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CONTENTS

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Patient Safety
—Introduction to the Activities of the JMA and AMA—

JMAJ 44(9): 381, 2001

Hokuto HOSHI

Executive Member, Board of Trustees, Japan Medical Association

In 1997, the Japan Medical Association (JMA) recognized the need to regain public trust in medicine after frequent medical accidents, and began to discuss the issue within the organization. From 1998 the JMA and the American Medical Association (AMA) began to hold regular bilateral meetings to exchange constructive ideas about these problems. At the second meeting in 2000, Dr. Nancy W. Dickey, former AMA President, and Dr. Eitaka Tsuboi, JMA President, prepared their ideas about the main issues, and completely by coincidence they came up with the same points related to the issue of patient safety. Ideas were exchanged about the importance of thinking from the perspective of risk management in preventing recurrence of medical mistakes. It became clear that it is necessary for the current policies to achieve patient safety in the United States to be presented in Japan at this meeting, and also to make clear the common features of and differences between the situation in Japan and the United States, and this led to the First JMA Seminar on Patient Safety. After having the opportunity to hear Dr. Joanne E. Turnbull, Director of the National Patient Safety Foundation, discuss the importance of understanding human error from a psychological perspective, at the AMA General Assembly, it was felt that this approach needed to be introduced in Japan as well, leading to the Second JMA Seminar on Patient Safety. Lectures by both distinguished guests made many important suggestions and discussed several specific proposals, and thus contributed greatly to the development of efforts in Japan for patient safety.

In the following articles, Dr. Tsuboi describes activities of the JMA to ensure patient safety followed by Dr. Dickey and Dr. Turnbull, who delineate the efforts of the AMA on patient safety.

Patient Safety Issues
—Challenge of the JMA to Protect Patient Safety—

JMAJ 44(9): 382–384, 2001

Eitaka TSUBOI

President of the Japan Medical Association
President of the World Medical Association

As the oath of Hippocrates states, the duty of physicians is to protect the life of patients and provide them with safe medical treatment. As physicians, we must do our utmost to ensure patient safety at all times. Yet unanticipated reactions do occur, even during routine medical procedures. As physicians, we must provide treatment while evaluating risk, considering the expected effects and possible side effects of each medical procedure. The difficult part is that any medical treatment has some risk, and therefore safety issues are an integral part of the practice of medicine.

Some unexpected reactions can be prevented with better information, such as side effects from medication or complications from recovery after operations. With sufficient preparation, including clear explanation of procedures and their consequences, it is possible to anticipate such reactions.

On the other hand, there is another category of medical errors that involve human errors, such as misconnected medical devices, giving the wrong medication, or treating the wrong patient. This is the category of medical errors that cannot be excused and should not be ignored. Health care personnel and health care facilities must deal with these serious problems at the organization level.

A third kind of medical errors, which do not directly involve health care personnel, is the unexpected malfunction of medical devices or medical instruments, because of the presence of a contaminant, for example. In Japan, many voluntary recalls have occurred recently, but simply removing products from the market cannot solve the underlying problems. Manufacturers need to take more responsibility for their products, and they should be able to develop and provide products that are safe for health care professionals to use.

When side effects or complications are foreseeable, physicians need to consider carefully the way in and the degree to which patients should be informed of possible adverse outcomes. The problems cannot be solved with formal statements to the effect that the patient will not complain if anything goes wrong. It may be impossible for the physicians to their patients every detail of all the possible side effects or complications. Insufficient explanation from medical professionals is the main reason why patients feel little trust, and is a contributing factor to the false image that the medical profession covers up its mistakes. Each country has a different culture and a different medical system, but the medical profession in each must find an appropriate way to take responsibility to establish a dialogue with patients in order to explain procedures and also educate them.

Whether the number of medical errors has actually been rising recently is debatable, and unfortunately without sufficiently detailed data

for Japan it is impossible to answer conclusively. Even so, there are calls in Japan for legal changes and establishment of a formal medical errors reporting system, based on recent small-sample estimates of medical errors in the United States and the United Kingdom. Unfortunately, these calls for change assume that since the medical profession will not do enough on its own, public intervention is required. This mischaracterization of the medical profession is not acceptable. The problem of medical errors is in fact one of the best opportunities for the medical profession to play its role as a professional organization.

So what has the Japan Medical Association done to deal with issues of patient safety? In 1973 the JMA created its own system called JMA Professional Medical Liability Insurance. It still operates under the same system which at the time a limit on compensation of 100 million yen (US$1 million) was quite a considerable sum. This year, optional coverage to cover up to 200 million yen (US$2 million) was introduced to cover increasingly expensive lawsuits. However, this insurance system protected patients by establishing the responsibility of the medical profession in cases of medical liability lawsuits. Furthermore, by publishing case records of medical liability lawsuits, it also contributed somewhat to errors prevention. The primary goal was not, however, prevention of medical errors or patient safety assurance, but rather to use continuing medical education programs to improve the quality of care.

JMA policy has changed dramatically in recent years. Now the emphasis is on preventing medical errors rather than simply responding to them, on measures to make medical care safer, and ensuring patient safety. The 1997 establishment of the JMA Medical Safety Policy Committee started discussions based on the new concept of "medical safety." This committee issued a report in March 1998 entitled, "Risk Management in Medical Care," which set out the basic framework of the idea of medical safety. Achieving safety in medical care was defined as, "seeing things from the patient's perspective, and building an environment in which patients can feel secure when receiving medical treatment." The report also pointed out the dangers of falling into a strategy designed only to fight lawsuits. If lawsuits and disputes were the main object, then medical professionals would resort to "defensive medicine," avoiding risky procedures and even refusing to accept high-risk patients, thus damage the interests of patients. Based on this report, in February 2001, "JMA Training Seminar for Promoters of Medical Safety," was developed as a distance-education class, and six hundred students nationwide enrolled for the first term.

More recently, the JMA focus has shifted to patient safety from medical safety. At the same time that the Medical Safety Policy Committee continues its work, a new Office to Ensure Patient Safety was established in July 2000 as a permanent part of the JMA to develop concrete measures to assure patient safety. In July and September 2000, in cooperation with the American Medical Association, two Patient Safety Seminars were held. Both seminars emphasized a common understanding in both the United States and Japan that finding the systematic causes of medical errors and developing measures to prevent their recurrence was more appropriate than simply finding and punishing individuals involved in medical accidents. The need to change from the old, punishment-based systems was acknowledged, and detailed discussion occurred about problems in the health care system, legal issues, patient-physician relations, fact-finding and communication with patients, and the need for mutual understanding and greater communication among different kinds of medical professionals.

I would like to discuss three areas for ensuring patient safety in greater detail: (1) wider use of internal reporting systems for hospitals, and a system for common usage of information and evaluation; (2) building a system using medi-

cal associations to provide and collect information; (3) improvements in medical devices, instruments, and pharmaceutical products.

Many health care facilities have recently begun to take steps to improve their internal reporting systems. But for prevention to be effective, all hospitals must implement a system based on a common format to allow independent analysis of these reports. It is therefore not desirable for a single, national organization to collect and control all the data.

This is where local and regional medical associations can use their organization to collect and provide information. Using the Internet, for example, they can build a system to find out quickly which issues are of concern to health care personnel.

One such issue of growing concern is the problem of errors in the use of pharmaceuticals with similar names, and misconnections of medical devices. To address these issues, last year the Ministry of Health and Welfare took the lead in introducing a new system of certification. But the system has not been widely used, since it overlooked the real concerns of health care personnel. As a result, medical associations, along with other professional associations, are in the process of gathering the opinions of health care personnel, in order to develop a better system to ensure safe use of medical devices and materials.

There are several other issues remaining to protect patient safety. One is the question of how to compensate victims when medical errors occur. The process of medical liability lawsuits has become both complex and time-consuming. It is not enough to rely on Japanese civil courts procedure, which is based on establishing proof of negligence. For cases where negligence is not an issue, we should consider establishing a new compensation fund.

From the perspective of preventing future medical errors, it may be necessary to give legal protection from prosecution to people who report them. In addition, the tendency of police and administrative agencies to focus on these issues in response to changing levels of public opinion should be carefully monitored.

Whenever medical errors occur, the key to reassuring patients of medical safety and preventing future errors is to look objectively for the reasons for the error. We must act out of a concern for prevention, taking into account the actual conditions of medical practice and concerns of health care personnel.

Finally, when thinking about patient safety, the medical profession must renew our commitment to continue to work diligently to understand the kinds of high expectations and fears that patients have about medical treatment.

It Is Good Medicine—Is It Safe Medicine?

JMAJ 44(9): 385–391, 2001

Nancy W. DICKY

Past President, American Medical Association

Responses to New Reports on Medical Error

In the recent (March 2000) British Medical Journal devoted to the issues of error and safety in medicine, the opening editorial noted that the "error prevention" movement has clearly accelerated. Major changes in the way we think about our work and changes in the way that the press and the public view our work have begun to occur. Why? What has suddenly happened?

The issues of error and safety are not totally new. For over a decade there have been studies in the American literature about errors and their possible cumulative effect. Nearly four years ago, the American Medical Association determined that it needed to do something about the errors that seemed to plague the headlines and the front pages of our major newspapers. But certainly when the Institute of Medicine's report, TO ERR IS HUMAN, came out in November 1999, the attention of the country and of the world was focused upon the issues of medicine and healthcare, its safety and its dangers. In the Executive Summary of the IOM report, it is noted that, ". . . at least 44,000 Americans die each year as a result of medical errors. The results of the New York study suggest that the number may be as high as 98,000."

The report went on in that startling vein and compared the number of deaths of Americans from medical error, preventable error, to that of deaths from motor vehicle accidents, breast cancer and AIDS. And in every case, the IOM report said that medical error exceeded each of the others as a cause of death. Those are headline-grabbing numbers. In fact, there are some that accused the IOM of playing to the media of taking a handful of studies and "screeching" their results out in order to get attention. It certainly seemed to work. Within weeks of the release of the report, the US Congress was holding hearings and several bills had been considered for introduction after the Christmas break, and scholars and researchers and others were lining up to talk about what needed to be done.

But something that has begun to happen in the last few months: a number of scientists have taken a critical look at the numbers that are referred to in the IOM report. There has been criticism that those numbers are incorrect, and, perhaps, they even grossly exaggerate the problem. In fact, a non-researcher myself, when I look at a study where the study itself offers over 100% variance from the low estimate to the high estimate, I have less faith in the numbers. Yet, in the repeated press references in the last 9 months, virtually every one has referred only to the high estimate—the 98,000 deaths—and even rounded it up to six figures.

This article is a keynote speech in the Seminar on Patient Safety held at the JMA office in Tokyo on July 16, 2000.

Many physicians in the US are very angry that the American Medical Association did not attack the numbers early on. Those physicians are delighted with the recent criticisms of the studies, estimates and headlines. As a practicing physician, I believe that the numbers are perhaps less important than the reality of preventable error occurring. And whether the number is 100,000 or 44,000 or even less than 1,000, those are preventable errors or fixable numbers, we should commit ourselves to taking action to reduce or eliminate them. Medicine is a very complex process, increasingly including over a dozen people on each treatment team, including 10 or 20 or more medications for each patient, and including extraordinary numbers of diagnostic and treatment interventions. The practitioners are human beings who are providing care for other human beings who are richly diverse and not machines, not multiple parts that look exactly the same, and fit together in an exact and replicatable manner. For all of these reasons, it is unlikely that we will achieve perfection, but we should commit ourselves to doing what is necessary to reduce to the lowest possible level the preventable errors that put our patients at risk.

