Editorials

The Increasing Incidence of Hepatocellular Carcinoma

PRIMARY hepatocellular carcinoma, one of the most common tumors in the world today, is occurring with increasing frequency in the United States, as shown in the study by El-Serag and Mason in this issue of the *Journal*.[1] The most likely reason for this rising incidence is the spread of hepatitis virus infection in the population. Indeed, there is no better example of a tumor that is associated with persistent viral infection than hepatocellular carcinoma. Two viruses cause almost all these tumors: hepatitis B virus (HBV) and hepatitis C virus (HCV).

The global distribution of hepatocellular carcinoma correlates with the geographic prevalence of chronic carriers of HBV, who number 400 million worldwide. The highest rates are in Southeast Asia and sub-Saharan Africa. In these areas the rates of HBV infection range from 10 to 25 percent and are maintained by vertical transmission of the virus from mothers to infants or infection of children under the age of 10 years by horizontal spread within families.[2] With persistent HBV infection, the risk of hepatocellular carcinoma increases by a factor of 100.[3] Indeed, among those who become infected with HBV at birth, men have an estimated lifetime risk of hepatocellular carcinoma of 50 percent, and women have a risk of 20 percent.[2] These tumors have a poor prognosis, with five-year survival rates of less than 5 percent.

Persistent infection with HCV is also an important risk factor for hepatocellular carcinoma. Four million persons in the United States have chronic HCV infection. The virus is usually transmitted by the parenteral route in adults,[4] and chronic infection develops in approximately 80 percent of persons who are exposed to the virus. Well-known and common modes of transmission include transfusion (before 1991, when screening of blood products for the virus began) and the use of intravenous drugs. The U.S. blood supply is currently safe, because all donors are now screened for antibodies to structural and nonstructural proteins of HCV. Since universal screening began, the risk of HCV infection after transfusion has been substantially reduced — probably to 1 per 100,000 units of blood transfused.[5]

It is noteworthy that up to 50 percent of persons with chronic HCV infection report no exposure to any known risk factor, and the route of infection in these persons is unknown. As is true for HBV, the relative risk of hepatocellular carcinoma among persons with chronic HCV infection and cirrhosis is approximately 100 times the risk in uninfected persons. Persistent HCV infection is the cause of 70 percent of the cases of hepatocellular carcinoma in Japan[4] and approximately 30 to 50 percent of the cases in the United States, with a shift in the peak incidence toward a younger age group. The important role of HCV infection in the development of hepatocellular carcinoma is discussed by El-Serag and Mason.

Some factors in the pathogenesis of hepatocellular carcinoma have recently been defined. Almost all tumors occur in the context of chronic liver-cell injury, inflammation, and increased turnover of hepatocytes. The subsequent regenerative response and fibrosis lead to cirrhosis, which is followed by mutations in hepatocytes and the eventual development of hepatocellular carcinoma. HBV may be involved at multiple steps in this oncogenic process. For example, persistent viral infection causes inflammation, increased cell turnover, and cirrhosis. Furthermore, during the typically long period of infection (10 to 40 years), the HBV genome may be integrated into the chromosomes of hepatocytes. This event causes or contributes to genomic instability as a result of point mutations, deletions, translocations, and rearrangements at multiple sites where the viral genome is randomly inserted into the DNA of the hepatocyte. One of the viral gene products, the HBx protein, activates transcription, and during persistent viral infection, it may increase the expression of growth-regulating genes involved in the malignant transformation of hepatocytes.[2]

How HCV induces hepatocellular carcinoma is unknown. Like persistent HBV infection, persistent HCV infection also initiates inflammation, cellular injury, regeneration, and cirrhosis, all of which may contribute to the oncogenic process. Important to clinical practice was the unexpected and striking finding that 20 to 85 percent of persons with alcoholism — whether or not they have liver disease — have antibodies to structural and nonstructural proteins of HCV, indicating past or ongoing infection. The use of the reverse-transcription–polymerase-chain-reaction assay to detect HCV RNA revealed that 15 to 50 percent of persons with alcoholism and liver disease, particularly those with cirrhosis, were infected with HCV.[4] A study of 7000 persons in northern Italy demonstrated that in people with alcoholism and HCV infection, rapid worsening of the chronic liver disease was followed in turn by cirrhosis and hepatocellular carcinoma.[6] Alcohol abuse impairs cellular immunity and inhibits the efficacy of antiviral therapy with interferon. There is no doubt that patients with chronic HCV infection should not drink alcohol, which will accelerate the liver disease caused by the virus.

