THE NATURE OF ADVERSE EVENTS IN HOSPITALIZED PATIENTS

Results of the Harvard Medical Practice Study II

LUCIAN L. LEAPE, M.D., TROYEN A. BRENNAN, M.D., J.D., M.P.H., NAN LAIRD, PH.D., ANN G. LAWTHERS, SC.D., A. RUSSELL LOCALIO, J.D., M.P.H., BENJAMIN A. BARNES, M.D., LIESI HEBERT, SC.D., JOSEPH P. NEWHOUSE, PH.D., PAUL C. WEILER, LL.M., AND HOWARD HIATT, M.D.

Abstract *Background.* In a sample of 30,195 randomly selected hospital records, we identified 1133 patients (3.7 percent) with disabling injuries caused by medical treatment. We report here an analysis of these adverse events and their relation to error, negligence, and disability.

Methods. Two physician-reviewers independently identified the adverse events and evaluated them with respect to negligence, errors in management, and extent of disability. One of the authors classified each event according to type of injury. We tested the significance of differences in rates of negligence and disability among categories with at least 30 adverse events.

Results. Drug complications were the most common type of adverse event (19 percent), followed by wound infections (14 percent) and technical complications (13 percent). Nearly half the adverse events (48 percent) were associated with an operation. Adverse events during surgery were less likely to be caused by negligence (17 percent) than nonsurgical ones (37 percent). The proportion of adverse events due to negligence was highest for diagnostic mishaps (75 percent), noninvasive therapeutic mishaps ("errors of omission") (77 percent), and events occurring in the emergency room (70 percent). Errors in management were identified for 58 percent of the adverse events, among which nearly half were attributed to negligence.

Conclusions. Although the prevention of many adverse events must await improvements in medical knowledge, the high proportion that are due to management errors suggests that many others are potentially preventable now. Reducing the incidence of these events will require identifying their causes and developing methods to prevent error or reduce its effects. (N Engl J Med 1991; 324:377-84.)

IN recent years, concern about the increasing cost of malpractice-insurance premiums has led to numerous tort reforms. At the same time, and largely independently of tort reform, interest in initiatives affecting the quality of care has grown. Curiously, however, the problem of medical injury has received comparatively little attention from either perspective. But an important objective for those concerned with both medical malpractice and quality of care is the prevention of iatrogenic injury. A first step in prevention is to develop a better understanding of the types of such injuries and their causes.

In our investigation of accidental injury in patients hospitalized in 1984 in the state of New York, we found that 3.7 percent of patients had injuries and that negligent care was responsible for 28 percent of them.[1] In this report we analyze these injuries, including the types of adverse events, the types most likely to result in serious disability, the types most likely to be caused by negligence, the effects of various risk factors, and the management errors that were responsible. Finally, we develop a conceptual framework encompassing notions of negligence, error, and preventability in an effort to understand iatrogenic injury better.

METHODS

The study design, sampling plan, and record-review process have been described elsewhere.[2] In brief, we evaluated 30,195 randomly selected records in 51 hospitals in the state of New York, using a two-stage process. All records were screened by trained nurses or medical-records administrators using 18 screening criteria. Records that met any of our criteria were then reviewed independently by two physicians who identified adverse events and instances of negligence. We defined an adverse event as an unintended injury that was caused by medical management and that resulted in measurable disability. Negligence was defined as failure to meet the standard of care reasonably expected of an average physician qualified to take care of the patient in question.

We asked the reviewers to describe each adverse event and its relation to medical care and to estimate the degree of disability that resulted. Disability was rated on a six-point scale[1] on which "serious" disability was defined as that persisting for more than six months (a score above 2 on the 6-point scale). When the two physicians disagreed, we randomly selected one of their two reviews in order to assign a single disability score to each patient. (The reviewers disagreed in 4 percent of the cases about whether the disability score was greater than 2.) The reviewers also identified the site inside or outside the hospital where the treatment that had caused the adverse event had taken place. In addition, the reviewers were asked to indicate whether each adverse event could have been caused by a reasonably avoidable error, defined as a mistake in performance or thought. If so, they classified the error, and if more than one class of error was found, they ranked the errors in order of seriousness. They then indicated the specific type of error within the class. Finally, the reviewers determined whether there had been negligence after they considered and recorded whether there had been deviation from accepted norms of treatment, the potential (not actual) consequences of the negligence, the frequency of risk, the degree of emergency, the complexity of the case, the presence of any coexisting conditions, and the extent to which there was a consensus about the correct therapy or diagnosis for a given situation. If they found negligence, they rated its severity on a three-point scale on which 1 indicated a slight degree of negligence, 2 a moderate degree, and 3 a grave degree.

