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1. Mason J, Freemantle N, Nazareth I, Eccles M, Haines A, Drummond M. When is it cost-effective to change the behavior of health professionals? *JAMA*. 2001; 286:2988-2992.
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In Reply: There are multiple aspects to any strategy to change behavior, which may influence cost-effectiveness and vary with content, setting, country, and funding agency. We agree with Drs Weeks and Wallace that physician time-costs will influence implementation loading; from the various US funding perspectives, different costs may be included and excluded. Similarly, if implementation research involves a certain pattern of incentives and if these are changed by the funding agency, this may well affect the amount of behavioral change. For example, from a pharmaceutical industry perspective, the costs of drugs become bottom-line profits; our model offers some insight to the motivations behind its promotional activities. The inclusion of health care costs of extended healthy life (which would themselves have benefits) remains a debated issue, though routinely excluded from calculations of treatment cost-effectiveness.[1,2]

Dr Steinman correctly asserts that academic detailing and drug utilization review may produce nonspecific benefits not reflected in our framework. However, it may also be true that fo-

cusing on some specific treatment areas may actually reduce quality of care in others. It may not always be possible to summarize the costs and consequences of treatment in a simple cost-effective ratio, and worthwhile behavioral change may not always be described by a single end point. In these circumstances, the model promotes ordered thinking and requires decision makers to calculate the various costs, facets of behavioral change, and their estimated impact upon health care. It may be necessary to consider a profile of policy costs and consequences rather than a simple policy cost-effective ratio. Economic evaluation has traditionally focused upon narrow efficiency concepts, making it appear partial. Its origins were actually more ambitious: to elicit a social valuation of alternative states of the world. Notions of equity, justice, compassion, and choice are integral to societal values and should be considered in allocative decisions, comparing the cost-effectiveness of treating different diseases and patient groups.

Dr Epstein comments that even when we have substantial high-quality evidence, its meaning may be disputed. Our model estimates were drawn from an evidence-based clinical guideline with appropriate multidisciplinary membership. Members were impressed by the mismatch between their perceptions of promotional claims and the evidence.[3,4]

The interpretation of evidence is central to the appropriateness of fetal movement monitoring as raised by Dr Lyman. The evidence is inconsistent and Lyman's conclusion depends upon his emphasis of the relative importance of available studies. Where there is disagreement about the value of a message, its implementation may be expected to achieve variable uptake.

We recognize that our model requires a number of simplifying assumptions and realize that it may be developed further. Its value is in promoting clarity of thought both when designing implementation research and identifying whether a policy of local implementation is likely to be cost-effective. Whether implementation is worthwhile is influenced by a number of variables that must be interpreted in the local setting. While we believe that our framework has generic value, the comments of these writers illustrate that the answers for each implementation policy decision cannot be assumed to generalize across different countries and settings.

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1. Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. *J Health Econ.* 1997;16:33-64.
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4. Mason JM, Freemantle N. The dilemma of new drugs: are costs rising faster than effectiveness? *Pharmacoeconomics.* 1998;13:653-657.

RESEARCH LETTER

Poliomyelitis and Parkinson Disease

To the Editor: Parkinson disease (PD), which is due to loss of dopaminergic neurons in the zona compacta of the substantia nigra,[1] may involve both genetic and environmental risk factors.[2] Poliovirus is believed to cause neuronal damage in the substantia nigra,[3] and thus a history of poliovirus infection may be associated with an increased risk of PD.[4]

Methods. We assessed the risk of PD in a large cohort of patients hospitalized for poliomyelitis in Copenhagen, Denmark, between 1919 and 1954.[5] This cohort represented more than 80% of all the cases of poliomyelitis registered by the National Board of Health in the population of Copenhagen during the same period.[5] A total of 5421 of these patients were alive on January 1, 1977, when the National Hospital Discharge Register (NHDR) was established in Denmark. The NHDR is a population-based register containing information on all somatic hospitalizations and, since January 1, 1995, all outpatient treatments. For each patient with poliomyelitis, we identified 4 controls in the Danish Civil Registration System, matched for sex, age, and geographical residence as of January 1, 1977. All subjects were linked to the Danish Hospital Discharge Register to identify all verified cases of PD (ICD8 code 342.99 and ICD10 code G20.9). The 2 cohorts were followed from January 1, 1977, until date of diagnosis of PD, disappearance, immigration, death, or the end of 1999, whichever came first. The ratio between PD incidence in the exposed and unexposed cohorts, respectively, served as measure of the relative risk (RR) of PD. Confidence intervals (CIs) for the RR were estimated assuming a Poisson distribution of the observed cases.