Aflatoxins also contribute to the development of hepatocellular carcinoma. These toxic compounds are produced by *Aspergillus flavus* and *A. parasiticus* and contaminate food supplies such as corn, peanuts,

milo, sorghum, and rice in some regions of the world. The liver metabolizes aflatoxins to reactive intermediates that bind selectively to guanine residues in the DNA of hepatocytes. Several studies have demonstrated that aflatoxin B1 induces a specific guanine-to-thymine point mutation in codon 249 of the p53 tumor-suppressor gene.[7] This mutation inactivates the p53 protein, allowing unregulated cellular proliferation, and thereby contributes to the pathogenesis of hepatocellular carcinoma.

Cirrhosis is a very important risk factor for hepatocellular carcinoma. In patients with hemochromatosis, the risk of hepatocellular carcinoma increases by a factor of approximately 200 with the onset of cirrhosis. However, the occurrence of cirrhosis in patients with autoimmune chronic hepatitis, Wilson's disease, primary biliary cirrhosis, or alcohol abuse without coexisting HCV infection increases the risk of hepatocellular carcinoma by a factor of only 2 to 5. The cause of these differences is unknown. Patients with chronic HBV and HCV infection and cirrhosis should be monitored with serum alpha-fetoprotein determinations and ultrasonography of the liver to detect these tumors at an early stage, when surgical resection may be possible. However, it is unclear how often these tests should be performed and whether early detection actually prolongs survival in patients with cirrhosis.

Can we prevent hepatocellular carcinoma? In Taiwan, vaccination of children against hepatitis B reduced the rate of chronic infection from 10 percent to less than 1 percent, and follow-up revealed a striking reduction in the incidence of hepatocellular carcinoma.[8] These results further strengthen the evidence of the role of HBV in the pathogenesis of the disease and indicate that vaccination is essential for its primary prevention. The incidence of hepatocellular carcinoma may be further reduced by eliminating aflatoxin from the food supply in areas of the world where agricultural products are stored under conditions that favor the growth of *A. flavus* and *A. parasiticus.*

Any antiviral treatment that eradicates HBV or HCV infection or inhibits the progression of chronic liver disease to cirrhosis should, in principle, help prevent hepatocellular carcinoma. Treatment with interferon alfa and ribavirin has eradicated chronic HCV infection in some patients,[9,10] and it may lead to a reduction in the incidence of hepatocellular carcinoma in such patients. One study reported a decreased incidence of hepatocellular carcinoma associated with chronic HCV infection after treatment with interferon alfa[11]; however, another recent, prospective trial found no reduction in risk after such therapy.[12] Large, prospective studies are needed before we can draw firm conclusions about the possible protective effects of antiviral treatment against hepatocellular carcinoma. With the development of new and more effective antiviral therapies and the implementation of preventive approaches, it is highly likely that the incidence of one of the most common and devastating tumors in the world can be reduced.

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MANAGEMENT OF SEVERE ULCER REBLEEDING

THE number of patients hospitalized for upper gastrointestinal bleeding from ulcers has decreased substantially in recent years. The decrease reflects a variety of factors: the widespread use of histamine H_2–receptor blockers and proton-pump inhibitors, the eradication of *Helicobacter pylori* in patients with ulcers, and increased awareness among patients with ulcers of the potential dangers of taking nonsteroidal antiinflammatory drugs. Nonetheless, severe upper gastrointestinal bleeding remains a common medical emergency.[1]

In the past two decades, the responsibility for the initial diagnosis and treatment of gastrointestinal bleeding has shifted in most medical centers from general surgeons and radiologists to gastrointestinal endoscopists.[2] The current standard of care is emergency endoscopic diagnosis followed by stabilization

of the patient's condition in a monitored-care unit or intensive care unit and endoscopy to reestablish hemostasis. This approach is used for both esophageal and gastric varices and nonvariceal lesions, such as peptic ulcers.[1-3]