Each adverse event was subsequently classified with regard to type of injury by one of the authors after reading the descriptions of each case prepared by both physician-reviewers. An adverse event was considered an operative complication if it occurred within the first two weeks after surgery or if it was thought to have been caused by the operation, regardless of when it occurred. Operative complications were subclassified as technical (e.g., injury occurring during an operation, bleeding, or difficulty with wound healing), nontechnical (e.g., pulmonary embolism, myocardial infarction, and pneumonia), related to wound infections, caused

From the Departments of Health Policy and Management (L.L.L., A.G.L., A.R.L., B.A.B., L.H., J.P.N., H.H.) and Biostatistics (N.L.), Harvard School of Public Health; the Department of Medicine, Brigham and Women's Hospital (T.A.B., H.H.); and Harvard Medical School (T.A.B., J.P.N.), all in Boston; and Harvard Law School, Cambridge, Mass. (P.C.W.). Address reprint requests to Dr. Leape at the Harvard School of Public Health, 677 Huntington Ave., Boston, MA 02115.

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by surgical failure (to cure, relieve, or prevent symptoms, such as pregnancy after tubal ligation), or late (bad results and delayed complications).

Nonoperative categories of injuries included those that were related to a procedure (which were further classified in the same manner as the operative complications), diagnostic mishaps (injuries that resulted from an improper or delayed diagnosis), therapeutic mishaps (injuries resulting from complications of noninvasive therapy), and those related to drugs. The last were treated separately because of the number and importance of drug reactions. We also established separate categories for fractures, injuries related to anesthesia, postpartum injuries, and neonatal injuries, because of the unique nature of the adverse events in these groups. Because we were concerned about all types of adverse events in hospitalized patients, not only those caused by physicians, we also established separate categories to include falls and system errors, two categories of adverse events that may be more likely to be caused by nursing or support personnel.

We oversampled patients in several high-risk, low-volume specialties, such as neurosurgery and vascular surgery, to ensure that there were adequate numbers in each category of injury. To project the numbers in the sample to those of the entire population, we used weights for all our analyses. Thus, the percentages given do not correspond directly to the numbers in the sample. The final determination of the occurrence of an adverse event or case of negligence was based on a calculation of the average of the two reviewers' scores.

The significance of the differences in the rates of negligence and disability between categories of adverse events and locations was tested for the categories in which there were at least 30 adverse events. Standard errors were computed for the difference between the rate of negligence or disability in the category studied and that in all other categories combined, with use of the SESUDAAN package of the Research Triangle Institute[3] to adjust for the complex sample design and the Bonferroni procedure for simultaneous inferences.[4]

Table 1. Types of Adverse Events and Proportion of Events Involving Negligence.

Type of Event	No. of Events in Sample	Weighted Proportion of Events*		
		In population	Due to negligence	With serious disability
		percent		
Operative				
Wound infection	160	13.6	12.5†	17.9
Technical complication	157	12.9	17.6	12.0†
Late complication	137	10.6	13.6‡	35.7
Nontechnical complication	87	7.0	20.1	43.8
Surgical failure	58	3.6	36.4	17.5
All	599	47.7	17.0	24.0
Nonoperative				
Drug-related	178	19.4	17.7‡	14.1‡
Diagnostic mishap	79	8.1	75.2†	47.0‡
Therapeutic mishap	62	7.5	76.8†	35.4
Procedure-related	88	7.0	15.1	28.8
Fall	20	2.7	—	—
Fracture§	18	1.2	—	—
Postpartum¶	18	1.1	—	—
Anesthesia-related	13	1.1	—	—
Neonatal	29	0.9	—	—
System and other	29	3.3	35.9	36.0
All	534	52.3	37.2	25.3
Total	1133	100.0	27.6	24.7

*Dashes denote categories for which there were too few observations to determine a percentage.

†$P<0.001$ for the difference between this rate and all others in the same column.

‡$P<0.01$ for the difference between this rate and all others in the same column.

§Includes nonoperative fractures only.

¶Includes noncesarean deliveries only.

Results

Adverse Events

As reported elsewhere, we identified 1133 adverse events in our sample of records for 30,195 patients hospitalized in New York in 1984.[1] Table 1 lists the distribution of the kinds of adverse events and negligence-related adverse events we discovered. Nearly half the adverse events (48 percent) resulted from operations. Wound infections were the most common surgical adverse event, accounting for 29 percent of surgical complications and nearly one seventh of all adverse events identified in the study.

