Editorials

Private Arsenals and Public Peril

In the aftermath of the shootings at the Westside Middle School in Jonesboro, Arkansas, Karen Curtner, the principal of the school, said, "The issue here is not the weapon or the gun that was used. That has really nothing to do with what happened. We have to look further than that."[1] Jim Simon, an Arkansas gun-control opponent, agreed. "The problem isn't the guns," he said. "It's what the kids are doing with them."[2] National Rifle Association (NRA) spokesman Bill Powers declared, "Lawful arms ownership has nothing to do with this tragedy."[1] And another NRA spokesman concurred: "This is not a gun issue, it's a society issue, and it's troubling."[3] Arkansas's governor, Mike Huckabee, also weighed in, arguing that the easy availability of firearms was not a cause of the shooting.[4]

But sticks and stones were not the weapons that the two boys — 11 and 13 years old — used to kill 5 people and wound 15 others. When captured, the boys carried 10 loaded firearms, some of them rapid-fire semiautomatic rifles capable of accepting high-capacity ammunition magazines and hundreds of rounds of ammunition. They quickly got off 44 shots.

Despite the unmistakable role of firearms in the killings, commentators in the wake of the tragedy preferred to focus on psychological and social explanations. Dozens of such analyses flooded the newspapers, magazines, and talk shows. Some suggested the existence of a different value system in the South, one that breeds a subculture of violence. Others blamed the pervasive glamorization of violence in movies, videos, and television shows (including certain cartoons). Divorce, the absence of fathers, and the lack of early love and bonding were the explanation, said others. Some concluded that the boys were just bad (some psychologists dubbed them sociopaths). Not surprisingly, some invoked a loss of moral authority and a breakdown of the American family.[5]

Some commentators merely threw up their hands, frustrated that so many were using the event to prove what they already believed,[5] and some derided all the experts as a "mob of meaning makers."[6] The author of a book about values in journalism was disturbed that so many people offered simplistic explanations and jumped to "cosmic conclusions" based on virtually nonexistent facts.[6]

Equally unsatisfying is the welter of recommendations that were offered. Revamp the juvenile law in Arkansas so that the perpetrators can be tried as adults; make them an example for others. Encourage the active participation of parents in determining what kind of television programs their children can watch. Introduce the V chip to reduce automatically the amount of violence children see on television. Finally, hold parents criminally liable for the heinous acts of their children.

Though we may never know precisely *why* the boys did what they did, we certainly know *how*. They first tried to break into the 11-year-old boy's parents' cache of firearms, but failing that, took three guns from unsecured places in that house. They then broke a window in the basement of the same boy's grandfather's house and removed many more firearms. Positioning themselves in the woods the length of a football field away from the school door, they opened fire. Telescopic sights helped their aim: 27 rounds hit their targets. Given these facts, how can anyone accept the contorted logic that lawful arms ownership has nothing to do with this tragedy, or that this is not a gun issue? The vast array of powerful firearms available to the boys is remarkable. Would the carnage have been so great if the boys had been unable to gain access to the grandfather's private arsenal? Would so many people be dead if such lethal weapons had not been in either collection? Parenthetically, it goes without saying that even a single semiautomatic weapon left loaded, unlocked, and accessible is a dangerous arsenal in itself.

Does anyone need to have a private arsenal of high-powered weapons? They are of no value for hunting, and their use for target practice seems dispensable. They are certainly not needed for protection against crime. Moreover, they are worse than useless. In recent years, large stashes of firearms have figured importantly in other major losses of life. Hundreds of guns were found at Waco, and cash from the sale of stolen weapons was used to build the bomb that devastated the federal building in Oklahoma City.

Children and adolescents are by definition immature, and many lack judgment. Life's embarrassments, rejections, and torments may send them into fits of temper, even rage, and may prompt a desire for revenge. Impulsively, some children lash out at others and at themselves. Nonetheless, they are only murderous when they have the means, and a loaded gun is the "perfect tool."

We must ratchet down our nation's firepower. It is time to eliminate semiautomatic firearms from private homes. The 1994 federal ban on new assault weapons with high-capacity ammunition clips must be tightened to stop the manufacture and sale of military weapons modified to have a sporting appearance. A ban on these large ammunition clips should also include those produced before 1994. Kits to convert semiautomatic weapons into fully automatic machine guns should be outlawed. A federal

code for storing firearms in the home should be developed, and all firearms should be registered with local authorities. It is time to end the firearm industry's status as America's last unregulated industry; a federal agency should be given standard-setting authority over the industry and its products.