What is an error? That is part of the difficulty in the next steps toward error prevention. We must define what it is that we are attempting to reduce. The IOM report said that safety is ". . . Freedom from accidental injury," and it says that error is, "Failure of a planned action to be completed as intended or use of wrong plan to achieve an aim." Some errors are easy to define, for example, perhaps the issue of medication error, which is one or more of the following: wrong drug, wrong dose, wrong route of administration, wrong patient, wrong time. Others are more difficult to define and to understand, such as a leaky anastomosis after surgery. Was it the wrong procedure? Was it the right procedure but done improperly? Was it the right procedure done properly but the patient's tissue simply not adequate to hold the repair?

In each of the instances of an admitted and known error, we seek to place blame. We blame the physician who failed to remember a patient's drug allergy, the surgeon who misplaced a stitch in the anastomosis, the nurse who failed to check the concentration of adrenaline before she administered the medication. We tend to believe that individual diligence should prevent errors, and so the very existence of errors damages our professional self-image.

This view of errors is simply wrong. Yes, some errors are due to negligence, but most are latent errors arising from poorly designed processes and systems. Hence, this recent and overwhelming commitment to deal with errors must be addressed by looking at ways to change the system. According to William Hendee, Ph.D., Senior Associate Dean at the Medical College of Wisconsin, "The key to reducing this risk (of errors) is to create a health care environment that eliminates a culture of blame and punishment and replaces it with a culture of vigilance and cooperation that exposes the weaknesses that can combine to cause error."

National Patient Safety Foundation

Over the last 9 months, there has developed a widespread commitment to improvement. That commitment was given a shot in the arm by the November 1999 release of the IOM report. However, long before that report was released there were activities which were already occurring and which received a shot in the publicity elicited by the IOM report. In 1997, the American Medical Association responded to a series of highly publicized errors in medicine by forming the National Patient Safety Foundation. This is not for profit organization formed by the commitment of industry (3M and C.N.A. Healthpro) and the profession (AMA). It brought nearly the stakeholders to the table, and it was an attempt by professionals and the profession to say to professionals,

patients, and society that we would do more than say we were sorry when something went wrong, we would be proactive in seeking reassurances to prevent such problems.

The NPSF is committed to research, education, and advancement of solutions. We initiate and fund studies to identify preventable causes of error, and then to remove them. We have funded 8 studies in patient safety and we are in the final stags of funding 4 more this year. The measure of our success is the number of individuals and institutions who have expressed an interest in or have actually submitted a proposal for a study. The breadth of the studies has included such diverse topics as the effectiveness of ICU warning monitors, to evaluation of the problems of look-alike or sound-alike drugs. The NPSF has co-hosted the first two national conferences on the topic of safety, known as the Annenberg conferences.

Since then we have had a national stakeholder conference for CEOs to understand the necessity of their participation and commitment, and we are in the final planning stages for our first Solutions Conference where awards will be given to the best proposed solutions in at least four categories.

The National Patient Safety Foundation is also working with a number of medical specialty societies to write curriculum to teach students and professionals about the issues of recognizing system problems of how to create safe systems, of how to create systems that are vigilant and cooperative, rather than blaming and punitive. Eventually, it is the goal of the NPSF, to have curricula for training of medical students, residents in graduate training, pharmacists, nurses and virtually all others in the fields of healthcare. The goal of such curricula is knowledge about how to create good systems, how to enhance existing systems, and how to protect patients.

One of the most exciting of the NPSF's ventures has been the work that we have done with the Food and Drug Administration (FDA), the group that approves pharmaceuticals for the market. Recognizing that drug related issues were among the most frequently cited errors, the NPSF and the FDA set out a process that outlined all of the steps from early research efforts on a drug through the experimental evaluation, to the marketing and then routine use of a drug, over a series of meetings. An agenda that looked at all of the steps and the potential concerns for patient safety was created. This is an immense agenda and one that will take even committed leaders more than a year or two to complete. However, with the full agenda in front of us, it is possible to prioritize the areas of concern and turn attention and dollars to the areas likely to reap the most benefit for the greatest number, rather than simply moving the research or solutions to the one someone knows best.

Veterans Health Administration and the Aviation Safety Model

Another early player has been the Veterans Health Administration (VA). The VA has committed millions of dollars to setting up systems within their hospitals and care delivery systems to encourage reporting of error and then intensively investigating what happened and why. Some types of error are so frequent that the VA has found that it must look at classes of error. They simply do not have the workforce to investigate each error. The VA has also embarked upon a study of the error prevention system used by the aviation industry in the US delivery system.

Our aviation industry has a very complex system of encouraging pilots to report near misses, so that evaluation of those near misses will hopefully prevent catastrophes in the future. However, the aviation reporting system was not perfect the first attempt. They had to make many modifications to prove it workable. Now they have a system where a pilot is held harmless if a report is made within a defined period after the incident. The report is made to a different agency than the oversight and inves-

tigation agency, which then sterilizes it, taking out the names of pilots, the flight numbers, dates and times, so that the agency that would ultimately be the oversight agency cannot retaliate against the individual making the report. Can a similar system be devised for medicine? Would it have similar positive impact on preventing problems? The VA has embarked on a project to try to answer those questions, the results of which will be applicable to the entire system.

Government and Professional Groups Working for Quality Improvement

The Agency for Healthcare Policy and Research which may have been familiar to some of you now has a new name: the Agency for Research and Quality (ARQ). ARQ is the agency which has helped to collate and write practice guidelines and to identify centers of excellence in care. It has made a commitment to using a portion of its energy and, perhaps more importantly, a part of its dollars to fund patient safety research, and then the dissemination of the results of research, in an attempt to assure that best practices in safety are rapidly adopted across the nation. The paucity of research committed to patient safety makes this commitment of money a most important action in moving patient safety forward.

The activities of a number of other groups simply must be noted, as they have been central to the progress on this issue. The American Society of Anesthesiologists was the first and perhaps the most effective advocates for patient safety. Fifteen years ago, anesthesiologists in the US were facing outrageous medical malpractice rates. They were among the specialties paying the highest amount for insurance, and in fact, many of them could no longer afford the insurance. They turned their attention and their money to asking why. And they found that there was an unacceptably high morbidity and mortality rating with anesthesia. They began doing research about what was happening and why, and they delineated safe practices, they invented when necessary new equipment. Over the course of a decade, they not only improved measurably the morbidity and mortality of anesthesia for patients, but happily, their insurance went down from being the most expensive to simply average. And we, at the National Patient Safety Foundation, have tried to emulate them. We would like all of medicine to be able to celebrate similar successes.

The Leap Frog group is a group of purchasers of health care which has recently turned its energy to using their purchasing power to seek out the systems committed to safety. They are not simply charitable, they know that safe, error free medicine is cheaper medicine, and they want to reap some of those profits.

Some individual industries are committed as well. Minnesota Mining and Manufacturing, known to most of us as 3M, has invested substantially in moving the issues of safety forward. They were one of the founding members of the NPSF, putting up over a million dollars, and they have helped to fund the Annenberg conferences and the solutions conference.

Prospects for Recommendations of the Institute of Medicine Report

Much is being done, and as mentioned before, the IOM report was not the genesis of interest in patient safety, as many of these activities were well along before the report came out. However, the report infused public and legislative interest, it created media interest, and it energized many who had been long working on the issues. The IOM report purported to lay out a national agenda for reducing errors in health care and improving patient safety. It also noted that a major force for improving patient safety is the intrinsic motivation of health care providers shaped by professional ethics, norms, and expectations. They also pointed to external environmental factors, such as availability of knowledge and tools to

improve safety, strong and visible professional leadership, legislative and regulatory initiatives, and actions of purchasers and consumer to demand safety improvements. Factors inside the health care organization include strong leadership for safety, an organizational culture that encourages recognition and learning from errors, and an effective patient safety program.

The committee which wrote the report, *TO ERR IS HUMAN*, noted that it intended to strike a balance between regulatory and market based solutions and between the roles of organizations and individuals. The report laid out a four-tiered approach:

1. Establishing a national focus to create leadership, research, tools, and protocols to enhance the knowledge base about safety.
2. Identifying and learning from errors through the immediate and strong mandatory reporting efforts as well as the encouragement of voluntary efforts, both with the aim of making sure the system continues to be made safer for patients.
3. Raising the standards and expectations for improvements in safety through the actions of oversight organizations, group purchasers, and professional groups.
4. Creating safety systems inside health care organizations through the implementation of safe practices at the delivery level . . . this is, they said, the ultimate target of all of the recommendations.

Under the guise of establishing a national focus, the IOM recommended that a Center for Patient Safety be created, in order to set national goals and create knowledge. The ARQ was seen as a likely place for the formation of such center. It was noted by the IOM other industries which had been more successful with safety activities all had a central agency committed to leading and monitoring the process. ARQ has been supportive of the profession and has a substantial budget, though perhaps not large enough the job at hand. This recommendation has received almost unanimous support as being a good thing to move patient safety forward. In fact, one of the successful legislative moves has been the addition of over 20 million dollars to the budget of ARQ to support research, information dissemination, and goal setting.

Under the guise of identifying and learning from errors, the IOM recommended formation of a national mandatory reporting system. Reporting would start with hospitals but would eventually be required of other institutions and ambulatory delivery settings. They also recommended that voluntary reporting efforts should be encouraged, and that Congress should pass legislation to extend peer review protections to data related to patient safety and quality improvement. This series of recommendations has perhaps received the greatest amount of discussion, criticism and anticipation. Multiple pieces of legislation were considered to facilitate these actions. And yet, as we look closer at the issues involved, there are many, many problems with these recommendations.

As discussed before, there is, as yet, not a widely acceptable definition of what an error is, thus what must be reported may be variable, or worse: open to interpretation. There is concern that those who heard the recommendations for reporting did NOT hear the recommendations for moving away from blame and punishment, and that any bank of information would ultimately be used to identify "bad" doctors or nurses or pharmacists. In fact, some have criticized the rapid support of some Congressmen as looking for an attractive but ineffective solution. Telling your constituency that you have fixed the problem by demanding reports of errors is a promise to fix the problem with an empty promise!

Some of the concerns about reporting are:

1. There is no protection as yet for the information so that punishment and recrimination may well occur. It has not been uncommon for nurses or pharmacists to lose their jobs when an error occurs. Physicians are concerned about reading about a mistake in the newspaper, branding them "bad" doctors. In

a report that begins and ends by talking about the importance of changing the culture away from blame and punishment, it is antithetical to some that the first thing they want to do is collect data about who is making mistakes and how.

2. Thirty-two states currently have mandatory reporting systems, but there is no evidence that any of them are safer than the 18 states that do not have such systems.
3. There are literally warehouses of information already collected that are gathering dust. We need to decide what and how we are going to do with the information gathered before building more bureaucracy to collect more information.

It is clear that this is NOT a simple or clear-cut recommendation. It will continue to get a good deal of discussion, and ultimately it may lead to legislation. The discussions will have to include what kind of protections are needed for confidentiality, and whether voluntary is better than mandatory reporting.

Under the series of recommendations of setting performance standards and expectations for safety, The IOM recommends that those accrediting bodies and others who oversee health care institutions should focus greater attention on patient safety. They also recommend that public and private purchasers of health care should use safety records as one way of differentiating between systems. That is, they should pay more or more readily contract with those systems that have proven they have fewer errors. IOM has suggested that health professional licensing bodies should implement periodic re-examination and relicensing of professionals, and that such examination should include knowledge of patient safety issues. It recommends that societies place a higher priority on curricula regarding patient safety, using journals and meetings to advance the knowledge base. And finally, there is recommendation that the Food and Drug administration increase attention to the safe use of drugs in the entire process of development, marketing and use of pharmaceutical products.