Drug complications were the most common single type of adverse event (19 percent). Table 2 lists the classes of drugs responsible for adverse events in the order of their frequency, and Table 3 shows the various types of adverse events caused by drugs. These events covered a broad spectrum, from those that were unpredictable and unpreventable, such as allergic reactions to drugs to which the patient had had no known previous exposure, to those that might have been unavoidable, such as marrow depression from antitumor drugs, to those that resulted from errors in administration or monitoring, such as bleeding associated with the use of anticoagulant agents.

Negligence

Overall, 28 percent of the adverse events were judged to have resulted from negligent care, but there was wide variation among categories (Table 1). Seventeen percent of the adverse events related to operations were due to negligence, ranging from 13 percent of the wound infections to 36 percent of the surgical failures (e.g., persistent back pain that responded to a second operation to remove a disk that had been treated inadequately in a previous laminectomy). Of the adverse events due to drug treatment, 18 percent resulted from negligence. By contrast, negligent care was identified as causing 75 percent of the adverse events due to problems in diagnosis (such as failure to diagnose an ectopic pregnancy) and 77 percent of those due to a therapeutic mishap (resulting from non–drug-related, noninvasive treatment).

Disability

The large majority of the adverse events did not result in serious disability. More than half the patients had minimal impairment, recovering completely in a month or less. Seventy percent recovered completely in less than six months.[1] Rates of serious disability were significantly lower than average for technical complications of surgery (12 percent) and drug-related adverse events (14 percent), and significantly higher than average for diagnostic mishaps (47 percent) (Table 1).

Effects of Age

We noted previously that patients over the age of 64 had adverse events and negligence-related adverse events at rates more than double the rate of patients under 45, and although only 27 percent of the hospi-

Table 2. Drug-Related Adverse Events, According to Class of Drug Involved.

Drug Class	No. of Events	Weighted Percentage
Antibiotic	29	16.2
Antitumor	31	15.5
Anticoagulant	20	11.2
Cardiovascular	13	8.5
Antiseizure	15	8.1
Diabetes	8	5.5
Antihypertensive	10	5.0
Analgesic	6	3.5
Antiasthmatic	5	2.8
Sedative or hypnotic	4	2.3
Antidepressant	1	0.9
Antipsychotic	2	0.7
Peptic ulcer	1	0.5
Other	33	19.3
Total	178	100.0

talized population in New York in 1984 was over 64, those patients accounted for 43 percent of all the adverse events.[1]

Table 4 shows the frequency of each type of adverse event per 1000 discharges from the hospital in each of four age categories, based on the weighted number of patients in each age group in the sample. Drug-related complications were the most common type of adverse event for patients in all age groups, except those 16 to 44 years old, among whom drug complications ranked second to wound infections. Elderly patients were next most likely to have adverse events from noninvasive therapeutic mishaps and late surgical complications. Wound infections were the most frequent type of adverse event in young adults. Children had the lowest rates in every category.

Surgical failures constituted a much higher fraction of the total number of adverse events in young adults than in the other age groups. The operations most commonly associated with such failures were tubal ligation, procedures for back problems, tendon repair, meniscus repair, excision of pilonidal cysts, nasal reconstruction, cervical cerclage, and repair of tibial fractures — operations that are seldom performed in elderly patients or children.

Most other types of adverse events were more common among elderly patients. In the elderly, four classes of events occurred two or more times as often as was observed in younger patients: nontechnical postoperative complications, noninvasive treatment mishaps, fractures, and falls. The increased rates may reflect more frequent use of interventions, as well as increased risk of an adverse event with a given condition or treatment. For example, the elderly may have more noninvasive treatments per hospitalization than younger people.

Site of Adverse Events

The largest number of adverse events (41 percent) resulted from treatment provided in the operating room (Table 5). The next most frequent (27 percent) were those that occurred in the patient's hospital room. The emergency room, intensive care units, and labor and delivery rooms were each the site of approximately 3 percent of the adverse events. The number of events occurring in all other locations in the hospital added up to 5 percent of the total. Most adverse events occurring outside the hospital were attributed to interventions in the physician's office. (The only out-of-hospital adverse events measured in our study were those that resulted in hospitalization.)

Table 5 also shows the percentage of adverse events at each site that were caused by negligent care — an overall proportion of 28 percent. In the operating room the proportion was 14 percent, in the patient's hospital room it was 41 percent, and in the emergency room it was 70 percent. The differences at other sites were not significant. Rates of disability also varied according to site. The percentage of patients with serious disabilities was significantly lower than average in the case of adverse events occurring at home (8 percent) or in the labor and delivery room (10 percent). Other differences were not significant.