It is also time to lay to rest the myth that keeping firearms in the home protects people against personal injury.[7] Obvious, serious methodologic errors in the design of surveys that purport to demonstrate a protective effect invalidate such conclusions.[8,9] Mass shootings such as the one in Jonesboro are avoidable, as are local epidemics of gun-related suicide in teenagers. It would take political will to buck the well-funded lobbies of the gun manufacturers and the National Rifle Association. So far, unfortunately, few courageous legislators have stepped up to the plate.

Our children are murdering our children. Oliver North, the former Iran–Contra figure, now a radio personality, said recently that it would be unconscionable for gun-control advocates to try to make political hay out of the Jonesboro shooting.[6] Quite the contrary, in my opinion. Perhaps it is still possible to derive some good from this unspeakable tragedy.

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MULTIDRUG RESISTANCE — A SIGN OF THE TIMES

RESISTANCE to antibiotics is a problem that confronts all of us, thwarting treatment of inpatients and outpatients and compromising therapy for animals, fish, and agricultural crops.[1] The frequency of resistance in bacteria and the numbers of drugs to which they are resistant are increasing. Multidrug resistance marks this decade, as further evidenced by the report by Glynn et al. in this issue of the *Journal* of a strain of *Salmonella enterica* serotype typhimurium, known as definitive type 104 (DT104), in the United States that is resistant to five drugs.[2] Salmonella, normally harbored in animals, can cause infections in people. Although in most cases salmonella infections do not require treatment, each year thousands of people do need lifesaving antibiotics for such infections. The DT104 strain, whose frequency is rising in the United States, has been plaguing animals and people in Europe for the past decade. There, the organism has acquired resistance to seven drugs that are used to combat it.[3]

Two major factors contribute to antibiotic resistance: the antibiotic itself and the type of resistance traits being selected for. As a further complication, these traits can be spread among different bacteria. The resistance displayed by salmonella reflects the environment in which the organism thrives. Over 40 percent of the 23 million kg (50 million lb) of antibiotics produced in this country is used in animals. Of this, more than 80 percent by weight is used subtherapeutically for growth promotion; the rest is for therapy. Both uses can increase the likelihood of multidrug resistance.

Fourteen years ago, a multidrug-resistant strain of *Salmonella enteritidis* serotype newport associated with hamburger was traced to a farm using antibiotics to promote growth in cattle.[4] At that time, in an editorial in the *Journal*, I urged a reevaluation of and an eventual discontinuation of the subtherapeutic use of valued human antibiotics — namely, penicillins and tetracyclines — for growth promotion.[5] Although a number of high-profile groups have reported the potential public health implications of this use of antibiotics, none could quantify it, and no change has occurred.[6] Action has been delayed by arguments over which practice was responsible for resistance: subtherapeutic or therapeutic use of antibiotics. However, in Europe and elsewhere, restrictions on the use of antibiotics for growth promotion were legislated in the late 1970s in response to the spread of a multidrug-resistant strain of typhimurium from animals to people.

We now know that the use of even alternative growth promoters produces unwanted consequences. Drugs designated as not for use in humans when they were introduced about 20 years ago now form the core structure of some of medicine's newer antibiotics. For instance, the use of avoparcin, a glycopeptide growth promoter, has selected for vancomycin-resistant enterococci among animals.[7] The same vancomycin-resistant clone of enterococci has been found in animals and people.[8] Likewise, the use of the growth promoter virginiamycin has selected for enterococci with resistance to it, but more important, to quinupristin–dalfopristin (Synercid), an antibiotic that was recently approved for use in humans.[9]

These findings have made it even clearer that the

use of growth promoters affects the drug resistance of environmental reservoirs, with direct consequences for the treatment of disease in humans. The findings led to a ban on avoparcin in the European Union countries and, recently, on virginiamycin in Denmark. Last year in Berlin, Germany, a group of World Health Organization consultants recommended the gradual discontinuation of the use of antibiotics as growth promoters in the face of newly documented risks to human health. There has been no change in their use in the United States.