Few if any of these recommendations have been criticized, and in many of the arenas that I described earlier, there is ample evidence that much of this is already occurring and more will certainly follow. In the last area, that of implementing safety systems in healthcare organizations, the IOM has recommended that health care organizations and professionals within them should make continually improved patient safety a declared and serious aim. They are looking for strong, clear, visible leadership. They want to see non-punitive systems for analyzing errors, and they want to see prompt implementation of proven safety practices. As you can see, some of what the IOM has recommended will happen soon or is already happening, but some of their recommendations will be hotly and protractedly debated. It is certain, that they have at the very least moved these discussions from the sidebar to everyone's main agenda. Perhaps they even contributed to the convening of this meeting.

Likelihood of New Legislation

What happens next? In the United States we will most assuredly see legislation. The profession of medicine, the American Medical Association, the National Patient Safety Foundation, and surely the IOM will all be involved in moving this issue forward, though as you have heard, we do not have a unified message. It is imperative that as legislation is created, we take the opportunity to enhance safety, not create more problems for professionals or institutions.

Importance of Media

It is imperative that we work with the press, the media, to assure that they understand the issues and report fairly. One of my greatest concerns as a physician who sees patients regularly is that our patients are reading headlines that are terrifying, especially if taken out of

context. They need to be reassured that health care in our system is safe. It is among the best in the world. It can be made better and their physicians, hospitals and others are working diligently to assure that it will be better and safer. However, if it is treated in the media as a "yellow journalism" event, if it is treated irresponsibly, it could actually drive patients away from health care. It could drive a wedge between patient and physician, when you and I know that trust in one's physician is one of the keys to successful health care. On the other hand, the press can—if they choose—help move forward solutions and can facilitate patient efforts toward more error-free health care. Reports of concerns can carry information about the solutions, and can tell patients what kind of questions to ask to assure them they are getting the best possible care. They give as many column inches to breakthrough solutions, as they do to the results of error and mistake.

Practitioners and Patients

Health care practitioners have a role in evaluating potential areas of concern, as well as participating in evaluation of specific incidents. They have an obligation to follow the literature about safety and solutions as they do the emerging science of their specialty. They must address issues of concern with their patients, and be good citizens when it comes to advancing these issues in their institutions.

And finally, patients have a role as well. They must be responsible for making educated decisions. They should participate in decision-making and know where the most likely pitfalls are, and what they can do to protect themselves. With the increasing mobility of patients, and the increasing sophistication of medicine, patients see numbers of different doctors, most of who will not get to know them well. Medicine is more complex and patients are likely to be taking many medications. And even the old medicines produce potential problems with things like generics causing "old friends" looking different. Patients need to know their medications. They have an obligation to ask when a prescription is filled and it looks different than the usual medication. If they have allergies, they should not assume that each of us knows and makes other providers aware. They should tell every provider who is prescribing or administering that they are allergic. The repetitive caution could save their life.

One of my favorite stories is about the man who checked into the hospital and promptly hung an $8\frac{1}{2} \times 11$ inch card around his neck with his name in big block letters. The nurses said, "Why have you done that? Your name is on your wristband, and we know who you are." He simply smiled and said, he wanted to be sure they couldn't get confused or distracted. Each time they came in they chuckled, but, you know, they didn't give him anyone else's medicine, they didn't hang someone else's blood product, and they didn't care if he got his wristband wet in the shower. Patients may even be able to teach us a thing or two.

The future is bright for improving health care safety. These issues will respond positively to the targeted attention and resources of healthcare. The same kind of careful diagnosis of the problems, and then delineating treatment for the specific cause, will lead to marked improvement, just as cancer treatment and infectious diseases have responded to the energetic actions of medical research. Having made the commitment to assess the extent of the problem and then create solutions, we should have good news reports for the public, the profession, and even the legislators.

We look forward to working with you to see this progress rapidly evolve.

A Systems Approach to Error Reduction in Health Care

JMAJ 44(9): 392–403, 2001

Joanne E. TURNBULL

Executive Director, National Patient Safety Foundation

Investigation of Error at Hermann and Hermann Children's Hospital

Hermann and Hermann Children's Hospital is a 624-bed teaching hospital located in Houston, Texas. The hospital contains 496 beds designated for care of adults and 128 beds for care of children. The hospital serves both private and academic physicians. The hospital is a trauma center, affiliated with the University of Texas Medical School-Houston, and has active training programs in all major disciplines.

Our story, which appeared in the New York Times Magazine on June 15, 1997 allows me to introduce you to Jose Eric Martinez. Jose, who would now be 4 years old, died from a Digoxin overdose in August, 1996. At the time of his death, I was responsible for performance improvement at Hermann Hospital, and also responsible for the hospital's triennial accreditation survey by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO). The JCAHO survey is very important to U.S. hospitals, because without JCAHO approval, hospitals will not receive funds from the government. The survey was two weeks away when Jose's death occurred.

Our hospital's story is not one in which a single individual is responsible for the death of this baby. Rather, our hospital's story tells of the breakdown in care processes. Injury and death to patients occur when "holes" in the each component of the care process "line up" and an error reaches the patient. The story begins with the baby's admission for a loading dose of Digoxin after a routine checkup revealed minor symptoms of congestive heart failure and ventricular septal defect. These were not life threatening problems. Jose was expected to either outgrow these problems or else they would be corrected with surgery when he grew a little older.

A physician-in-training (resident) conferred with the attending physician on the correct loading dose and maintenance dosages of Digoxin, and then wrote admission orders. Unfortunately, the resident misplaced a decimal point and the loading dose was written as .90 mg, instead of 0.09 mg or 90 mcg. — ten times the therapeutic dose. The attending physician missed the error upon reviewing the entire batch of admitting orders. The admitting resident checked out to the resident who would be the House Officer for the night and discussed how the drug should be administered — this time correctly discussing the dosage amount and unit of measurement.

The order sheet was faxed to the pharmacist who was concerned about the amount of the dose and paged the admitting resident in an

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attempt to verify the order. The page was not returned. The pharmacist also called the unit where the child was admitted to discuss the concern with the nursing staff. All nurses were in report, so the pharmacist did not fill the order, but set it aside to be completed when the concerns were addressed. At this time, there was much conflict between pharmacy and nursing staff, presumably around issues such as the length of time it took for drugs to be delivered to the nursing unit. The pharmacist did not feel comfortable asking that a nurse leave the report meeting to attend to this problem.

A little later, the courier brought the original order sheet along with a lot of other orders. A pharmacy technician prepared all of the orders and then the same pharmacist checked the technician's work. This time, the pharmacist was checking for how the drug was dispensed and did not connect the Digoxin with the problematic order that had been set aside. The order was filled and sent to the nursing unit.

The unit nurse also questioned the volume of medication. She verified the order with another nurse who agreed that it seemed to be too much and should be checked with the doctor. The two nurses went to the house officer who was covering for the night and asked "Is this right?" The house officer reviewed the order at the nurse's request and remembered his earlier discussion of the dosage calculation with the admitting resident. The night resident recalculated—correctly this time—but when verifying the dosage amount on the order sheet missed the misplaced decimal point. The resident approved the medication by answering

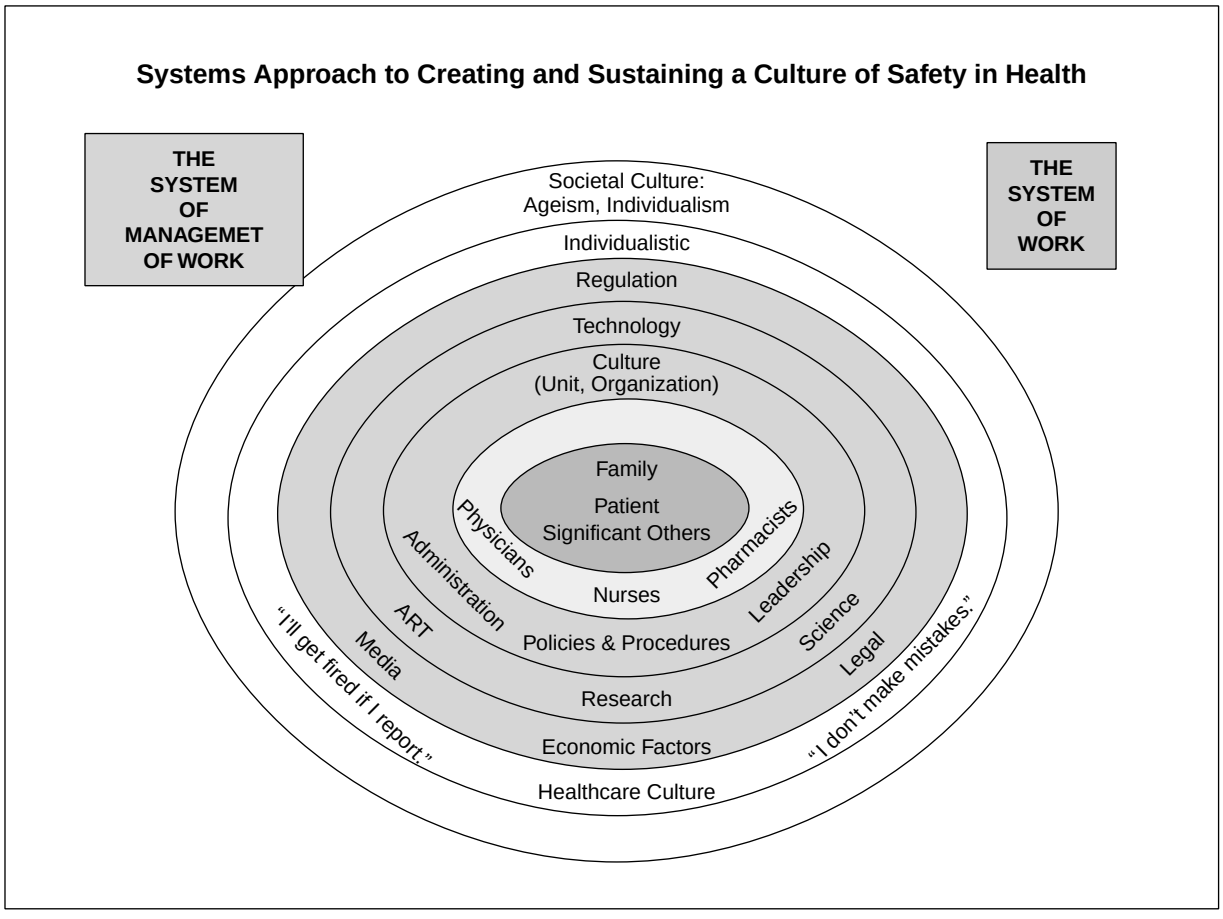

Fig. 1 Systems Approach to Patient Safety

the nurse "Yes, give the 90".

Troubled, the nurse administered the medication in the ordered amount. The child's heart rate decreased and the resident was immediately called to check the child. The resident discovered the medication error and ordered Digibind, a drug to counteract the Digoxin toxicity. The Digibind was ordered and administered as quickly as possibly, but the infant arrested and was coded. After approximately three hours of resuscitation efforts, the baby died.

The next day I received a call from an administrator who needed to tell me about "an incident." After hearing all these details, I called my partner, the Medical Director. In our conversation we agreed that the doctors, the nurses and the pharmacist were all qualified and caring professionals. Not one of them wanted to hurt this tiny patient. We pledged to address this tragedy as a "system's problem" and to design the system of medication care processes such that something like this never happened again. And that is the real story... how we made system's changes to reduce errors. I must emphasize that no one person could accomplish what we accomplished. This is the work of a team: Dr. John H. Rex, Director of Infectious Disease and Epidemiology at Hermann Hospital, Dr. Steven J. Allen, an anesthesiologist by training and the hospitals Medical Director, Kathryn Vande Voorde, a Doctor of Pharmacy, and Katharine Luther, a nurse who is now the Director of Performance Improvement at M.D. Anderson Cancer Center.