Physicians' Errors

The classification of errors is shown in Table 6, which includes the first choices of each reviewer. Because two physicians reviewed almost every case, the total number of observations shown is nearly double the number of cases for which there was a question of error. The physician-reviewers used their own criteria to identify errors in management, and they were asked to list the errors whether or not negligence was involved. They identified one or more management errors corresponding to 58 percent of all the adverse events, but only 28 percent of the events ultimately met our requirements for a judgment of negligence. For each class of error, the percentage of cases that were ultimately attributed to negligence is shown in Table 6.

The most common class of error, accounting for 35 percent of all the errors in this series, involved the performance of a procedure or operation. Errors in prevention (i.e., failure to take preventive measures)

Table 3. Types of Drug-Related Complications.

Type of Complication	No.	Weighted Percentage
Marrow suppression	29	16.3
Bleeding	26	14.6
Central nervous system	26	14.6
Allergic/cutaneous	25	14.0
Metabolic	18	10.1
Cardiac	17	9.6
Gastrointestinal	14	7.9
Renal	12	6.7
Respiratory	5	2.8
Miscellaneous	6	3.4
Total	178	100.0

were the next most common (22 percent), followed by diagnostic errors (14 percent). Errors in diagnosis and prevention were the most likely to be considered negligent (75 percent and 60 percent involved negligence, respectively). Thus, errors in performance were the most common but the least likely to be attributed to negligence. In contrast, diagnostic errors, though much less common, were very likely to be attributed to negligence.

Types of Error

Because the reviewers were asked to list all the types of error they found, the numbers shown in Table 7 for each class are higher than those in Table 6. In addition, since the reviewers were not limited to assigning a single category to each error, the percentages exceed 100.

Although technical errors were the most common class of error observed, the sum of the various types of "errors of omission" composed a higher percentage of the total in several classes. These included failure to take precautions to prevent accidental injury, avoidable delays in treatment, failure to use indicated tests or to act on the results of such tests, and the entire gamut of diagnostic errors.

Disability as a Function of the Gravity of Negligence

Adverse events resulting from negligence were more likely than other adverse events to lead to serious disability, defined as a disability with a score greater than 2 (Table 8). Only 20 percent of the patients who had adverse events not attributed to negligence had serious disabilities, whereas 38 percent of those who had adverse events due to negligence had such disabilities.

The percentage of adverse events resulting in serious disability increased progressively with the gravity (severity) of the negligence. Nearly three fourths of the patients who had adverse events attributed to grave negligence (grade 3) had serious disabilities. Two thirds of these patients died, as compared with 10 percent of the patients with adverse events not resulting from negligence.

Table 4. Rates of Adverse Events According to Age.

Type of Event	Age (yr)*			
	0–15	16–44	45–64	≥65
	events per 1000 discharges			
Operative				
Wound infection	1.77	4.93	6.59	6.15
Technical complication	1.70	3.77	8.25	5.34
Late complication	1.01	2.40	5.17	6.77
Nontechnical complication	0.20	1.33	2.97	5.46
Surgical failure	0.39	2.22	0.84	1.22
All	5.07	14.65	23.82	24.95
Nonoperative				
Drug-related	2.36	3.87	11.18	11.46
Diagnostic mishap	1.71	1.78	3.56	5.08
Therapeutic mishap	0.38	0.81	2.54	7.04
Procedure-related	0.76	1.58	4.16	3.85
Fall	—	0.19	0.30	3.19
Fracture	0.22	0.31	0.24	0.84
Postpartum	0.05	1.18	—	—
Anesthesia-related	0.07	0.89	0.30	0.09
Neonatal	1.88	—	—	—
System and other	0.41	0.54	1.57	2.34
All	7.84	11.15	23.85	33.89
Both operative and nonoperative	12.91	25.84	47.43	58.85

*Dashes denote categories for which there were too few observations to determine a rate.

Table 5. Sites of Care That Resulted in Adverse Events.

Site	No of Events*	Weighted Proportion of Events†		
		In Sample	Due to Negligence	With Serious Disability
		percent		
In hospital				
Operating room	1019	41.0	13.7‡	22.0
Patient's room	495	26.5	41.1‡	30.4
Emergency room	71	2.9	70.4‡	24.8
Labor and delivery room	123	2.8	27.7	9.8§
Intensive care unit	53	2.7	30.2	50.4
Radiology	32	2.0	36.9	35.8
Cardiac catheterization laboratory	28	0.9	—	—
Ambulatory care unit	19	0.8	—	—
Other	47	1.7	—	—
All	1887	81.2	26.4	25.9
Outside hospital				
Physician's office	153	7.7	31.2	21.0
Home	48	2.7	11.4	8.2‡
Ambulatory care unit	32	1.4	53.6	13.7
Nursing home	11	0.9	—	—
Other	26	1.1	—	—
All	270	13.8	30.2	17.0
Unknown	61	5.1	38.6	25.6
Total	2218	100.0	27.6	24.7

*Numbers shown are based on the total number of reviews, not the number of cases.