Peptic ulcers account for at least 50 percent of all episodes of severe upper gastrointestinal bleeding. Endoscopy is advocated for the treatment of active bleeding (ranging from persistent oozing to spurting) and nonbleeding visible vessels[4,5] and, in some cases, nonbleeding adherent clots.[1-3] The initial rates of hemostasis exceed 94 percent in most large series in which standardized techniques were used for coaptive thermocoagulation — the compression and welding together of the walls of a blood vessel — of underlying arteries.[1,6,7] However, the rates of recurrent bleeding are substantial, particularly in patients with large or deep ulcers, severe coagulopathies, severe coexisting conditions, hypotension, or bleeding that develops during hospitalization.[1,3,8]

What is the best approach to patients with severe recurrent bleeding after initial endoscopic control of bleeding ulcers? The options are further endoscopic treatment with the same or a different technique, emergency surgery, or elective surgery after the reestablishment of hemostasis by endoscopy.

In a large, randomized trial at a single medical center, Lau et al. studied the first and second options.[9] The results of their comparison of emergency surgery with endoscopic retreatment for recurrent bleeding after initial endoscopic control of hemorrhage are reported in this issue of the *Journal*. Endoscopic retreatment, like the initial treatment, consisted of the injection of epinephrine followed by coaptive thermocoagulation. Retreatment resulted in long-term hemostasis in 73 percent of the patients in this group, but 27 percent required surgery, which resulted in severe postoperative complications in 46 percent. Long-term hemostasis was achieved in 93 percent of the patients who were assigned to surgery after initial endoscopy, but the rate of major complications was significantly higher in this group than in the group assigned to endoscopic retreatment (36.4 percent vs. 14.6 percent).

The study by Lau et al. is particularly important because it was conducted by a very experienced team of endoscopists who are also skilled gastrointestinal surgeons. They were able to enroll a sufficient number of patients at a single center to complete this monumental work. Their initial endoscopic results were very good, and endoscopic retreatment was standardized. Two studies have reported that the use of a combination of epinephrine injections and thermocoagulation for initial endoscopic control of bleeding ulcers yields significantly better results than the use of either treatment alone.[7,10] It is possible that the use of a technique other than thermocoagulation (such as hemoclips, a bipolar probe, or an argon plasma coagulator), with or without epinephrine injection, for endoscopic retreatment[1] might have further increased the rate of long-term hemostasis in the study by Lau et al.

Unlike the standardized approach used for endoscopic treatment, the types of surgery used in the study varied and were presumably related to the experience of the surgeons as well as to the anatomical findings in individual patients. Whether endoscopic retreatment of patients in the surgical group in whom surgery was unsuccessful would have averted the need for surgical retreatment and reduced the complication rate was not addressed.

How generalizable are their results? The patients studied by Lau et al. — elderly men and women with severe recurrent bleeding, other serious conditions, high rates of bleeding during hospitalization, and large ulcers — were similar to those treated throughout the world.[1-10] The rates of prevalence of *H. pylori* infection, use of nonsteroidal antiinflammatory drugs, and coagulopathy were also similar to those in other studies. Whether other groups of gastrointestinal surgeons would have had better or worse results in similar patients is unknown, since emergency surgery is particularly risky in such patients.[11,12]

What are the broader implications of this study? First, among patients with severe bleeding ulcers, the overall rate of recurrent bleeding after initial endoscopic treatment with epinephrine injections and thermocoagulation was low, only 8.7 percent. This rate was lower than the rates of 15 to 25 percent reported with the use of epinephrine injections or thermocoagulation alone in other analyses, including meta-analyses.[1-10] Second, treatment should be administered by a skilled gastrointestinal endoscopist. However, endoscopic treatment is not successful in a substantial minority of patients. Thus, there is a need for better techniques or devices. Third, endoscopic retreatment with epinephrine injections and thermocoagulation was associated with a higher rate of ulcer perforation than was the initial endoscopic treatment (4.2 percent vs. 1.1 percent), but the overall rate of complications was still much lower in this group than in the surgery group.