Systems Approach to Patient Safety

What does a commitment to a systems approach to reducing error in medicine mean? Healthcare's conventional approach is to blame physicians, nurses and pharmacists for error, which is depicted in this graphic of reactive error management. The new field of safety science tells us that "latent" errors, which are hidden, are the real culprits. "Latent" errors usually occur long before an actual injury appears. Management decisions related to resource allocation and budget, to cut staff, for example, are latent errors, which may not appear for a long time. Providers (doctors, nurses, pharmacists) of health care services are left with inadequate tools and training. In the language of safety science, providers (doctors, nurses, pharmacists) of health care services are at the "sharp end," those vulnerable places in the system where errors are likely to appear. They are blamed, policies are revised. Nothing changes.

A Systems approach requires healthcare to rely on knowledge from other disciplines—like human factors, engineering, and organizational development—and integrate this knowledge into medical practice. A systems approach means learning from the lessons of other high reliability organizations, like aviation. A Systems approach requires healthcare to acknowledge that it is a high risk industry; error and the potential for error is everywhere. The conventional approach in medicine, called the "Old Look" expects doctors, nurses and pharmacists to be infallible and relies on several false assumptions, such as: 1. things happen *only* when people make mistakes, 2. people and organizations who fail are bad, and 3. blame sufficiently motivates people. By contrast, the Systems approach acknowledges that medical miracles and new technology means that clinicians deal with ever increasing complexity in care processes, escalating change, increased expectation for perfect outcomes, information overload, and new patient vulnerabilities as sicker people are kept alive for longer periods of time.

The "New Look" in patient safety acknowledges the inherent risk of failure in the complex practice of medicine. Moreover, the "New Look" acknowledges that risk is always emerging and is not always foreseeable. Finally, the "New Look" acknowledges that people are going to make mistakes no matter how hard they try, that the healthcare system itself is fal-

lible, and that alert, well-trained clinicians are crucial.

High Reliability Organizations and Error Reduction

There is new research that can help us, and this research comes from studies on high reliability organizations (HRO's). HRO's perform high-risk activities with very little error. Aircraft carriers, nuclear power, aviation, and aerospace are all examples of high reliability organizations. HRO's share certain attributes or characteristics. They acknowledge and audit risk, they pay a lot of attention to process control, have a strong leadership commitment to reduce risk, and reward individuals who report error. What does it mean to pay a lot of attention to process control? HRO's have specific rules and procedures for each process. Training of personnel is key. Redundancies are built into work processes as safeguards. Team work is of key importance. Decisions are made by the people who do the work rather than by administrators who are far removed from the care processes.

There are two major components to our error reduction program: 1. A Reporting System which includes development of a classification system and 2. The implementation of Root Cause Analysis. The classification scheme is depicted as an inverted triangle which shows the frequency of the types of incidents that are reported. Relatively rare are the accidents which result in fatalities and serious injuries. These are called sentinel events, and these incidents always require immediate attention. Sentinel events always require a root cause

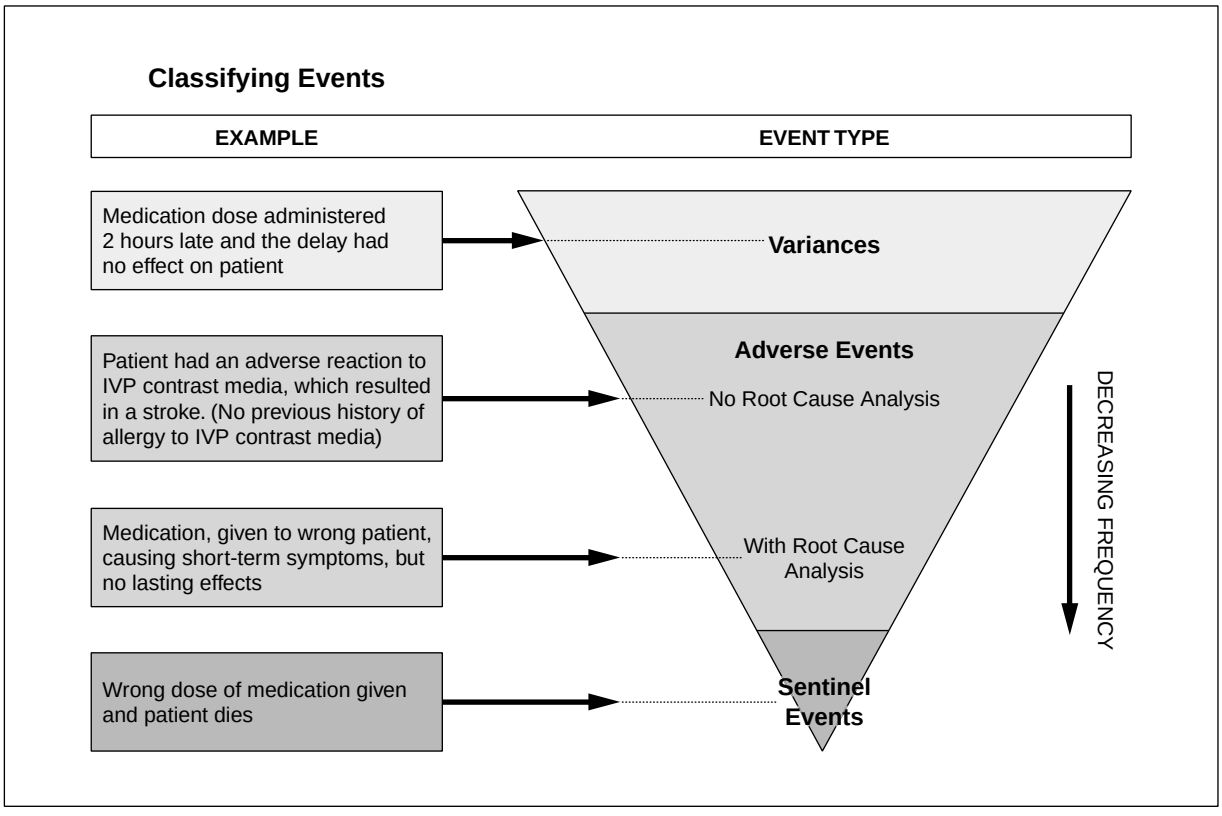

Fig. 2 Classifying Events in Medical Errors

analysis. More common are reports of adverse events and variances from normal operations. The examples in this classification scheme show a "variance" in which a medication dose was administered two hours late with no ill effects. Adverse events are divided into two types: those which require a root cause analysis, and those which do not.

Implementing Root Cause Analysis in Health Care Organizations

We were surprised that doctors, nurses and pharmacists liked the experience of participating in a root cause analysis so much that we did not have the staff resources to match the number of requests to perform them. For this reason, criteria must be established for adverse events which require a root cause analysis so that staff resources are used appropriately. In this schema, an adverse drug reaction requires no root cause analysis, while medication given to the wrong patient does requires a root cause analysis. Incidents and Variances are thought of as "precursors" to sentinel events. It is from analyzing the trends in this database that we can learn where vulnerabilities are in the system. What is critical here is for all members of the healthcare team — administrators, doctors, nurses, pharmacists — to participate in developing the classification scheme and the definitions. It is also important to build definitions on existing research and accepted definitions.

In our hospital, we defined a serious adverse outcome as death, prolonged hospitalization, or disability after hospital discharge. Following the concepts used in other studies, a serious ADE was defined as an unintended consequence of drug administration that was associated with either an actual serious adverse outcome or potential risk of such an adverse outcome.

It is important that the forms developed for reporting be easy to use and not a burden to the practitioner. In our system, serious adverse events are voluntarily reported to the Risk Management and Performance Improvement departments. To add in this review process, the clinical pharmacists and case managers who daily reviewed almost all charts were also asked to report possible ADEs. The pharmacy-based portion of this process is fully monitored, with active recording of the pharmacy staff of essentially all interactions wherein they give advice that results in a change in medication order.

As we began a systematic application of root cause analysis, we encountered some anticipated confusion between individual and system causes of failure analysis. We developed a strategy to mitigate this confusion — and the tendency toward individual blame — by asking the directors of the risk management and performance improvement departments to independently assess the circumstances of each process involved in the adverse event. In this way, they served as a cross-check to each other so that members of the organization would learn more effectively how to identify system causes of adverse events. Root cause analyses were achieved within seven days of the event. All information describing each event was coded and entered into a database. Reliability of the coding of the factors underlying each event was conducted by achieving consensus among a multidisciplinary group of physicians, pharmacists, nurses, and administrators.

Engineers have used the tool of root-cause analysis to uncover underlying causes since the Three Mile Island nuclear accident in the early 1980's. With the advent of the JCAHO sentinel event policy in 1997, root cause analysis began to be adapted to health care to examine the underlying (root) causes of adverse events. We began the development of our methodology for root-cause analysis with JCAHO requirements, and modified our approach based on the lessons learned from early root cause analyses. Participants in each root cause analysis included those individuals directly involved in the event along with the medical staff, policy makers, and managers from the relevant medical services. A trained facilitator guided each

root cause analysis session, and during the session, a trained scribe categorized and documented the discussion on a standardized template, the Ishikawa diagram.

The root cause analysis group would meet once or twice as appropriate. Facilitators were trained to focus primarily on systems and processes, rather than individual performance, and to move from special cause variation to common causes in organizational processes. This means that the facilitator moved discussion from (a) the details of the event to (b) the area and services that were involved, and finally to (c) an identification of root causes. Participants were told explicitly that they would, in all likelihood, experience a tendency to place individual blame, and that the facilitator would move any attempt to place blame from an individual to a system focus. In addition, participants were informed that the root cause analysis process would repeatedly dig deeper by asking "Why?" questions until no additional logical answer(s) could be identified. At the conclusion of the root cause analysis session, underlying causes of the event were summarized. Finally, participants suggested changes that could be made in systems and processes that would reduce the risk of similar adverse events occurring in the future. Methods for monitoring the efficacy of these changes were also developed by the participants, and the results of the intervention are subsequently monitored by and reported on by a subset of the participants.

Example of Root Cause Analysis in Hermann and Hermann Children's Hospital

The first root cause analysis of the circumstances leading to the digoxin overdose and the infant's death identified a series of contributory factors:

(a) the intended dose was 90 micrograms,
(b) the dosing unit was incorrectly converted from micrograms to milligrams by the prescriber,
(c) in combination with a stray punctuation symbol, the dose was thus taken as 0.90 milligrams,
(d) an initial faxed copy of the order was set aside when the pharmacist recognized the dose as excessive but could not promptly reach a physician for clarification of the order,
(e) a hard copy of the order later received in the pharmacy as part of a large batch of other orders was filled by a pharmacy technician but was not recognized at the time of review by the pharmacist as corresponding to the previously noted problem order and,
(f) the nurse recognized the dose as excessive and consulted with a covering resident physician, who
(g) based on the memory of a conversation regarding this dose calculation with the prescribing physician verbally, confirmed that the dose should be "90" but did not realize that a unit conversion error had occurred.

The root causes of this event included:

(a) shift change (of the resident physicians),
(b) use of a "workaround" (that is, a duplicate order delivery because of prior faxing of a non-STAT order so that turnaround time might be reduced),
(c) communication (delays in returning a page, trailing zero, infant's weight not clearly used in a dose calculation in the order),
(d) lack of clear accountability (multiple physicians, multiple caregivers),
(e) inability to resist authority gradient (both the pharmacist and the nurse were concerned about the order, but neither felt empowered to halt it),
(f) failure to follow policy (faxing of a non-STAT order), and
(g) lack of a constraining or forcing function which are process changes.

Constraining functions reduce the possibility of a given type of error. A forcing function completely eliminates the possibility of a given

type of error. In this case, the computer did not have a strong lock-out for digoxin doses that exceeded a certain dose/unit weight).