†Dashes denote categories for which there were too few observations to determine a percentage.

‡$P<0.001$ for the difference between this rate and all others in the same column.

§$P<0.01$ for the difference between this rate and all others in the same column.

Discussion

Preventability, Error, and Negligence

Many of the adverse events we identified were neither preventable nor predictable, given the current state of medical knowledge — for example, idiosyncratic drug reactions in patients who had not taken the drugs previously, postoperative myocardial infarctions in young patients without previous evidence of heart disease, and adhesive intestinal obstructions. Other unpreventable adverse events occurred with predictable frequency, but patients accepted the risk of treatment because of the potential benefits. Examples of these include radiation injury and bone marrow suppression from chemotherapy. Preventing these "unpreventable" adverse events will require advances in biomedical knowledge.

Most adverse events are preventable, however, particularly those due to error or negligence. Our findings confirm the observations of others[5] — that errors in medical practice are common. Studies in other areas of human endeavor, such as the generation of nuclear power, shipping, and the airline industry, confirm that some degree of error is inherent in all human activity.[6] In highly technical, complicated systems, even minor

Table 6. Types of Errors Leading to Adverse Events, as Classified by the Reviewers in a Weighted Sample.

Type of Error	No. of Reviews	Errors Observed	
		In Entire Sample	Ultimately Judged Negligent
		percent	
Performance	537	35.2	28.2
Prevention	232	21.9	59.6
Diagnosis	168	13.8	74.7
Drug treatment	87	8.9	52.8
System and other	32	2.4	66.0
Unclassified	220	17.9	43.4
All	1276	100.0	47.3

errors may have disastrous consequences. Medicine is no exception; errors in the performance of highly technical procedures, such as brain or open-heart surgery, can also have catastrophic results.

Our physician-reviewers identified management errors in more than half the adverse events we studied. Technical errors were by far the most common class of error, but relatively few of these were judged to result from negligence. In contrast, errors of omission — failure or delay in making a diagnosis or instituting treatment, and failure to use indicated tests or take precautions to prevent injury — were often classed as negligent. When the errors of omission were combined, they were more common than the errors of commission.

Error is not the same as negligence.[7] In tort law, medical negligence is defined as failure to meet the standard of practice of an average qualified physician practicing in the specialty in question.[8] Negligence occurs not merely when there is error, but when the degree of error exceeds an accepted norm. The presence of error is a necessary but not sufficient condition for the determination of negligence.

Sometimes the evidence of negligence appears clear-cut, as when a physician fails to evaluate a patient with rectal bleeding. Other cases are less obvious. For example, depending on the circumstances, each of the following could be considered either negligent or not: a mistaken diagnosis of acute appendicitis, misinterpretation of a chest film of pneumonia as instead showing congestive heart failure, puncture of the pleura during the insertion of a central venous catheter, and perforation of the bowel during an operation to remove adhesive intestinal obstruction.

In the case of the mistaken diagnosis of acute appendicitis, the patient may have had a classic history, typical findings on physical examination, and laboratory-test results supportive of the diagnosis. If the physician then failed to make the diagnosis, it would be both an error in diagnosis and a case of negligence. If, however, the diagnosis was made but no appendicitis was found, there would also have been an error in diagnosis, but not one involving negligence, because the surgeon would have followed the generally accepted standard of practice. With the present state of medical knowledge, such errors are unavoidable and therefore not negligent.

Furthermore, the standards of practice that form the basis for such judgments are often not well defined, and thus they may be susceptible to considerable variation in interpretation. Perfection can never be the standard of practice, since the vagaries of biology and human behavior make perfection unattainable, in either execution or outcome, for any form of treatment. Accordingly, standards of practice must always include an acceptance of some degree of error.