Results. Subjects were followed for an average of 20.5 years, yielding a total of 555 537 person-years of follow-up. Overall, history of poliomyelitis was associated with a RR for PD of 2.3 (95% CI, 1.4-3.6) (TABLE). In analyses stratified according to poliomyelitis severity, increased PD risk was observed in patients with a history of paralytic poliomyelitis (RR, 2.2; 95% CI, 1.1-4.3) and primary lymphocytic meningitis (at the time of cohort exposure believed to primarily reflect polio virus infection[6]) (RR, 4.1; 95% CI, 1.4-11.9). Nonsignificant associations were found for nonparalytic poliomyelitis (RR, 1.9; 95%

Table. Relative Risk of Parkinson Disease Among Patients With Polio Compared With a Nonexposed Cohort Matched by Age and Sex

Patient Group	Persons, No.		Observed Parkinson Cases, No.		RR (95% CI)*
	Patients With Polio	Age-/Sex-Matched Cohort	Patients With Polio	Age-/Sex-Matched Cohort	
Total	5421	21626	29	50	2.3 (1.4-3.6)
Paralytic	2003	7979	13	23	2.2 (1.1-4.3)
Nonparalytic	2335	9317	7	14	1.9 (0.7-4.7)
Primary lymphocytic meningitis	592	2367	7	7	4.1 (1.4-11.9)
Suspected polio	491	1963	2	6	1.3 (0.2-5.7)

*Relative risk (RR) calculated according to person-years at risk. CI indicates confidence interval.

CI, 0.7-4.7) and in patients only suspected of having poliomyelitis (RR, 1.3; 95% CI, 0.2-5.7).

Comment. Although it has long been hypothesized that poliomyelitis is associated with an increased risk of PD,[4] to our knowledge this has never been empirically demonstrated. The observed increased PD risk does not necessarily imply that poliovirus is directly implicated in PD pathogenesis. Rather, we speculate that by reducing the number of neurons essential to normal neuronal functions, the virally induced damage may enhance the effect of normal age-related neuronal degeneration and thus precipitate PD.[1,4]

We acknowledge possible limitations of our data. Because patients with poliomyelitis may be admitted to hospitals or may attend outpatient clinics more often than other persons, detection bias could arise. However, in Denmark, the diagnosis, evaluation, and treatment of PD normally take place at neurological departments or neurological outpatient clinics. Moreover, although patients with PD initially may consult private neurologists or general practitioners, the vast majority of patients with PD will at some point undergo clinical evaluation or hospitalization at specialized hospital departments because of the complexity of the disease. Therefore, we think that most Danish patients with PD would be registered in the NHDR, and we consider detection bias to be an unlikely explanation for our findings.

Patients with polio may present a wide range of neurological symptoms, which could cause diagnostic ambiguity. If diagnostic misclassification would explain our observations we would have expected the risk of PD to be particularly increased in patients with paralytic polio. However, an increased risk of PD was also observed in patients with nonparalytic polio. Moreover, the likely inclusion of patients with nonpolio virus-related meningitis in the group of patients with primary lymphocytic meningitis may indicate that the observed PD risk is not particular to the poliovirus but also applies to other viruses infecting the central nervous system.

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CORRECTION

Incorrect Measure: In the Original Contribution entitled "Cognitive Functioning of Long-term Heavy Cannabis Users Seeking Treatment" published in the March 6, 2002, issue of THE JOURNAL (2002;287:1123-1131), the legend for the Figure should indicate that error bars represent SEM, not SD.