It will become increasingly difficult to train surgeons to perform emergency surgery for bleeding ulcers and to maintain these skills, because fewer and fewer such operations are being performed. In contrast, the ability to train gastrointestinal endoscopists and for them to increase their proficiency has improved because they are the ones who now care for most such patients. With respect to the cost of the two approaches, my colleagues and I recently reported that successful endoscopic therapy was considerably less expensive than emergency surgery for patients with bleeding ulcers.[8,13] Moreover, most patients prefer endoscopic therapy to surgery as the

initial or subsequent treatment for the emergency control of gastrointestinal hemorrhage.[1-3,6,8]

How can the equipment or techniques used for the endoscopic control of bleeding ulcers be improved? One suggestion is to ligate the underlying artery during endoscopy.[1] Another is to use Doppler ultrasonography to guide additional endoscopic therapy until no blood flow is detected in the artery.[1] There may also be a role for a third endoscopic treatment in selected patients with recurrent bleeding from an ulcer. In addition, monitoring the pH and maintaining a neutral pH may be important. Lau et al. administered relatively high doses of proton-pump inhibitors but did not monitor the pH. Finally, the role of elective surgery after endoscopic retreatment should be evaluated. In some studies, preemptive elective surgery in high-risk patients decreased the rates of recurrent bleeding, morbidity, and mortality.[11,12] Clearly, the last chapter in the treatment of bleeding ulcers has yet to be written.

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MANAGING PSYCHOSIS IN PATIENTS WITH PARKINSON'S DISEASE

MANAGING psychosis is one of the most difficult challenges in the care of patients with Parkinson's disease. This complication occurs in 10 to 15 percent of such patients and consists of visual hallucinations, the belief that one is being persecuted, fears of personal endangerment, or feelings of being followed, spied on, or threatened.[1,2] Psychosis is a major source of distress for patients. It exacerbates the burdens of family members and is associated with earlier transfer to nursing homes and increased mortality.[3]

In managing psychosis in patients with Parkinson's disease, clinicians face a "motion–emotion" conundrum. The dopaminergic drugs that can improve the motor disability caused by Parkinson's disease are associated with the emergence of symptoms of psychosis; conversely, the use of conventional neuroleptic drugs to reduce psychosis exacerbates parkinsonism. This problem remained unresolved until the recent development of atypical antipsychotic drugs that can control psychotic symptoms without producing extrapyramidal disturbances. The article by the Parkinson Study Group in this issue of the *Journal*[4] demonstrates that low doses of the atypical antipsychotic drug clozapine improve psychosis in patients with Parkinson's disease without exacerbating the motor disability caused by parkinsonism.

In a randomized, double-blind, parallel-group study of 60 patients with Parkinson's disease and psychosis, treatment with clozapine was associated with global improvement and reduced symptoms of psychosis, as assessed with the Brief Psychiatric Rating Scale and the Scale for the Assessment of Positive Symptoms. There were no deleterious effects with respect to parkinsonism, and tremor was significantly improved in the group receiving clozapine. In the clozapine group there were reductions of approximately 25 percent in the scores on the psychosis scale, as compared with 5 percent in the placebo group; thus, although their psychosis improved, the patients continued to have some residual symptoms.

The study group was reasonably typical of patients with Parkinson's disease and psychosis. All the patients had either new-onset psychosis or recent worsening of symptoms. Patients who had received an antipsychotic drug within three months before the study began were excluded. Adjustments of the dosage were allowed until the final week of the study; the mean final dose was approximately 25 mg daily, with a range of 6.25 to 50 mg. The study also demonstrated that clozapine did not impair cognitive function; scores on the Mini–Mental State Examination remained unchanged in both groups.

This report describes an important advance in our

ability to treat one of the most disabling conditions encountered in patients with Parkinson's disease. Physicians now have better options for the management of the parkinsonian motor syndrome in patients with advanced disability, those in whom psychosis is most likely to occur. The addition of clozapine may allow some patients to continue living at home for longer periods and will facilitate the care of many of those living in nursing homes.