Programs of quality assurance should strive to re-

Table 7. Incidence of Specific Types of Errors in a Weighted Sample.*

Type of Error	No.	Percent†
Performance (697)		
Inadequate preparation of patient before procedure	59	9
Technical error	559	76
Inadequate monitoring of patient after procedure	61	10
Use of inappropriate or outmoded form of therapy	24	3
Avoidable delay in treatment	41	7
Physician or other professional practicing outside area of expertise	13	2
Other	75	14
Prevention (397)		
Failure to take precautions to prevent accidental injury	178	45
Failure to use indicated tests	79	23
Failure to act on results of tests or findings	80	21
Use of inappropriate or outmoded diagnostic tests	6	1
Avoidable delay in treatment	120	31
Physician or other professional practicing outside area of expertise	16	4
Other	77	19
Diagnostic (265)		
Failure to use indicated tests	134	50
Failure to act on results of tests or findings	83	32
Use of inappropriate or outmoded diagnostic tests	3	1
Avoidable delay in diagnosis	149	55
Physician or other professional practicing outside area of expertise	17	6
Other	24	10
Reason not apparent	16	5
Drug treatment (153)		
Error in dose or method of use	67	42
Failure to recognize possible antagonistic or complementary drug–drug interactions	10	8
Inadequate follow-up of therapy	65	45
Use of inappropriate drug	38	22
Avoidable delay in treatment	21	14
Physician or other professional practicing outside area of expertise	8	5
Other	18	9
System (68)		
Defective equipment or supplies	8	8
Equipment or supplies not available	8	5
Inadequate monitoring system	8	10
Inadequate reporting or communications	11	26
Inadequate training or supervision of physician or other personnel	15	31
Delay in provision or scheduling of service	10	14
Inadequate staffing	5	6
Inadequate functioning of hospital service	7	8
Other	12	20

*Numbers in parentheses after each category of error are the number of errors found by the reviewers for that category. Because the reviewers were asked to list as many errors as they found, the numbers in each class are larger than those in Table 6. In addition, since the reviewers were not limited to identifying a single reason for each error, the percentages exceed 100.

†Percentages are of the total number of errors in each category.

Table 8. Disability and Gravity of Negligence.*

Type of Adverse Event (Grade)	No. of Events	% of Total	Severity of Disability					
			Class 1	Class 2	Class 3	Class 4	Class 5	Class 6
			percent					
With negligence								
Slight (1–1.5)	76	7.2	77.4	16.2	4.1	0.5	1.9	1.8
Moderate (2–2.5)	141	13.3	47.0	17.2	4.3	7.8	0.5	21.7
Grave (3)	63	7.1	19.8	5.9	0.5	7.8	1.1	65.6
Without negligence	853	72.4	64.5	16.0	2.7	5.3	1.8	9.7
All	1133	100	59.9	15.4	2.9	5.5	1.6	14.7

*Negligence was graded by case, as the average of the scores from the two reviews or the score from the single review when there was only one. Percentages do not correspond directly to numbers of events because of weighting.

duce rates of error to an optimal level. Because the cost of preventing adverse events entirely would be prohibitive, defining an optimal level requires a realistic assessment of the effectiveness of efforts to reduce their occurrence. In industry, an error rate that exceeds defined norms is deemed unacceptable. We believe that similar considerations should apply in medicine. For example, in the absence of evidence of negligence, a rate of wound infection of 1 percent in the primary repair of hernias may be acceptable, since it is well recognized that infections occasionally develop even with carefully executed operations, and trying to reduce their occurrence further would not be cost effective. However, even without evidence of negligence, if the infection rate for such operations exceeds 5 or 10 percent, it is reasonable to conclude that the aseptic precautions followed during the operation need review and improvement. Norms for acceptable levels of various adverse events need to be established. Hospitals can then target their quality-assurance activities to the areas most likely to respond to such efforts.

Risk Factors

An important step in reducing the incidence of adverse events is to identify the patients at highest risk. The number and variety of adverse events described in this study testify clearly to the diversity of hazards in modern medical care. In a typical hospitalization, a patient may have hundreds of encounters with doctors, nurses, hospital staff, and equipment. Unexpected results or errors can occur with each encounter, perhaps causing an adverse event.

Many factors increase the risk that a patient will have an adverse event during hospitalization. Our findings suggest that one major determinant is the complexity of the disease or treatment. If, as seems likely, every intervention carries some level of risk, patients with complicated disease are more likely to have adverse events, if only because their care requires more interventions. Thus, it is not surprising that nearly half the adverse events we identified resulted from operations. In even a simple operation there are dozens, even hundreds, of maneuvers, from skin preparation to wound closure, as well as many interventions in the postoperative care. Each presents an opportunity for an adverse event. Our findings are very similar to those of a California study in which half the potentially compensable events (comparable to what we have called adverse events) were found to result from treatment in the operating room.[9]

The high number of drug-related adverse events in our study may also be related in part to the quantity and variety of medications administered to hospitalized patients.