Today, the use of antibiotics for growth promotion is only part of the issue. Therapeutic use of antibiotics in animals has taken center stage, as requests increase for the use of newer-generation drugs for animals. Although the need may be real, there is great concern that this practice may lead to the selection of resistant strains of consequence to human health, especially if the use in animals does not follow the same standards of rational and appropriate use applied to human therapy. The issue has become most relevant with respect to the fluoroquinolones. An expert panel convened by the Food and Drug Administration recommended caution in the approval of quinolones for use in animals because of the potential consequences for people. There was good reason for concern. Soon after fluoroquinolones were given to animals in the Netherlands, fluoroquinolone resistance appeared in another zoonotic organism, campylobacter.[10] With the introduction of quinolones for use in poultry, resistant strains of campylobacter are now appearing in the United States.[11] More important, typhimurium DT104 that is resistant to fluoroquinolones has emerged in Europe.[3]

Although the use of antibiotics as growth promoters strongly encourages selection for drug resistance, so do therapeutic uses of these drugs, especially when provided in feed or water, where they remain active and are widely dispersed. Just recently, in an unprecedented move, Bayer Pharmaceuticals, the manufacturer of ciprofloxacin, issued statements warning against the misuse of fluoroquinolones for animals, since "inappropriate use could lead to a risk that fluoroquinolones [will] become less effective in treating certain human diseases" (McIntyre D, Ebsworth DR: personal communication).

Antibiotic resistance, initially a problem in hospitals and developing countries, today affects the world at large. Some strains of disease-causing bacteria in the United States may now be untreatable: the vancomycin-resistant enterococcus, *Mycobacterium tuberculosis, Pseudomonas aeruginosa,* and *Acinetobacter baumanii*. In the face of this escalating problem, five underlying principles may be of value in understanding the issue and approaching a solution.

First, given sufficient time and drug use, antibiotic resistance will emerge. There are no antibiotics to which resistance has not eventually appeared. The penicillin-resistant *Streptococcus pneumoniae* took 25 years to become today's clinical problem. Fluoroquinolone-resistant Enterobacteriaceae took 10 years to emerge clinically. To these we can now add vancomycin-insensitive *Staphylococcus aureus*[12] and erythromycin-resistant *Strep. pyogenes.*[13]

Second, resistance is progressive, evolving from low levels through intermediate to high levels. Unless acquired as a transferred genetic element, resistance often appears in the form of small increases in the minimal inhibitory concentration. Fluoroquinolone resistance among *Escherichia coli* requires several sequential mutations to reach a high, clinically relevant level. Penicillin-resistant *Strep. pneumoniae* emerged after a gradual progression from reduced susceptibility to high-level resistance. These examples reveal an important message: increasing minimal inhibitory concentrations are a marker for future resistance. The few vancomycin-insensitive strains of *Staph. aureus* that have been detected are harbingers of future strains with full-blown resistance.

Third, organisms that are resistant to one drug are likely to become resistant to others. The first tetracycline-resistant gonococcus appeared among strains that were already resistant to penicillin. Fluoroquinolone resistance emerged among strains that were resistant to both tetracycline and penicillin. For *Staph. aureus, Strep. pneumoniae,* and *M. tuberculosis,* resistance to any single agent can be used to predict the organisms that are more likely to become resistant to a second or third drug.

Fourth, once resistance appears, it is likely to decline slowly, if at all. There are no counterselective measures against resistant bacteria. The slow loss of resistance is linked to poorly reversible genetic and environmental factors. The insertion of a resistance transposon into a cell's DNA may alter the insertion site so that the same mechanism cannot be used to excise the transposon. With time, plasmids and their new hosts can enter into a symbiotic relationship, in which the growth of the host relies on the presence of the plasmid.[14] Multidrug-resistant *E. coli* persisted among chickens despite the removal of the drug selecting for resistance and thorough cleaning of the cages.[1] The fastest way to reverse resistance is to replace these strains with susceptible strains.

Fifth, the use of antibiotics by any one person affects others in the extended as well as the immediate environment. For example, housemates of patients treated with antibiotics for acne had large numbers of drug-resistant flora on their skin.[15]

If, as I wrote in 1984, it was time to tally the score,[5] it is even more essential to do so in 1998. We need to minimize the environmental impact of antibiotics. The smaller the extent of exposure to antibiotics, the less likely the selection and transfer of resistance traits among environmental bacteria and the

lower the probability that a resistant pathogen will arise. Education of consumers and health care providers should reduce the misuse of antibiotics for viral diseases. Their use in animals should be limited to prophylaxis and therapy in a way that does not perpetuate the selection of resistance. A guiding principle of antibiotic use for any purpose must be the protection of the susceptible commensal bacteria in our environment. They are our chief allies in reversing the crisis of multidrug resistance.