Psychosis associated with Parkinson's disease most often occurs in patients who are older, who have more advanced disease, and who manifest greater cognitive impairment.[1,2] Although psychosis is rare in patients with Parkinson's disease before they begin to use dopaminergic drugs, the dose of levodopa is not greater in those with psychosis than in those without it.[2] Moreover, intravenous administration of levodopa in patients prone to have hallucinations does not exacerbate the hallucinatory events.[5] These observations suggest that restoring the dopaminergic function of the central nervous system may permit but does not cause psychosis.

Patients with Parkinson's disease and dementia who are at risk for psychosis have atrophy of the nucleus basalis and a cortical cholinergic deficiency.[6] The cholinergic deficiency or the interaction between the cholinergic deficiency and dopaminergic drugs may create the cerebral conditions required for the emergence of psychosis. Dementia with Lewy bodies, an increasingly recognized disorder characterized by parkinsonism, dementia, visual hallucinations, and fluctuating cognition, is also distinguished by cholinergic deficiency,[7] and a deficit in cholinergic function appears to contribute to psychosis in patients with Alzheimer's disease.[8] Thus, several degenerative disorders with overlapping clinical manifestations share the common neurochemical substrate of a deficiency of cholinergic function.

Atypical antipsychotic drugs are characterized by less dopamine D2-receptor antagonism and more serotonin 5-HT_2–receptor antagonism than classic neuroleptic drugs.[9] The lower D2-receptor occupancy or the altered balance between dopaminergic and serotonergic antagonism results in preserved or improved antipsychotic potency, with a reduction in extrapyramidal symptoms — parkinsonism, dystonia, and tardive dyskinesia.

Side effects must be carefully monitored when atypical antipsychotic drugs are used. Sedation is a common problem, and clozapine induces agranulocytosis in 0.6 to 1.2 percent of patients. This complication can be fatal if not discovered early and requires weekly monitoring of white-cell counts for the first six months of therapy and evaluations every other week after that.[10] The Parkinson Study Group found that low doses of clozapine (average dose, approximately 25 mg per day) are sufficient to control psychosis in patients with Parkinson's disease. This dose is markedly lower than that typically used to treat psychosis in patients with schizophrenia (500 mg per day or more), and clinicians must adjust their prescribing practices to avoid excessive sedation and other side effects in patients with Parkinson's disease. Atypical antipsychotic drugs are substantially more expensive than conventional neuroleptics; these costs may be offset by the savings realized by reducing hospital stays resulting from aspiration pneumonia, decubitus ulceration, and falls and fractures, all of which are associated with the use of conventional neuroleptic drugs.

Additional atypical drugs with less demanding requirements for surveillance may also be useful in treating psychosis in patients with Parkinson's disease, but they have not been subjected to the same rigorous study as that reported for clozapine by the Parkinson Study Group. Other atypical drugs that are available and possibly useful in the management of psychosis in these patients are olanzapine, quetiapine, and risperidone. These drugs vary in the degree of D2-receptor antagonism, and their usefulness in treating psychosis in patients with Parkinson's disease without worsening parkinsonism is expected to vary.

The ability to control delusions and hallucinations without compromising motor function is a great advance in improving the lives of patients with Parkinson's disease. The use of clozapine in the management of psychosis in these patients represents another example of improved patient care resulting from progress in neuroscience. The public that has consistently supported basic scientific research is reaping the benefits of increased understanding of brain function and an improved ability to intervene in brain disorders so as to increase function and enhance the quality of life. The study by the Parkinson Study Group also illustrates the growing interface between neurology and psychiatry. In this case, drugs developed for the treatment of a psychiatric condition, schizophrenia, have an important role in treating psychosis in patients with neurologic disease. Conversely, the study of psychosis in patients with Parkinson's disease should contribute to our knowledge about the neurobiologic basis of delusions and hallucinations. As neuropsychiatric disorders are increasingly studied, an understanding of the neurobiology of human behavior and emotion may begin to emerge.