We began a systematic data collection process on all adverse and sentinel events in August, 1996. Once a month, a multidisciplinary group of senior administrators and clinicians met to establish consensus for the root causes analyses. Common trends are identified across root cause analyses. The findings summarize 120 root cause analyses from August, 1996 to December 1999. The broad, underlying causes identified for serious adverse events are:

- human factors (such as impaired communication and slips and mistakes),
- performance deficits (failure to follow a specified protocol),
- environmental factors (staffing, time of day, and acuity/census),
- knowledge deficits (for example, untrained personnel administering complex chemotherapeutic agents on unfamiliar units),
- equipment or materials factors,
- policy and procedure deficits (for example, no policy limiting the number of hours worked and resulting in fatigue)

Two events involved intravenous administration of oral medications that had been prepared in a syringe or bag that used the same type of adapter as the patient's IV lines. This slide was freely submitted by a pediatric surgeon to illustrate the difficulty that clinicians face when they must use poorly designed equipment that does not take into account human factors. The surgeon said, "You will have an error reported very soon, and I will be the one to make it." The surgeon's statement also indicates the culture change from hiding errors (we call it "cover up") to openness and accountability. The categories for these root causes were not predetermined, but rather emerged and were refined over time. Other groupings are possible, but these seemed most helpful to us.

The support of senior leadership in implementing Root Cause Analysis in a Blame-Free Environment is essential. The death of the infant was the critical initial turning point in the process by which the institution began to learn to consistently approach all such events in a non-punitive fashion. The Performance Improvement Department, encouraged and supported by the national leaders in the area of patient safety, took the lead in implementing and refining the root cause analysis process with subsequent sentinel events. This process was widely publicized to both hospital staff and physicians. While this cultural change was not readily and immediately understood or believed by all, the reality of the consistently non-punitive responses to the results of the initial and subsequent root cause analyses was gradually seen, accepted, and ultimately embraced by the hospital staff.

The delivery of a consistent and clear message by senior leadership was critical to the acceptance of this process by employees and physicians. At our institution, the chief executive officer, the chief operations officer, and the executive vice-presidents all consistently and publicly supported this process. Attempts to assign individual blame were deflected and refocused on system-related issues at every turn. The following mission statement summarizing the hospital's commitment to reducing adverse drug events was formulated and widely distributed:

- Promote an organizational culture that is highly committed to error prevention.
- Increase multidisciplinary collaboration and communication between the three disciplines (medicine, nursing, and pharmacy) involved in the medication use system to reduce inefficiencies and probably of error.
- Plan and implement a safe medication use process.
- Implement a multi-disciplinary effort to improve the collection, reporting, and evaluation of medication errors.

While the mission statement was written for the medication use process, it is applicable for all types of errors.

Administrative Policies to Prevent Error Recurrence

The senior administrators extended great latitude to the leaders of the root cause analyses to immediately implement changes in response to newly identified problems. The motto was "Safety first, convenience and committee-approval later." For example, shortly after a decision was made to completely restrict concentrated potassium chloride solutions to the pharmacy, it was discovered that this action plan failed to eliminate equally dangerous concentrated potassium phosphate solutions. Within a few hours of this discovery, an interim approval to limit this additional formulation to the pharmacy was obtained from the chair of the Pharmacy & Therapeutics committee. Seeing such clear and prompt response to root cause analyses gave all participants a sense of contributing in a visible fashion to the process of improving the care environment. Employees were steadily encouraged to report both serious and trivial adverse events promptly to hospital administration. A formal root cause analysis was performed for reported adverse events that met the established criteria. Monthly meetings of a multidisciplinary team were held to ensure consistency of these analyses.

Several root causes led us to design and implement specific interventions. An example of environmental desensitization is false alarms on monitoring equipment in intensive care units. These are so frequent that staff ignore them. An adverse event occurred when a patient extubated and a real alarm sounded and no one paid attention. Another concept is diffusion of responsibility. This is the tendency for an individual to assume that someone else will take care of a problem. "If everyone is in charge, no one is in charge." This is important because one feature of our interventions is to establish accountability for specific care processes. What is striking is the tall blue bar which shows that impaired communication among staff is the greatest underlying cause of error. Because this was the greatest cause of error, our performance improvement efforts were targeted here.

Collectively, the results of the root causes analyses prompted changes to daily operations that can be categorized as:

- changes in policies,
- forcing or constraining functions, and
- leadership.

Changes from different categories were often related. The revisions to the medication use policy related to (a) ensuring that ordering also attends to patient safety and (b) identification of high-risk drugs are good examples of this confluence of changes.

Medication Process Policies to Prevent Error Recurrence

For the purposes of establishing accountability, we divided the medication use process into four steps:

- Ordering,
- Dispensing,
- Administration, and
- Monitoring.

Physicians are responsible for ordering, Pharmacists for dispensing and Nurses for administration and monitoring. Errors occur at each step and there are different solutions for each step. We knew from the research literature that 40% of errors occur in the ordering process, so we started there. Since impaired communication is the root cause, an intervention targeting communication was devised for each of these four care processes.

A change in our culture was a necessary first step. We were forced to admit that our previous methods did not work. We did not measure variation in practice. None of us had the right education, specifically in areas like multidisciplinary teamwork, human factors, and measuring care processes. We learned that our process had too many, wasted steps. Most importantly, our culture was characterized by blame and punishment and fear.

After the baby's death, the medication use policy was revised. The following requirements became the part of every order:

- beeper number (pager) on the order,
- printed name (legible signature),
- no trailing zeros,
- zeros written before a decimal point,
- spelling out the words "microgram" and "unit",
- no abbreviated drug names, and
- calculation in the order itself of the weight-based doses for pediatric patients.

Additional requirements were developed for high-risk drugs. High risk drugs were defined as chemotherapy agents, IV magnesium sulfate, IV insulin, IV digoxin, IV heparin, IV potassium (with the exception that electrolyte additives in maintenance fluids and parenteral nutrition fluids are not considered high-risk drugs), any calcium-containing drug, and IV vasoactive drugs (e.g., epinephrine, phenylephrine, norepinephrine, dobutamine, dopamine). This supplemental policy requires:

- that the order for these agents be written by a senior resident physician, fellow or attending (constraining function),
- extensive dose/unit weight checks in the pharmacy computer that block printing of a medication label if weight is not available or if boundary limits are exceeded (forcing function), and
- that two nurses recalculate the dose prior to administration, with one nurse being required to be full-time permanent hospital staff (staffing issues).

No order was accepted unless these conditions were met.

In addition, all concentrated potassium solutions were removed from floor stock. IV administration of concentrated potassium was involved in a second fatal event. This removal of this high risk drug from floor stock (forcing function) was based on existing research that documents 7,000 drugs per year in the United States due to concentrated potassium solutions being kept on nursing units. A number of fatalities had recently been well publicized, and these provided additional motivation for uncompromising implementation of the high-risk drug policy.

Medical Staff Policies to Prevent Error Recurrence

Incentives were created to give motivation to the medical staff. The medication ordering policy was the primary quality goal for the medical staff. The rest of their goals were simple, and already being achieved. Regular chart auditing further supported the general medication policy and the high-risk drug policy. The current level of compliance with these policies exceeds 91 percent. A clear indication of a culture beginning to change was the "ownership" of this policy by the medical staff. Specifically, medical staff leadership unanimously and spontaneously declared that 91% was not tolerable, and that the goal for the coming year would be 100%. Still, many physicians relied on nurses to make sure this policy was complied with, and nurses expressed resentment at being put in the position of a "babysitter" or a "policeman."

Nursing Staff Policies to Prevent Error Recurrence

For the nursing staff, there were three interventions. The first, the communication intervention, centered on helping nurses overcome what is called in the science of human factors, the "Authority Gradient." Authority Gradient refers to the inability of a subordinate to confront someone in a position of authority. The Authority Gradient can be seen between pilots and copilots, and bosses and subordinates. In the case of the infant's death, the nurse involved was trained in another culture to be subordinate to physician's orders. This is not the case in U.S. Nursing Schools where nurses are trained to question physician's orders if they think something is wrong. The nurse in this case knew that the order was wrong, yet adminis-

tered the drug. These cards were made to help the nurses confront authority. All of the nurses carried them. When a nurse felt that a physician did not listen to him or her, this card was shown.

Inability to counter the authority gradient appeared as a discrete root cause in only two analyses, but is of special significance in the medical work environment. Physicians are not always prepared to have orders questioned, and hospital staff may deliberately avoid confrontation. In addition to the card, a chain of command for questioning medical orders that might compromise patient safety was developed for nursing personnel. While this approach does not dissolve the authority gradient, the chain of command gives the nurse a sanctioned mechanism for quick review and advice regarding an order with the immediate supervisor, followed by more extensive support from progressively higher administrative levels.

Where possible, real-time forcing functions are preferred over constraining functions (process designs that make it difficult to commit an error) and delayed feedback from audit processes. For example, the lack of height, weight, and allergy information in the pharmacy computer was identified as a problem. While this information existed in the patient's chart in the patient care area, it was not consistently coded into the computer system. An early effort to ensure this via vigilant action on the part of the patient care area staff increased the rate of compliance from 60% to >90%, but this level of compliance then began to fall over time. It was only when the computer system began to reject orders on patients lacking these data that the compliance rose to >95%, where it remains to this day.

Staffing issues and increased acuity or census issues are also often related. When the census rises in an area, additional personnel may be assigned. This increases the possibility that personnel unfamiliar with a given unit will be working at a time of heightened activity. Awareness of this increased potential for a problem to develop is crucial to patient safety. To this end, an early warning system known as the Red-Yellow-Green system was developed, with green zone representing normal operations and red zone representing a difficult situation.

Each nursing unit defined its zone criteria, sometimes in surprising ways. For example, the medical intensive care unit nursing staff found that its green zone occurred when the unit was full of high acuity (very sick requiring a lot of nursing care) patients. Without discharges or new admissions, the work of the nursing staff could be efficiently planned and was less likely to be disrupted. When a unit is known to be in its red zone, nursing management works to support the staff in extra ways. For example, lunch or dinner for the staff might be sent to the unit.

The chain of command for questioning medical orders that might compromise patient safety was also developed for pharmacy personnel. Again, this approach does not dissolve the authority gradient, but the chain of command gives the pharmacist a sanctioned mechanism for quick review and advice regarding an order with the immediate supervisor, followed by more extensive support from progressively higher administrative levels. This process has been strengthened within the pharmacy by implementation of concurrent review of all questioned orders by a clinical pharmacist. These highly trained clinical pharmacists often possess a doctoral degree in pharmacy and are quite experienced with directly seeking clarification from the prescribing physician. Consultations by these pharmacists have been tracked since 1996. Of the 3,000–5,000 consultations that occur quarterly, approximately 1,000 result in an intervention which either prevents a potential adverse event or corrects a subtherapeutic drug dose. Although initially meeting some resistance, this process is now well received and appreciated by physicians on the medical staff. In addition, a clinical phar-

macist rounds daily with the team in essentially all of our intensive care units, and is thus present for immediate consultation on the orders for these complex patients. This process has also recently been supplemented by direct prospective surveillance for adverse drug events in selected units. Other changes in the pharmacy were that doses were limited to single strength, vendors were changed to avoid look-alike drugs, and look-alike drugs were color coded when vendor changes are not possible.

To see if our interventions, made any difference, we did the following calculations. Accurate calculation of patient days and case mix-adjusted patient days requires that all patients who were admitted during any calendar month have been discharged so that final case coding and calculation of the case mix index may be performed. Upon inspection of recent discharge records, it was found that >99% of patients were discharged within three months of admission. Discharge coding data were readily available through March 1999, so the 29-month period from August 1996 to December 1998 was selected for reporting.