Characteristics of patients also increase the risk of an adverse event. Elderly patients, for example, are far more likely not only to have more complicated disease, but also to have underlying degenerative conditions that increase the risk of such nontechnical postoperative complications as myocardial infarction, pulmonary embolism, and pneumonia. Insults or errors that are tolerated well by children or young healthy adults can be lethal in patients who are weakened by disease or who have impaired vital organs. In addition, elderly patients are at increased risk of falling and therefore of hip fractures.[10]

Another factor that may account for the increased rate of adverse events in the elderly is the presence of coexisting conditions. Greenfield has shown that such conditions are a strong predictor of serious hospital complications (such as pulmonary embolism, septicemia, or stroke after hip surgery). Patients with severe coexisting conditions on admission are more than seven times as likely to have a complication as those without such conditions (Greenfield S, Apolone G, McNeil BJ, Cleary PD: personal communication).

Yet another risk factor is the location where care is provided. The high rate of negligence in adverse events resulting from treatment in the emergency room could be caused by several factors. Because no operations and only a few procedures are performed in the emergency room, the adverse events we identified that occurred there were more likely to involve diagnostic errors or mishaps of noninvasive treatment, which the reviewers frequently judged as negligent. Emergency rooms are sometimes staffed with part-time physicians who are not well trained in emergency care. Because they are frequently very busy, these physicians have less time to spend with each patient. Finally, some of the sickest patients enter the hospital through the emergency room.

Our experience is not unique. Dearden and Rutherford found that for 58 percent of patients with severe trauma treated in the emergency room there had been serious errors in treatment.[11] Although many of these errors involved mistakes or delays in diagnosis, most were errors in treatment. The risk of error was increased with certain characteristics of the patient, such as alcoholism and the presence of multiple injuries, but the investigators concluded that the treating physician's inexperience was the chief cause of the high rate of error.

Finally, we believe that the risk of injury, particu-

larly serious injury, is closely related to the medical nature of the intervention. A momentary lapse that delays the diagnosis of a skin rash is usually of little consequence, for example, whereas a similar lapse during a brain operation can have disastrous effects. It is unlikely that neurosurgeons are more prone to error than dermatologists, but the conditions under which they work are far less forgiving. As we have seen, certain specialties, such as thoracic surgery, obstetrics, and neurosurgery, had more adverse events than other specialties, but the events were not more likely to have been caused by negligence.[1]

Limitations of the Study

Our observations and conclusions must be interpreted within the limitations of a retrospective review of records. Several features of the study could have biased the results. First, we relied exclusively on data from hospital records. Although we have shown that adverse events can be identified accurately from information in hospital records,[12] such records may not provide evidence or insight into the specific causes of an adverse event. For example, in some of our study patients, the adverse event was caused by failure to diagnose an ectopic pregnancy. From the information in most hospital records, it would not be possible to tell whether such failures occurred because the physician (1) did not think of the diagnosis, (2) considered the diagnosis unlikely and therefore did no further follow-up examinations or testing, or (3) considered the diagnosis possible and recommended further testing, but the patient did not come for the test (in which case the outcome would not have been considered an adverse event). Nor can we tell whether (4) both the physician and the patient sought the test, but the equipment was broken (or overbooked, unavailable on weekends, or the like), (5) the examination was performed but the results were not reported, or (6) any one of many other possible problems arose that can be imagined.

Second, we relied on implicit, not explicit, review. Because we studied the entire range of medical services, it was not possible to set up explicit criteria for every conceivable type of adverse event. Accordingly, we relied on the judgments of physicians. To minimize variability therein, we structured the record-review process by means of an Adverse Event Analysis Form, which required the reviewers to conduct their analysis in a standardized way and to address specific questions about causation.

Third, we used general internists and surgeons as physician-reviewers, not specialists. For a study of this scope and magnitude, it would have been both difficult and expensive to do otherwise, since the reviewers were required to identify adverse events of all types. In our pilot study, we found that internists and surgeons could identify adverse events with a high degree of accuracy.[13] As they had been instructed to do, the reviewers consulted with a panel of specialists when they needed to determine whether the care that had resulted in a possible adverse event met accepted standards.

Finally, our information on the follow-up of the patients was limited to data about care in the hospital (including the outpatient department). Although the reviewers had available the record of care provided at the same hospital after the index hospitalization, they had no access to the information in physicians' private offices. However, except for those that are rapidly fatal, adverse events not requiring hospital care are unlikely to result in serious disability.

Prevention of Adverse Events

As knowledge increases, in theory more adverse events will become preventable. Indeed, the safety and effectiveness of many current medical treatments result from the earlier reduction or elimination of complications similar or identical to those we have identified as adverse events here: high rates of heart block, bleeding, and mortality in the early years of heart surgery, problems associated with the initial attempts at organ transplantation, side effects of many drugs, and so forth. These were the adverse events of an earlier day, and they were greatly reduced in frequency after research led to an understanding of their causes.