Ultimately, it is the individual patient who benefits from the development of new treatments. Drug development is expensive, labor intensive, and slow. It is worthwhile, however, when it provides the clinician with a new option to relieve a patient's delusional fear that he or she is in danger of being kidnapped or killed, without reducing the patient to the bed-bound, trembling state characterized by severe parkinsonism. Physicians now have a well-proved addition to their armamentarium of treatments that can drive away the demons and improve the well-

being and quality of life of patients with Parkinson's disease.

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POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

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Sounding Board

Is Informed Consent Always Necessary for Randomized, Controlled Trials?

CONSIDER this paradox: if a physician reads a case report about a novel method of ventilation for critically ill patients and wants to try it in the next several patients with respiratory failure he or she treats, the physician may do so provided the patients have given general consent for treatment. On the other hand, if a physician is interested in performing a randomized, controlled trial to determine rigorously which of two widely used antibiotics is more effective at treating bronchitis, he or she must prepare a formal protocol, obtain approval from the institutional review board, and seek written informed consent from potential participants. In each case, the physician is performing an experiment. In each case, there is uncertainty about the best way to treat the patient. Yet in the context of clinical care, the experiment can be done with virtually no external scrutiny, whereas in the context of a clinical trial, the experiment is prohibited unless substantial hurdles are overcome. This is true even when the experimental therapy (e.g., a promising but risky method of ventilation) involves risks that are unknown or substantially different from those of the alternatives.

To put it another way, physicians can do almost anything they want in the name of therapeutic innovation, but only if there is no attempt to gain systematic knowledge from the intervention. Or, to paraphrase Smithells, "I need permission to give a new drug to half my patients but not to give it to all of them."[1] In this article we argue that the current approach to informed consent is at least partially off target, in that patients are often "protected" from clinical trials under circumstances in which the risks associated with participation in the trial are virtually nil, but they receive no protection from physicians who want to experiment with new treatments in the name of therapeutic innovation.

The reasons for the current approach are not mysterious. In a simplistic sense, all medical interventions may be characterized as either therapy or research. Research differs from therapy in many important ways. The goal of research is to gain new knowledge, and any benefits from the research are reaped primarily by future patients. The aim of therapy is to benefit the patient at hand. These differences have predictably led to an elaborate process designed to protect patients involved in clinical trials, whereas minimal constraints are placed on physicians providing clinical care.

This emphasis on protecting subjects during research should not be surprising. Since the Nuremberg trials, society has been wary of the conflict of interest that is present in all research — that the interests of the current patient may be sacrificed to other interests, such as those of future patients or even those of the investigators. Indeed, the distrust of society seems justified, because even after the adoption of the Nuremberg Code[2] and the Declaration of Helsinki,[3,4] examples of abuse in the conduct of research have been documented throughout the world.[5]

An analysis of the goals of informed consent can provide insight into the paradox described above. Informed consent is either general or specific. A patient gives general informed consent for treatment as part of the process of establishing a fiduciary relationship with a physician. Specific informed consent is necessary whenever the proposed intervention involves a high risk–benefit ratio, either in an absolute sense or in comparison with the alternatives, or whenever the preferences or values of the patient are relevant to the decision at hand. The distinction between these two tiers of informed consent is illustrated by the fact that physicians typically order routine tests and prescribe standard medications under the general consent for treatment but obtain specific consent before undertaking a major diagnostic or therapeutic procedure, before prescribing a potentially toxic medication, or whenever a patient's values and preferences would be expected to have a substantial influence on the clinical course chosen.

We suggest that the obligation to seek specific consent for research should likewise depend on the risk–benefit ratios of the intervention and the alternatives as well as the degree to which the patient would be expected to have preferences about the various options for diagnosis or treatment that are under investigation. We believe that as with clinical care, in the case of many randomized, controlled trials, the patient's participation can and should be considered to be authorized by his or her general consent for treatment and that specific consent should not be required.