Case mix index was defined as the acuity weight (a calculation of the amount of nursing care needed based on the severity of the patient's illness) for the Medicare-diagnosis related group (DRG; this is a method of prospective payment by the U.S. government). The case mix index was assigned by coding of the medical record after discharge. The number of inpatient days was defined as the number calendar days between admission and discharge, and case mix-adjusted days was defined as inpatient days multiplied by case mix index. Because the implementation of root cause analysis and corrective action was a continuous process that began after the first root cause analysis in October 1996, it was impossible to have a true "before and after" period. So that we might have a comparative time frame over which to assess improvement, we divided the study into an initial baseline 12-month period (August 1996 through July 1997) and a 17-month follow-up period (August 1997 through December 1998). The initial twelve-month baseline period was selected for two reasons. First, the major interventions implemented as a consequence of the early root cause analyses were largely in place by July 1997. Second, we knew from other ongoing work that August was a month in which we experienced significant decreases in patient satisfaction scores at our hospital. Two factors had been observed to combine to produce this decrease:

(a) increased census and acuity due to increased trauma-related admissions, and
(b) increased vacation-related absences which required increased usage of temporary nursing staff.

Based on our observation that acuity and staffing issues play a major role in medical error, the inclusion of August twice in the follow-up period is a deliberate measure taken to ensure that any observed reduction of the rate of serious adverse drug events is not due to random variation. Finally, the frequencies of adverse drug events for the two periods were compared by treating them as hazard rates of an exponential survival density function.

Challenges for Implementing Policies for Preventing Error Recurrence

There are several major problems in introducing a proactive risk reduction program in a hospital center on two areas. Most obvious are the legal risks that come with openly discussing and measuring medical error. The very nature of a root cause analysis requires participants to honestly identify and summarize multiple possible causes of the adverse event. This process cannot proceed if the participants or the institution fear that generation of such a summary might place them or the institution at increased legal risk. Projects related to performance improvement in the most states in the United States are protected from "discovery" (that is, can be used as testimony in a malpractice case)

under state law. The working group for each root cause analysis was thus convened as a subcommittee of the hospital's Performance Improvement Review Committee and all reports were issued under the aegis of this committee. The non-discoverability of the proceedings was repeatedly explained to the participants by the facilitator during each root cause analysis.

This proactive approach to medical error reduction is very different from conventional risk management efforts in the United States. The purpose of conventional risk management is minimize the financial losses to an institution based on litigation (lawsuits) that result from injury to patients. This is a "reactive" system and is not designed to prevent or reduce error. To reduce medical errors, a program of proactive risk reduction must be implemented, and methods must be used that identify places of vulnerability in the healthcare system.

In a proactive organizational error management model, senior management decisions are made to identify vulnerability. This vulnerability are those latent (hidden) workplace conditions which promote active failure. In this model, direct caregivers (doctors, nurses and pharmacists) work in teams and are intent on identifying and stopping error. Outcomes of error reduction are measured to make sure that changes are improvements. Proactive error management methods integrate knowledge from engineering, cognitive psychology, human factors and organizational development into the delivery of healthcare services. These proactive error reduction methods have been proven in other high-risk industries. This model addresses human factors, technical factors, and organizational factors.

According to engineering science, every step in a work process adds complexity and thus increases the probability of error. The lesson is that healthcare processes must redesigned and simplified to reduce unneeded complexity. This knowledge can be implemented immediately to make the system safer. Engineering tells us the following changes in this order will have the greatest impact on protecting patients from error:

- forcing functions,
- automation and computerization,
- order entry,
- preprinted orders and protocols,
- checklists,
- rules and double checking,
- education,
- information.

Cognitive psychology emphasizes that human beings are fallible and prone to error. In a typology or classification of common error, slips are defined as actions that occur during familiar impulses. For example, when we hear the door bell ring and pick up the telephone. In this case we know what to do but we do it poorly. Slips are the most common types of error. Mistakes are less common. Mistakes are errors in judgment that occur when familiar rules or habits do not apply. In an unfamiliar situation, we must make a judgment without adequate information. The lesson here is that we must design our care processes to compensate for the human condition. Near misses are mistakes that are caught in the process before they reach the patient. Capturing these near misses is where great learning occurs. Near misses should be entered into the database with injuries and death. Common causes of mistakes include: habit, interruptions, boredom, fatigue, hurry, anger and fear. These are the working conditions of doctors, nurses and pharmacists in the U.S. Is it the same in Japan?

Clearly, this is not a simple problem. We must work together. The National Patient Safety Foundation invites the Japan Medical Association to join us as full partners in solving this problem on an international level.

Genetic Diagnosis—Bioethics

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Abstract: The entire human genome will be completely analyzed very shortly and mankind must resolve the issue of how this knowledge will be applied to general medical care in the 21st century. Due to the progress which has hitherto been achieved in gene analysis technology, genetic testing for carrier detection, pre-implantation diagnosis, prenatal diagnosis, presymptomatic diagnosis, predispositional testing, and other tests has become technically easier to conduct. The progress in gene analysis technology has also made it highly possible for prenatal diagnosis, that presently relies on amniocentesis and CVS, to shift to less invasive methods that utilize maternal-fetal blood. What mankind must resolve is how advanced medical technology will be adequately utilized and how it will be justified from the standpoint of bioethics. If technological progress is pursued without addressing the ethical, legal, and social issues that stem from this technology, it will have difficulty gaining public support. Ethnically original bioethics will not evolve in Japan if the unique culture, customs, and practices that exist in this country are ignored. There is an urgent need to address this issue.

Key words: Genetic testing; Genetic diagnosis; Bioethics

Introduction

The Human Genome Project, which aims to map the entire human genome, has announced that the task will be completed in 2003, two years earlier than 2005, the year originally targeted for the project's completion. What will subsequently evolve from this project? Undoubtedly, pharmaceutical and various other industries will develop from the information that the project will provide. In addition, if gene analysis methods are simplified due to the facilitated use of the microchip, the issues of cost and labor will be quickly resolved.

One of the foremost issues in medical care in the 21st century is how the knowledge and technology derived from gene analysis will be applied in primary care.[1)] Its utilization will undeniably become widespread and prevalent in medical care. However, the fact that gene analysis has made it easier to decode an individual's genetic information has also engendered a major problem. The progress achieved in the decoding technology will enable genetic information

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to be collected from hair, saliva, nail, and even a single cell, in addition to blood samples.

Recently, pre-implantation diagnosis has come to the fore. The development of the technique of fractionally extracting fetal blood cells from maternal-fetal blood has enabled genetic information of fetuses to be successfully decoded using these cells even in Japan. If the accuracy level of this technique rises, there is the likelihood that it will replace amniocentesis or cervical villus sampling (CVS), the more invasive forms of prenatal diagnosis that are currently utilized.

In other words, decoded human genetic information will become readily accessible. However, there is concern that genetic information may be abused in the areas of employment and insurance not only for tested individuals, but for their family members as well. Genetic information, in some cases, links the members of an entire community. Genetic disorders are often over-represented in ethnic groups and intensive genetic research could be exaggerated in the presence of specific problems.[2)] Another issue that must be confronted is the therapeutic gap, i.e., the development of diagnostic techniques despite the shortage of available therapy and effective prevention of genetic diseases. Therefore, in view of these circumstances, it is natural that there are critics who disparage the present situation, which brings to mind the development process of the atomic bomb in physics. What lies in wait with the progress in molecular biology? Will modern science (technology) lead to true happiness and prosperity for mankind?

Genetic Testing

The process of diagnosing patients based on data obtained from gene analysis is called DNA diagnosis or genetic diagnosis in Japan. Recently, the term, genetic testing, has become prevalent; and it also includes chromosome testing and other tests related to heredity.

In addition to genetic testing of probands, some of the other types of tests are carrier detection, presymptomatic testing (for autosomal dominant disorders such as Huntington disease), susceptibility testing (testing for the BRCA 1 gene linked to the genetic type of breast cancer), prenatal tests, and pre-implantation diagnosis.

There is a strong need to strictly define the term DNA diagnosis because the majority of the tests carried out by many private DNA testing laboratories or genetic testing services are DNA tests and they are not a DNA diagnosis, which should be given in conjunction with the family history and an accurate interpretation of the mutant gene in question. Pretest counseling is indispensable. Subsequently, there is concern that the public will send in their samples unquestioningly to such services or laboratories under the misconception that a DNA diagnosis will be provided. In many cases, it is not easy to determine the type of diagnostic technique that should be used and to read and interpret the data that is obtained.

Presently, genetic testing services have begun to conduct cancer linked gene analyses and tests for delayed nervous diseases. There are many cases where such tests are complacently conducted and the testing services are faced with the difficulty of informing the client of the discovery of mutated cancer linked genes and providing adequate answers and appropriate counseling. Subsequently, the testing services are forced to recruit the services of a medical geneticist in order to address the needs of the client.

Principle of Bioethics

What standards of assessment and reasoning should be employed in the debate on bioethics? How should bioethics be interpreted? In the past, nations have sanctioned ethical standards and perspectives that are collectively adopted by the entire global community, in addition to standards that are compatible with the culture and religious mores of that particular country.

Willer has recently compiled the Christian concepts of the Lutheran church on genetic testing.[3] On the topic of prenatal diagnosis, he has written, "The ability to know prenatally whether or not a child will have a birth defect may raise difficult questions for some Christians. If a baby is born with a chromosomal abnormality, most people feel obligated to love and take care of the child. Should that belief change when a fetus is prenatally diagnosed with chromosome abnormality? Perhaps the parents feel that preventing the birth of the child is the most loving decision. On the other hand, the couple may decide to continue the pregnancy, believing God will provide the strength required to take care of such a child. What they believe about God can shed light on such choice".

However, what ethical standards do those who are not religious or defer to religious precepts rely on? Naturally, it is difficult to pinpoint one ethical perspective or standard that is deferred to in a diverse society. In his debate on bioethics with regard to genetics, Burugio has written the following thought-provoking comment.[4] "In the 18th century, philosophers taught us that all humans are born equal and after birth they are made unequal by men. Perhaps today, with our knowledge of genetics, we might say that the contrary is true: in other words, all men are born unequal and there is the danger that humans will make them equal. The answer is that both hypotheses are wrong; we are all equal in some ways and unequal in others, and any intervention, whether medical or political, which increase equality in one dimension will likely lead to decrease in another dimension." In a nutshell, a one-dimensional ethical perspective does not offer a realistic solution.

The pillars supporting bioethics are said to be the philosophies of James Mill's utilitarianism, Immanuel Kant's theory of duty, natural law, and Rawls's theory of justice.[5] Although a detailed explanation of these concepts will not be delineated here, the philosophy of Mill, which expounds the virtue of providing the greatest benefit to the vast majority with the least amount of risk, and the philosophy of Kant, which advocates the protection of individual rights, irrespective of whether those rights are in the minority, are at the extreme poles of the spectrum of thought.

The principles of bioethics that are presently endorsed by the majority of theorists and health care personnel are an amalgamation of such contrasting philosophies. Specifically, the four principles of Beecham and Childs exemplify this integration as listed below.[6]

1. Respect for the individual and the right to self-determination (autonomy).
2. Avoid injurious or harmful acts (non-maleficence)
3. Pursue the best interests or welfare of the individual (beneficence).
4. Strive for equity at all times, i.e., a comparison of risk versus benefit, cost versus effect, etc. (justice).

Genetic Testing, Genetic Diagnosis

1. Prior to undergoing genetic testing

The objective of genetic testing is to acquire the genetic data of a client. Its significance greatly differs from that of a liver function test since the genetic information that is obtained is a future assessment of the health of both the client and other blood relations. Therefore, counseling is essential for the client before genetic testing is conducted in view of the gravity of the information that is collected, as well as the fact that it is fundamentally a test to pinpoint genetic diseases. The frequency of the disease in question, its natural history, the recurrence rate (genetic prognosis), and other factors should be explained in layman's terms to gain the client's understanding (in conjunction with principle 1 above).