Future reductions in the occurrence of adverse events also depend in part on research into causes. In the case of adverse events that are currently unpreventable, progress will come from scientific advances, such as the development of less hazardous chemotherapeutic agents. In the case of events due to error, control will require scientific advances in some instances, but we believe that progress will also depend heavily on systems analysis, education, and the development and dissemination of guidelines and standards for practice. Automatic "fail-safe" systems — such as a computerized system that makes it impossible to order or dispense a drug to a patient with a known sensitivity — are likely to have an increasing role.

The reduction of adverse events involving negligence will also require an increased emphasis on education. To the extent that failure to meet the standard of practice is due to ignorance, improved dissemination and enforcement of practice guidelines might be effective. The development of better mechanisms of identifying negligent behavior and instituting appropriate corrective or disciplinary action is equally important.

Preventing medical injury will require attention to the systemic causes and consequences of errors, an effort that goes well beyond identifying culpable persons.[7] Such approaches have paid off handsomely in other highly technical and complicated enterprises, such as aviation.[6,14] A similar strategy may work in medicine as well.[5,15-17]

In this context, our description of adverse events represents an agenda for research on quality of care. Adverse events result from the interaction of the patient, the patient's disease, and a complicated, highly technical system of medical care provided not only by a diverse group of doctors, other care givers, and support personnel, but also by a medical–industrial sys-

tem that supplies drugs and equipment. Reducing the risk of adverse events requires an examination of all these factors as well as of their relation with each other.

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REVIEW ARTICLE

DRUG THERAPY

JOHN A. OATES, M.D., *Editor*
ALASTAIR J.J. WOOD, M.D., *Associate Editor*

FLUOROQUINOLONE ANTIMICROBIAL AGENTS

DAVID C. HOOPER, M.D.,
AND JOHN S. WOLFSON, M.D., PH.D.

THE introduction of fluoroquinolone antimicrobial agents (Fig. 1) into clinical use is an important recent advance.[1-3] These drugs, also called quinolones, include norfloxacin, ciprofloxacin, ofloxacin, enoxacin, and pefloxacin. Of these, norfloxacin, ciprofloxacin, and ofloxacin have been approved for use in the United States. Quinolones are orally absorbed, are potent in vitro against a broad spectrum of bacterial species, and have favorable pharmacokinetic properties. We shall evaluate here the current status of the quinolones, considering mechanisms of action and resistance, activity in vitro, pharmacokinetics, clinical efficacy, adverse effects, and clinical uses. A discussion of the structure–activity relations of the quinolones is beyond the scope of this article, and this topic has recently been reviewed elsewhere.[4,5]

Mechanisms of Action and Resistance

Uniquely among antimicrobial agents in clinical use, the primary bacterial target of quinolones is DNA gyrase (bacterial topoisomerase II),[6-9] an enzyme that introduces negative supertwists into DNA and separates interlocked DNA molecules. Quinolones antagonize these enzymatic activities, interfering with DNA replication, segregation of bacterial chromosomes, transcription, and other cellular processes and damaging DNA. Recently, binding to gyrase–DNA complexes has been reported.[10]

Spontaneous single-step mutation to quinolone resistance tends to be infrequent ($1:<10^9$), and when it occurs the resistance is of a low level for many bacterial species. High-level resistance can be selected by serial exposure of bacteria to increasing drug concentrations. Mechanisms of bacterial resistance to quinolones include chromosomal mutations that either alter DNA gyrase (resistance to quinolones alone) or reduce drug accumulation in association with changes in bacterial outer-membrane proteins (pleiotropic resistance). Destruction or modification of the drug by bacteria has not yet been described, and plasmid-mediated resistance to fluoroquinolones has not yet been found in clinical isolates.

Activity in Vitro

In general, quinolones have excellent potency in vitro[3,11] against most Enterobacteriaceae, fastidious gram-negative bacilli including species of haemophilus, and gram-negative cocci, such as *Neisseria gonorrhoeae*, *N. meningitidis*, and *Moraxella (Branhamella) catarrhalis* (Table 1). Among the drugs listed in Table 1, ciprofloxacin is the most potent. Quinolones are active against *Pseudomonas aeruginosa* but are less active against other species of pseudomonas. They also have good activity against *Staphylococcus aureus* and other staphylococci but are less active against species of streptococcus and enterococcus. They have minimal activity against anaerobes and none against *Candida albicans*. Quinolones are active against gram-negative

From the Infectious Disease Unit, Medical Services, Massachusetts General Hospital and Harvard Medical School, Boston. Address reprint requests to Dr. Hooper at the Infectious Disease Unit, Massachusetts General Hospital, 32 Fruit St., Boston, MA 02114-2696.