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PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY — PROGRESS MADE AND LESSONS RELEARNED

PROGRESSIVE multifocal leukoencephalopathy is an opportunistic demyelinating infection caused by a ubiquitous, usually nonpathogenic papovavirus known as JC virus. The symptoms and characteristic radiologic findings of progressive multifocal leukoencephalopathy are due to virus-induced lysis of oligodendrocytes, resulting in microscopic foci of myelin breakdown that coalesce to produce increasingly larger lesions.[1] The virus also infects astrocytes, in which morphologic features develop that are suggestive of neoplasia, including mitotic figures and multinucleated forms.

Progressive multifocal leukoencephalopathy is a disease of immunosuppressed patients. The disease was initially identified by Aström and colleagues as a rare complication of chronic lymphocytic leukemia and Hodgkin's disease.[1] Subsequent cases were reported in association with other leukemias and lymphomas, with cancer chemotherapy, with immunosuppression for rheumatic disease or after organ transplantation, and with chronic inflammatory diseases such as sarcoid, tuberculosis, or nontropical sprue.[2] With the advent of the acquired immunodeficiency syndrome (AIDS), the incidence of progressive multifocal leukoencephalopathy has greatly increased. Progressive multifocal leukoencephalopathy may be the presenting feature of human immunodeficiency virus (HIV) infection and accounts for as much as 4 percent of deaths among patients with AIDS.[3] Progressive multifocal leukoencephalopathy is a progressive condition. Although prolonged survival and clinical remission have been described in both AIDS-related and non–AIDS-related disease, most affected patients die within months.

The host and viral factors that lead to the development of progressive multifocal leukoencephalopathy are not well understood. Over 70 percent of adults carry antibodies to JC virus, and JC virus has been shown to persist in kidneys and to be shed in urine.[2] Work from a number of laboratories suggests that JC virus may persist in B lymphocytes as well as in kidneys, and studies using the polymerase chain reaction (PCR) have also detected JC virus in the brains of persons without progressive multifocal leukoencephalopathy.[2,4] It is not yet known whether the detection of JC virus in brain by PCR represents amplification of viral DNA from circulating lymphocytes or the amplification of virus in the brain itself; nor is it known whether progressive multifocal leukoencephalopathy results from the invasion of the brain by virus-infected B lymphocytes, as opposed to reactivation of latent viral infection of glial cells.[2,4] Molecular

studies of JC virus suggest that the selective tropism of the virus for oligodendrocytes and astrocytes may reflect the interaction of glia-specific promoters with the regulatory region of the JC viral genome, but it is not clear how this finding relates to the pathogenesis of progressive multifocal leukoencephalopathy. Recent experimental work by Chowdhury et al. has demonstrated that the HIV type 1 nuclear protein Tat has the capacity to increase transcriptional activity of the JC viral genome in glial cells.[5] This observation, if applicable to the replication of JC virus in the human central nervous system, would suggest that control of HIV infection could be of direct importance in developing therapeutic approaches to progressive multifocal leukoencephalopathy in patients with AIDS.

Early attempts to develop therapy for the disease were hindered by the extraordinary rarity of the condition, which made an organized therapeutic trial very difficult. There were also three technical difficulties: the lack of any imaging technique that might identify lesions of progressive multifocal leukoencephalopathy and thus permit the early initiation of treatment, the inability to confirm the presence of the disease by any procedure short of brain biopsy, and the absence of any means other than clinical examination to assess the response to therapy. Under these conditions, both vidarabine and acyclovir were tried in several patients and found to be ineffective. Cytarabine, on the other hand, was reported to produce clinical improvement in several cases, although in other cases it appeared to be ineffective.

Within the past decade, the enormous increase in the number of patients with progressive multifocal leukoencephalopathy due to AIDS has provided both impetus and a sufficient number of patients for organized therapeutic trials. At the same time, magnetic resonance imaging (MRI) has made possible both the provisional radiologic diagnosis of progressive multifocal leukoencephalopathy and the use of stereotactic biopsy to confirm the diagnosis by histologic or molecular methods. In this issue of the *Journal,* Hall et al., in a multicenter trial, have reassessed the efficacy of both systemic (intravenous) and intrathecal cytarabine in a group of patients with progressive multifocal leukoencephalopathy confirmed by MRI-guided stereotactic biopsy.[6] They found no significant difference in survival among patients treated with antiretroviral therapy alone, antiretroviral therapy plus intravenous cytarabine, or antiretroviral therapy plus intrathecal cytarabine.