Consider, for example, a hypothetical trial comparing two similar cephalosporins for preoperative prophylaxis. Both are widely used, but they differ markedly in cost, and their comparative efficacy in preventing wound infections is unknown. If both drugs have been in use long enough that their side-effect profiles are known to be similar, patients are unlikely to prefer one medication over another; it is also unlikely that the process of obtaining specific consent would serve the patient in any meaningful way. Other examples of this type of study are a randomized trial to assess whether low-dose heparin increases the longevity of intraarterial catheters in the intensive care unit, a randomized trial of two brands of antacid to control gastric acidity, and a randomized comparison of two methods of mechanical ventila-

tion to determine which method results in more rapid resumption of spontaneous, unassisted breathing. These hypothetical trials share several characteristics, which we have integrated into the following proposed criteria for determining whether the requirement of informed consent for a randomized, controlled trial can be waived.

First, informed consent should not be waived unless all the treatments offered in the trial could be offered outside the trial without the specific informed consent of the patient. This is often the case when a trial is comparing two therapies that are already in use or when an existing therapy or drug is being used for a new indication. In the hypothetical trials described above, the specific informed consent of the patient would thus not be required for any of the options being offered.

Second, the treatments should not involve more than minimal additional risk in comparison with any of the alternatives.[6] When the risks associated with each of the options are assumed to be similar, the patient could be treated outside the trial with any one of the interventions under study. Again, the examples we cited could meet this requirement. Of course, physicians would exclude a patient for a justifiable medical reason — for example, if the patient were known to be allergic to one of the medications being studied.

Third, genuine clinical equipoise must exist among the treatments. This state of balance is, of course, a general ethical requirement before a randomized, controlled study can be undertaken. There should be honest uncertainty about which treatment is superior.[7] If the informed consent of the patient is judged unnecessary, investigators have an even greater burden of proof to ensure clinical equipoise.

Fourth, no reasonable person should have a preference for one treatment over any other, regardless of the differences between the treatments being compared. This standard would cover not only the direct effects of the intervention being studied but also the indirect effects associated with research, such as whether the study would require extra visits to the clinic or other inconveniences.

Although the reasonable-person standard is widely used in the law, it is far from perfect.[8] For example, there is always the possibility that a patient may be unusual in ways that cannot be anticipated and that would lead the patient to have an unanticipated preference for one treatment over another. This problem arises with both general and specific informed consent, however, and cannot be addressed solely by demanding more rigorous standards for research.

The validity of the reasonable-person standard depends in large part on how it is implemented. We propose that studies for which a waiver of informed consent is requested should, like all other studies, be submitted to an institutional review board for review and approval. The institutional review board would therefore assume responsibility for applying the standard. Because an important function of the institutional review board is to ensure the involvement of the community through the representation of people without medical backgrounds, the board would be in the best position to apply the reasonable-person standard and to determine whether the informed-consent requirement could be waived.

How should the reasonable-person standard be applied with reference to the community in which the research is being performed? Since the abuses of the Tuskegee syphilis study, members of racial minority groups have been particularly sensitive to the implications of being involved in research without their consent.[9] Although we believe that exemptions to informed consent should be considered only when potential subjects would have no reason to decline participation, we recognize that for some the refusal to participate in research may not be related to the pertinent facts of a particular study but, rather, may be based on important historical and cultural issues of concern. Depending on the community and the context of the research, these issues may be grounds for insisting on specific informed consent for participation in the research.

Fifth, patients should be informed that the institution or clinical setting in which they are being treated uses the standards that we have described as guidelines for determining the need for specific instead of general informed consent. Thus, patients would have the opportunity to obtain additional information about the policy or to seek care elsewhere.

These criteria for the waiver of informed consent should be interpreted narrowly and applied conservatively. For example, a trial comparing a beta-blocker with an angiotensin-converting–enzyme inhibitor for treatment of hypertension should not be approved for a waiver of informed consent, because of the substantially different side effects of the two classes of drugs. Similarly, comparisons of medical treatments and surgical interventions should always require specific informed consent, even if the outcomes are presumed to be similar, because of the probable relevance of patients' preferences to the decision. Finally, specific informed consent should be required whenever a study compares therapies that involve a trade-off between efficacy and safety, as would be the case in a trial of the use of an anticoagulant to reduce the morbidity associated with strokes. This decision requires the balancing of benefits against qualitatively dissimilar risks, necessitating the involvement and specific consent of the patient.