An explanation of the genetic testing process should include the objective, method, content (the benefits and the disadvantages that will be derived), accuracy, especially the unavoidable limitations of the diagnosis, possible risks that

may accompany the testing, and other information that should be accurately relayed to the client (in accordance with principles 2 and 3). A signed informed consent document is required in order to conduct the tests. The client has rights of which he or she is unaware of, as well as the "right to know". Therefore, after the client has been fully informed about the diagnosis, he or she has the right to refuse the test; and it is the client who must make the final decision to undergo the test (in accordance with principle 1). It is critically important that the client is not exposed to any potential undue influence at this time and to take measures to ensure that the client is not inadvertently exposed to any disadvantages if the test is refused (in accordance with principles 1 and 2).

In the United States, some private DNA laboratories or testing services will not conduct cancer-related genetic tests if there is no history of cancer patients in the client's family.[7] Similarly, testing services in Japan will also be required to clearly define the responsibility of the company in the future. A fair equilibrium between costs that are paid and the results that are obtained must be maintained (in accordance with principle 4).

2. Permission by a guardian (DNA testing of children)

The decision to undergo DNA testing for clients who are incapable of making a legally competent decision, as in the case of young children, is made by a parental authority or legal guardian or representative; and the decision that is made in such cases must protect the interests of the client (in accordance with principles 2, 3). Therefore, implementation of the genetic testing in children in case of untreatable or non-preventable genetic diseases, which occur with the onset of adulthood is unethical. Despite the proven existence of a variant gene in the client, if there is no distinct benefit or if a disadvantage is derived from the treatment, it should not be pursued. In such cases, the decision should be made by the client when he or she has reached an age to make a legally competent decision (in accordance with principle 1).

3. In the aftermath of the testing

The diagnoses that are based on the DNA tests should be explained in terms that is understandable to the client (in accordance with principle 1). However, if the client is not well-informed about the disease, the task of providing an adequate explanation will not be facile because the clinical symptoms of a genetic disease will vary if the position of the same variant gene causing the disease differs. Therefore, it is impossible for a physician specializing in genetic diseases to know of the heterogeneity of all diseases. Consequently, in the case of specific diseases, working in tandem with a specialist will be required in order to relay accurate information to the client (in accordance with principle 2).

The next issue which must be addressed is how the client is informed of the existence of a variant gene that has been diagnosed. For example, if a client who has hitherto led a healthy, normal life, is diagnosed with the variant gene for Huntington's disease (which has a 100 percent penetrance), the issue which must be addressed is how the client will be mentally and emotionally supported after being informed. There are testing companies that will have the client undergo a psychological test to determine whether the client will be able to bear the results of the diagnosis before conducting genetic testing. In view of the tragic circumstances that these diseases produce, it is understandable that the extreme argument has evolved that advocates the establishment of such a system before genetic testing is conducted. Similarly, the period following the diagnoses of cancer-related genetic testing is acutely serious. Although the penetrance for cancer is not 100 percent in such cases, clients are more susceptible to groundless and exaggerated fears. The guidelines published by the Japan Society of Human Genetics states, "counseling following genetic diagnoses is essential

and counseling should be repeatedly provided as needed"[8] (in accordance with principles 2, 3).

Proper management of the genetic data and protecting client confidentiality are also important issues. The data must be protected from life insurance companies, private firms, schools, and other third-party institutions (in accordance with principles 1, 2). It is also important to remember that an individual's genetic information is also information or data that is shared and owned by blood relatives. Therefore, it is ethically appropriate to provide this data to a blood relative with the aim of preventing the onset of the disease or for use in its treatment.[8]

In 1998, the WHO advocated the following after confirming the importance of protecting the confidentiality of an individual's genetic data: "…counselors should inform people that genetic information may be useful to their relatives and may invite individuals to ask the relatives to seek genetic counseling"; and "the provision of genetic information to relatives about the family so as to learn their own genetic risks should be possible, especially when a serious burden can be avoided"[9] (in accordance with principle 2).

4. What solutions are needed in Japan?

What solutions are needed to resolve the various issues that have been thus far explained? Firstly, basic knowledge in genetics should be taught not only in the field of medicine and health care, but in primary education as one aspect of the information and knowledge about the human body. This is a vital means of combating unwarranted biases. Secondly, an infrastructure of genetic services, especially a system of genetic counseling should be established. Practical measures such as this are what is needed rather than dramatic advances in genetic research.

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Diagnostic Criteria for Age-Associated Dementia

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Abstract: The term *age-associated dementia* does not refer to any specific illness; rather, it is a general term for dementia that develops in old age, which mainly means 65 years or older. Alzheimer type dementia (ATD) and vascular dementia (VaD) are the representative dementing illnesses. Recent epidemiologic evidence has been reported showing that in Japan ATD has the highest prevalence. At present, 3 sets of criteria for diagnosing ATD are in use: ① Those in the 10th edition of the World Health Organization's International Classification of Diseases (ICD-10), ② those in the 4th edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), and ③ those developed jointly by a work group of the National Institute of Neurological and Communicative Disorders and Stroke of the United States and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). In Japan, the DSM-IV criteria are commonly used in the clinical practice, and the NINCDS-ADRDA criteria in research. There are also several different sets of diagnostic criteria for VaD. Like ATD, there are ICD-10 and DSM-IV criteria, and there also are criteria developed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) and criteria developed by a joint research group of the United States and Switzerland (National Institute of Neurological Disorders and Stroke [NINDS] and the Association Internationale pour la Recherche et l'Enseignement Neurosciences [AIREN]). The present article reviews the characteristics of these different diagnostic criteria.

Key words: Alzheimer type dementia disease; Vascular dementia; Diagnostic criteria

Introduction

The term *senile dementia* does not refer to any specific illness; rather, it is a general term for dementia that develops in old age, which mainly means 65 years or older.

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A wide variety of diseases present in old age with dementia as their principal manifestation. In the present article, two typical kinds of age-associated dementia, Alzheimer type dementia (ATD) and vascular dementia (VaD), will be considered, and their diagnostic criteria will be explained. ATD is also referred to as *Alzheimer's disease* (AD).

ATD and VaD together account for about 70% of senile dementia in Japan. VaD is known to have been more prevalent than ATD in Japan in the past, but recent epidemiologic evidence has been reported showing that the prevalence of ATD has surpassed that of VaD.[1)]

Diagnosis

Whether Alzheimer type dementia or vascular dementia, dementia must be diagnosed first. The latest diagnostic criteria of the American Psychiatric Association are set forth in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).[2)] Although criteria for diagnosing *dementia per se* were included before the book was revised (that is, in DSM-IIIR), there are no such criteria among the current diagnostic criteria.

The fundamental concept is one of an acquired state of chronically impaired intellectual function, but the following 4 conditions must be met: ① There is impaired ability to learn new information or to recall previously learned information, that is, multiple deficits in intellectual function including memory impairment; and in addition to memory impairment, ② there is also at least one of (a) aphasia, which is a language disturbance, (b) apraxia, which is impaired ability to carry out motor activities despite intact motor function, (c) agnosia, which is failure to recognize or identify objects despite intact sensory function, and (d) disturbance in executive functioning, which includes planning, organizing, sequencing, and abstracting; and due to these deficits, ③ there is impairment of occupational or social functioning, with significant decline in functioning from the previous level; and ④ the deficits are not seen exclusively during the course of consciousness disturbances typified by delirium.

Specifically, early changes can include asking about the same matter repeatedly, losing concern for, or interest in, things, becoming angry easily over trivial matters, and losing the ability to make plans. Although taken individually many of these changes would be considered nothing more than effects of aging, there is cause for serious concern when multiple changes develop and are seen continuously in daily life for more than six months.

For example, let's take a case in which there are the following complaints by a member of an outpatient's family:

> Grandma is very forgetful. She's been like that for about three years now, but early this year, she lost her new bankbook she had just got. That's the third one she's lost. Lately, when she gets dressed, she's been wearing light clothing even when it's cold, and sometimes she puts on things with the back of the garment in the front. At night she sleeps deeply.

Let's apply the diagnostic criteria to this case. Forgetfulness began 3 years earlier, and it interfered with the woman's daily life in that she lost her bankbook. Her wearing of light clothing in cold weather indicates disturbance in executive functioning, in that she dose not seem to be able to make judgments about conditions around her. Favorable sleep can be interpreted as indicating the absence of delirium. This amount of information is fully sufficient for dementia to be suspected. The approach used here consists of applying criteria for dementia to information obtained from the family or a caregiver of the affected individual. Family members who are highly familiar with the normal ways of the affected person should be asked about his or her symptoms and ways in the family. It is not unusual for there to be differences in the reliability of what family members who live with the affected person say about him or her, and what family members who merely occasionally

Table 1 DSM-IV Criteria for Diagnosis of Alzheimer Type Dementia

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
   (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   (3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

Code based on presence or absence of a clinically significant behavioral disturbance:

294.10 Without Behavioral Disturbance: if the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.

294.11 With Behavioral Disturbance: if the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., wandering, agitation).

Specify subtype:

With Early Onset: if onset is at age 65 years or below

With Late Onset: if onset is after age 65 years

Coding note: Also code 331.0 Alzheimer's disease on Axis III. Indicate other prominent clinical features related to the Alzheimer's disease on Axis I (e.g., 293.83 Mood Disorder Due to Alzheimer's Disease, With Depressive Features, and 310.1 Personality Change Due to Alzheimer's Disease, Aggressive Type).

visit the person say. Furthermore, the affected person probably should not be present when family members are asked about his or her symptoms. Whether one has dementia or not, hearing questions asked about one's own behavioral manifestations is not pleasant.

In some cases, such as those of persons who are alone, such information cannot be obtained. The affected person cannot be asked "Do you wander?" When dementia is mild, optimistic answers about one's own impairment are typical, and when dementia advances, understanding the questions becomes difficult for the patient. In such cases, a question test such as the revised Hasegawa Dementia Scale[3] is used. This test can be performed if one knows only the patient's date of birth beforehand. The full score is 30 points; if the score is 20 points or less, dementia can be suspected. However, dementia cannot be diagnosed by this test alone because patients whose motivation is insufficient or who are in a depressed state have lower scores.

Dementia is not seen only in the elderly. It occurs in young persons too, accompanying a variety of diseases including systemic and central nervous system diseases. The conditions of progressiveness and irreversibility are not included.

Criteria for Diagnosis of Alzheimer Type Dementia

Diagnostic criteria for ATD are introduced below. Currently there are 3 different sets of criteria for diagnosing this disease: ① the 10th edition of the World Health Organization's International Classification of Diseases (ICD-10),[4] ② DSM-IV, the criteria of the American Psychiatric Association, which were mentioned above (Table 1),[2] and ③ criteria developed jointly by a work group of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) of the United States and the Alzheimer's Disease and Related Disorders Association (ADRDA) (NINCDS-ADRDA) (Table 2).[5] In Japan, the DSM-IV criteria are commonly used in the clinical practice, and the NINCDS-ADRDA criteria mainly in research.

Because specific diagnostic markers that can be used prior to onset have not been found for ATD, diagnosis of this disease depends on symptomatology and clinical examination including imaging for differential diagnosis. Diagnosis of ATD using DSM-IV requires diagnosing dementia as described above, and then, broadly speaking, ruling out central nervous system conditions, systemic conditions, and drug toxicity.

The central nervous system diseases include cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, and brain tumor. All of these diseases can be diagnosed by characteristic signs together with imaging. Typical systemic conditions are hypothyroidism, deficiency of vitamin B_{12}, folic acid, or niacin, hypercalcemia, and neurosyphilis; these can be excluded by routine hematologic and blood chemistry tests. Finally, any drugs the patient is taking must be considered.