The results are in accord with those of three smaller studies.[7-9] In 1994, Antinori et al. studied four patients with progressive multifocal leukoencephalopathy who were treated with combined intravenous and intrathecal cytarabine and found that the drug did not result in clinical improvement or decrease the viral burden in the cerebrospinal fluid as measured by PCR.[7] Fong and Toma, using both retrospective and prospective data, found no clinical improvement in nine patients with AIDS-associated progressive multifocal leukoencephalopathy who were treated with cytarabine.[8] More recently, Matsiota-Bernard et al. reported that systemic plus intrathecal cytarabine decreased the cerebrospinal viral burden in two of three patients but had no effect on the clinical course.[9] The study by Hall et al., along with these smaller studies, thus puts to rest many years of anecdotal reports concerning the use of cytarabine in AIDS-associated progressive multifocal leukoencephalopathy and suggests that the drug has no role in treating this disease.

Progress in three areas may contribute to our understanding of optimal therapeutic approaches to this disease. The first is the use of MRI not only for initial diagnosis but as a means of monitoring changes in the size of lesions in response to therapy. The second area of progress is the use of PCR analysis of cerebrospinal fluid to diagnose central nervous system infections. This advance may permit future trials to be carried out without the need for brain biopsy. Although initially PCR had only limited accuracy in the diagnosis of progressive multifocal leukoencephalopathy, in more recent trials this method has been able to diagnose the disease in up to 85 percent of cases, with close correlation with the results of brain biopsy or autopsy study and with virtually no false positive results.[10,11] The PCR data from the present study, as yet unpublished, should provide valuable supportive evidence as to whether the use of PCR can obviate the need for brain biopsy in the diagnosis of progressive multifocal leukoencephalopathy.

The third area of progress involves therapy for AIDS-associated progressive multifocal leukoencephalopathy, specifically whether aggressive treatment of the underlying AIDS may influence the course of the leukoencephalopathy. Controlled clinical trials, similar to the present study, are currently evaluating drugs with specific activity against JC virus, including inhibitors of DNA topoisomerase I activity, such as camptothecin and related agents. In addition, preliminary data from two centers, cited by Hall et al., suggest that highly active antiretroviral therapy to control HIV infection, without specific therapy directed against JC virus, may result in regression of progressive multifocal leukoencephalopathy in patients with AIDS; this hypothesis is being tested in larger numbers of patients as well. The data obtained from these trials should be of great value in defining optimal therapy for progressive multifocal leukoencephalopathy in patients with AIDS and may also provide insight into the treatment of progressive multifocal leukoencephalopathy in patients with other disorders.

The present study and its findings are reminiscent of early efforts to treat central nervous system infec-

tions due to herpes simplex virus. In individual reports, some based on clinical diagnosis alone, the agent 5-iodo-2′-desoxyuridine (idoxuridine) was said to result in clinical improvement in patients with herpes simplex encephalitis. These reports were sufficiently encouraging to lead to two carefully controlled clinical trials, each of which used brain biopsy to confirm the diagnosis.[12] Both trials were halted, however, after idoxuridine was found to contribute nothing to the course of the disease other than toxicity. The present report, like the studies of idoxuridine, serves as a reminder that the efficacy of antiviral drugs cannot be determined from individual case reports, particularly when specific diagnoses are not confirmed or where there is variability in the natural history of the disease being treated.

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Sounding Board

Masked Monitoring in Clinical Trials — Blind Stupidity?

In randomized clinical trials of treatment, information about which subjects are receiving the new treatment and which are receiving the standard treatment is often withheld from both the researchers and the subjects. Such masking is a reasonable precaution to prevent bias. However, many trials have a special monitoring committee to decide when to stop or modify a trial, and this committee is also often asked to review masked data. Monitoring committees review interim results to make certain continued randomization does not expose one group of subjects to inferior treatment.[1-4] When a significant difference emerges, enrollment is stopped or the design of the trial is altered appropriately. Does it make sense to keep the nature of the treatment from monitoring committees, as well as researchers and subjects?