Our arguments may also have important implications for studies that fall under the heading of quality improvement.[10] Consider, for example, a study that seeks to identify the more effective disinfectant hand soap by using one brand for patients in one hospital

ward and a different brand for patients in another, with nosocomial infection rates as the outcome measure. The patients are to be randomly assigned to the wards. Should specific informed consent be sought from the patients enrolled in the study? If so, then what should be done if a patient chooses not to participate? (Should he or she be transferred to another ward, or should data not be collected on that patient?) Our criteria may be useful in determining the need for specific informed consent in a context such as this one.

Our arguments pull in two different directions. Greater respect for the autonomy of patients means that many experiments that are currently undertaken in the context of clinical care under the guise of therapeutic innovation should be subject to much greater scrutiny. Such a shift in thinking would have far-reaching consequences, from changing the way that surgeons approach consent for the use of new techniques in the operating room to altering the way that physicians prescribe drugs for indications for which they have not been approved by the Food and Drug Administration (FDA).

Yet we have argued that specific informed consent should not be mandatory for all randomized, controlled trials. Although this idea has been proposed before,[11-14] many will nevertheless find it objectionable. They may argue that it backtracks from crucial elements of human rights at a time when we need to be as vigilant as possible and that essential principles enunciated at Nuremberg and Helsinki must not be compromised under any circumstances. Furthermore, they may claim that informed consent is an essential protection against the exploitation of patients by research investigators. These are important objections.

In response, our proposal should serve as a reminder that the process of informed consent is not a goal or ideal in itself. Rather, informed consent is important because it is frequently essential for ensuring that the patient's right to self-determination is respected. Our proposal not only supports this important objective but also provides grounds for criticizing the inappropriate use of what are termed therapeutic innovations without the specific informed consent of the patient.

There is little evidence to support the claim that informed consent, as currently practiced, provides protection against the exploitation of patients in research. Studies have shown that patients rarely demonstrate an adequate understanding of consent forms[15-17] and often do not even understand the meaning or implications of randomization.[18,19] The most effective protection against exploitation comes not from the process of informed consent but, rather, from the careful oversight and scrutiny of conscientious institutional review boards. Boards that approve questionable studies on the assumption that the informed-consent process will protect research subjects against abuse abrogate their responsibility to defend patients against unethical research. Our proposal recognizes and emphasizes the essential role of institutional review boards in this regard.

In addition, there is a price that is paid when one insists on specific informed consent for all randomized, controlled trials. Many worthwhile studies will not be conducted if investigators are required to obtain specific informed consent. Many small but meaningful improvements in the quality of care will not occur if clinicians are forced to engage every patient in a dialogue about informed consent, especially when there is no reason to believe that the patient would have any preference regarding participation in the research. When unnecessary roadblocks prevent the easy evaluation of the comparative efficacy of new forms of technology and new interventions, these innovations tend to be adopted uncritically into practice.[20] And this result is unfortunate, given that many of them would probably be found worthless or even harmful if subjected to formal evaluation in a clinical trial.

These clinical and practical realities were recently acknowledged in the United States with regard to research under emergency conditions. For many years, research on emergency treatments was virtually paralyzed by the impossibility of obtaining informed consent from the subjects. For new therapies, such as the administration of hemoglobin substitutes in severe trauma and of thrombolytic agents in acute myocardial infarction, or new methods of performing cardiopulmonary resuscitation, systematic clinical trials could not be undertaken. In 1996, the FDA and the Department of Health and Human Services endorsed a waiver of informed consent for this type of research under certain clearly defined conditions. Although they acknowledged the importance of informed consent to medical practice, these agencies endorsed the waiver on the grounds that it would allow desperately ill patients access to new therapies and would result in important benefits to future patients.[21] The agencies recognized that without the waiver, this important work would never be done.[22]

We believe that the same rationale supports our proposal against the anticipated objections of those who prefer to see no exceptions made to the doctrine of informed consent. When benefits to society and to future patients can be gained without meaningfully compromising respect for patients' autonomy and without any serious increase in risk to those involved, blind insistence on informed consent is not only unnecessary, but also harmful.

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