Masked monitoring grows out of a general dictum in treatment trials: mask when possible. This dictum is born of the fear of treatment-related bias, and withholding information about treatment is seen as a way to maintain objectivity. The desire for the objectivity made possible by masking has even led to the suggestion that it should be extended to the process of writing the results of trials for publication.[5]

Masked monitoring is thought to increase the objectivity of monitors by making them less prone to bias. What is overlooked is what masking does to degrade the competency of the monitors.

The requirement of competency takes precedence over the desire for objectivity when research involves human subjects — a principle evident in the Nuremberg Code[6] and subsequent codes for research on human beings. Masking should not be imposed if it entails avoidable risks for patients.[7] Masked monitoring denies the monitors the key information they need to perform in a competent fashion, and incompetent monitoring poses a risk to research subjects.

Masked monitoring is achieved by coding the treatments (e.g., with the use of letter or number codes) and summarizing the results according to the coded treatment. The monitors thus have access to the results according to the treatment group, but because of the coding, they do not know whether the results are for the treatment being tested or the treatment being used for comparison. The monitors compare the treatment groups by subtracting the results in one group from the results in the other group, but because of the masking, they do not know whether the difference favors the test treatment or the control treatment.

The assumption underlying masked monitoring is that recommendations for a change in the study protocol can be made independently of the direction of a treatment difference, but this assumption is false. Usually, more evidence is required to stop a trial because of a benefit than because of harm. Trials are performed to assess safety and efficacy, not to "prove" harm. Therefore, it is unreasonable to make the monitors behave as if they were indifferent to the direction of a treatment difference.

Another weakness of masked monitoring is the stifling effect it has on the analytic processes needed to probe emerging treatment differences. A prudent monitoring committee will not act on a treatment difference without first performing a series of exploratory analyses to see whether the difference can be explained away and whether the results are consistent with what is already known about the treatment in question. Under conditions of masking, these analyses are unfocused and inefficient. Two sets of analyses must be performed: one set deemed reasonable if the difference is in favor of the test treatment and another set deemed reasonable if the difference favors the control treatment.

Once masking has been imposed, even with the understanding that it can be lifted on request, it tends to become permanent. There is a reluctance to request that the masking be removed, because the request itself comes to be seen as heralding recommendations for changing the protocol. The debate about whether to remove the masking can extend over several meetings of the monitoring committee, diverting attention from the more important task of thoughtful and informed monitoring.

There are also more prosaic reasons for being wary of masked monitoring. Masking complicates the preparation of interim reports submitted to monitoring committees and increases the chance of errors in the reports. Information likely to interfere with masking (e.g., treatment-specific side effects or certain laboratory determinations) has to be censored or presented separately from the coded data.

Furthermore, masking is rarely foolproof, even when the necessary precautions are taken. Sophisticated monitors can break the code on the basis of telltale side effects of treatments. Monitors tend to start speculating as soon as treatment differences emerge. The various degrees of certainty among committee members make for contorted dialogue because of the need to behave as if none of the members have broken the code. The nature of the dialogue and interaction required by the masking is at odds with the need for informed, competent monitoring.

If masked monitoring has so little to recommend it, as I have suggested, why is it practiced? One rea-

son concerns the value placed on objectivity in reducing the possibility of treatment-related bias in trials. Masked monitoring has an aura of impartiality. The urge to maintain objectivity in trials is reflected by efforts to mask the processes of treatment administration and data collection for the purpose of preventing treatment-related bias and by the constraints imposed on monitoring to make it more objective (e.g., stopping rules based on P values and restrictions on what the monitors examine and the number of examinations they perform). Another reason, perhaps, is that the route to objectivity is straightforward, through the imposition of rules, whereas the route to competency is much more complicated.

It is imperative that someone be aware of the nature and trend of the results as randomized treatment trials proceed. If the desire to ensure objectivity keeps the investigators from assuming this role, then it should be assumed by fully informed monitoring committees that perform in accordance with ethical principles and to the satisfaction of institutional review boards. The committee members should have the necessary skills and expertise to perform their job and should be free to act without constraint or the prospect of interdiction by the sponsors of the research.

We need to make sure that the drive for objectivity does not lead to trials with triple masking, in which neither the patients, nor the investigators, nor the monitors know what is going on. Institutional review boards and investigators must ensure that the monitoring process is sufficient to protect human subjects.

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