In the outpatient clinic, scattered small infarcts are frequently seen on imaging in patients who had been thought to have typical ATD with onset several years in the past. There are cases in which clinical stroke cannot be confirmed by interviewing family members, and other cases in which someone will say "Now that you mention it, I was told about a cerebral infarction in the hospital more than 10 years ago". There is a tendency to diagnose cases like this as *mixed dementia*, but it has been pointed out that a diagnosis of *ATD with cerebrovascular disease* is preferable.[6] One reason for this preference is that it is unknown whether development of dementia is causally related to cerebrovascular disease. This viewpoint is also used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), which is a large-scale cooperative research project being conducted in the United States to understand the clinical course of ATD. The viewpoint is a practical one.

Criteria for Diagnosis of Vascular Dementia

Several different sets of diagnostic criteria are also used for VaD. Like ATD, there are ICD-10[4] and DSM-IV (Table 3)[2] criteria; in addition, there are criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC)[7] in the United States as well as criteria prepared by a joint research group of the United States and Switzerland (National Institute of Neurological Disorders and Stroke [NINDS] and the Association Internationale pour la Recherche et l'Enseignement Neurosciences [AIREN]) (Table 4).[6]

These various diagnostic criteria cannot be introduced in detail here, but their characteristics will be discussed. In the American Psychiatric Association's DSM-IV, the presence of dementia and of cerebrovascular disease causing the dementia is a condition for a diagnosis of VaD. The term *multi-infarct dementia* (MID) found in DSM-IIIR is not used in DSM-IV. MID, which was proposed by Hachinski[8] some time ago, had been used as a synonym of VaD, but in the ICD-10 criteria, MID was clearly

Table 2 NINCDS-ADRDA Work Group Criteria for Diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:
- — dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- — deficits in two or more areas of cognition;
- — progressive worsening of memory and other cognitive functions;
- — no disturbance of consciousness;
- — onset between ages 40 and 90, most often after age 65; and
- — absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:
- — progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- — impaired of activities of daily living and altered patterns of behavior;
- — family history of similar disorders, particularly if confirmed neuropathologically; and
- — laboratory result of:
- — normal lumbar puncture as evaluated by standard techniques,
- — normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and
- — evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:
- — plateaus in the course of progression of the illness;
- — associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- — other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- — seizures in advanced disease; and
- — CT normal for age.

IV. Features that make a diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:
- — sudden, apoplectic onset;
- — focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- — seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:
- — may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- — may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and
- — should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:
- — the clinical criteria for probable Alzheimer's disease; and
- — histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:
- — familial occurrence;
- — onset before age of 65;
- — presence of trisomy-21; and
- — coexistence of other relevant conditions such as Parkinson's disease.

Table 3 DSM-IV Criteria for Diagnosis of Vascular Dementia

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.

D. The deficits do not occur exclusively during the course of a delirium.

differentiated from VaD by manner of onset. According to the ICD-10 criteria, MID is defined as dementia that meets all the criteria of VaD and develops gradually as mild ischemic episodes occur repeatedly. Furthermore, the term *MID* is not used in the ADDTC or NINDS-AIREN criteria. The diagnostic criteria in these two sets are arranged for *probable*, *possible*, and *definite* VaD, which is the type of classification used for Alzheimer's disease diagnostic criteria that are often employed in research. The ADDTC criteria consider only ischemic lesions; hemorrhagic and hypoxic lesions are not considered. In the NINDS-AIREN criteria, however, it is stated that VaD is a complex disorder caused by ischemic, hemorrhagic, and hypoxic cerebral lesions. The NINDS-AIREN criteria, therefore, can be readily accepted in Japan.

Furthermore, in the ADDTC criteria, a *mixed dementia* category is established in addition to the *probable*, *possible*, and *definite* categories. According to the ADDTC criteria, dementia cases in which one or more systemic or cerebral disease is present and thought to be causally related to the dementia should be diagnosed as *mixed dementia*. According to this viewpoint, therefore, mixed dementia can include cases with complications such as hypothyroidism or alcoholism. Acceptance of the ADDTC criteria is problematic for this reason.

One of the NINDS-AIREN criteria includes the condition that onset of dementia occur within 3 months following a recognized stroke. While acceptance of this condition for application to research subjects may be possible, it is doubtful that the condition is appropriate for use as a criterion in the normal clinical setting; the normal view would probably be that the condition is too strict. In any event, the current state of affairs is one in which, compared with diagnostic criteria for ATD, consensus has still not been achieved on diagnostic criteria for VaD, including the interpretation of imaging findings.

Cases diagnosed as *probable AD* by the NINCDS-ADRDA criteria were assessed by the CERAD pathological diagnostic criteria for AD,[9] and as a result of that assessment, approximately 80% of those cases were pathologically diagnosed as AD[10]; however, if diagnostic criteria for senile dementia are reviewed collectively, the operational criteria that are actually used are still insufficient. In the ATD diagnostic criteria for use in research, there is the item that cognitive impairment be confirmed by neuropsychological testing; this item

Table 4 NINDS-AIREN Criteria for Diagnosis of Vascular Dementia

I. The criteria for the clinical diagnosis of *probably* vascular dementia include *all* of the following:
   1. ***Dementia*** defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.

      Exclusion criteria: cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.
   2. ***Cerebrovascular disease***, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI) including *multiple large-vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as *multiple basal ganglia* and *white matter lacunes* or *extensive periventricular white matter lesions*, or combinations thereof.
   3. ***A relationship between the above two disorders***, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II. Clinical features consistent with the diagnosis of *probable* vascular dementia include the following:
   (a) Early presence of a gait disturbance (small-step gait or marche à petits pas, or magnetic, apraxic-ataxic or parkinsonian gait);
   (b) history of unsteadiness and frequent, unprovoked falls;
   (c) early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease;
   (d) pseudobulbar palsy; and
   (e) personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include:
   (a) early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging;
   (b) absence of focal neurologic signs, other than cognitive disturbance; and
   (c) absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of *possible* vascular dementia may be made in the presence of dementia (section I-1) with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of *definite* vascular dementia are:
   (a) clinical criteria for *probable* vascular dementia;
   (b) histopathologic evidence of CVD obtained from biopsy or autopsy;
   (c) absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and
   (d) absence of other clinical or pathologic disorder capable of producing dementia.

Fukatsu, R. and Nakano, M.: Vascular Dimentia. (Ed.: Homma, A. and Takeda, M.), *Rinsho Seishin Igaku Koza Vol.12 (Lecture on Clinical Psychiatry, Vol.12)*, Senile Mental Disorders. Nakayama Shoten, Tokyo, 1998: 173–200. (in Japanese)

is unique in that operational criteria have been established. In an article comparing 4 sets of diagnostic criteria for VaD, it was shown that there was little agreement among the different sets of criteria.[11)]

Conclusion

Compared with the situation in other countries, research on the use of diagnostic criteria and on clinical pathology is not especially active in Japan. The first antidementia drug targeting

ATD is in clinical use in Japan since November 1999. Development of antidementia drugs targeting VaD is also proceeding vigorously. The long-term care insurance system started in April 2000. Under these circumstances, voices saying that diagnosis of dementia is difficult are clearly heard. Yet the need for early diagnosis of dementia will grow. It is hoped that a more vigorous discussion will take place in Japan too.

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Psychotropic-induced Water Intoxication and Its Countermeasures

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Abstract: The incidence of polydipsia and water intoxication is high in psychiatric patients. We studied the status of water intoxication among 4,882 in-patients, mostly of psychiatry hospitals. The subjects were 58% men, 42% women, mean age 53.6, and 72% of them were diagnosed as schizophrenia and related disorders. Using the polydipsia behavior assessment scales developed by us, we found polydipsia approximately 20% of the subjects. As for clinical factors related to polydipsia, a significant number of polydipsia patients were found among men and smokers, and also a significant number of patients diagnosed as schizophrenia, mental retardation or epilepsy. As for the relation to the drug therapy, polydipsia patients received significantly higher doses of antipsychotics compared to non-polydipsia patients. Anti-epileptics and anti-parkinsonism agents were more frequently used in the polydipsia patients. When serious cases among these polydipsia patients were defined as "pathological polydipsia", there were, however, no difference in the antipsychotic doses between the pathological and the non-pathological polydipsia patients. It was concluded that while the drug therapy is highly relevant to development of polydipsia, other factors were more relevant in serious cases.

Key words: Water intoxication; Psychotropics; Excessive water consumption; SIADH

Introduction

Within the daily clinical milieu in psychiatry, patients who consume large quantities of water are often observed to develop disturbance of consciousness or seizure due to hyponatremia. This phenomenon is described as water intoxication.

Development of water intoxication is discussed often in relation to treatment with psychotropics, but the incident was first reported in 1930s prior to development of psychotropic agents. For instance, Hopkins and Sleeper *et al.* measured the daily urine quantities of 92 schizo-

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Table 1 Past Reports on Polydipsia and Polyuria

Author	Jose & Perez-Cruet	Blum *et al.*	Lawson *et al.*	Okura and Morii	Vieweg *et al.*	Evenson *et al.*	Godleski *et al.*	Bremner and Reagan	Matsuda	Nakayama *et al.*
Year reported	1979	1983	1985	1986	1986	1987	1988	1991	1992	1995
No. of cases	239	241	S:35 non-S:7 N:31	225	103	2,201	34	877	247	2,252
Country	USA	USA	USA	Japan	USA	USA	USA	UK	Japan	Japan
Incidence (%)	6.6	17.5	S:20	3.1	39	6.2	59	3.5	20	12.0
Mean age			S:30.9 non-S:32.1 N:33.5		M:37.6 F:47.0	PD:50.9 All:60.3	All:36.4 PD:34 non-PD:40	PD:42 All:49	41.9	
Risk factors		(smoking)	schizo-phrenia			schizo-phrenia (female)		schizo-phrenia (male)		

S: schizophrenia, non-S: nonschizophrenic patients, N: normal controls, PD: polydipsia, non-PD: non-polydipsia
M: male, F: female

phrenic patients and reported that the quantities were about twice as much as those of healthy persons. Table 1 lists past reports concerning polydipsia and polyuria.

As the causes for water intoxication, SIADH (Syndrome of inappropriate secretion of antidiuretic hormone) which is abnormal secretion of ADH (anti-diuretic hormone), side-effects of psychotropics, and morbid conditions of psychosis are suggested, but no definite conclusion has so far been drawn. This paper focuses on the result of the largest ever scale study conducted on about 5,000 patients supervised by Prof. Kamijima of Showa University Faculty of Medicine, with particular emphasis on the clinical features of polydipsia and water intoxication and its countermeasures.

Clinical Picture of Polydipsia and Water Intoxication

In view of the high prevalence of water intoxication among psychiatric patients, with some cases culminating in death, many studies have so far been conducted. However, there are so far no definition agreed by the researchers of this area and several terms such as "psychogenic polydipsia" and "compulsive water drinking" are used.

In the present study, the patients observed to have any one of the signs including bodyweight gains of at least 3 kg/day, polyuria or incontinence, low specific gravity urea, and hyponatremia among those who have developed polydipsia were defined as showing "pathological polydipsia". The patients who developed the CNS symptoms such as disturbance of consciousness, seizure or vomiting were defined as suffering from "water intoxication".

1. Subjects

In our study, the subjects were 4,882 inpatients of 10 psychiatric hospitals and psychiatric wards of 2 general hospitals. The subject breakdown shows 58% of men, 42% women, mean age 53.6, and the average duration of illness was 24.6 years. Diagnostically, 72% were schizophrenia and related disorders, 11% had

Table 2 Evaluation Sheet for Polydipsia

A. Has the following behavior been observed <u>for two days or more in the last six months</u>? Please check the box.		
• Is seen always holding a glass in hand	☐ (1) Yes	☐ (2) No
• Stops at a faucet or a kettle with a glass in hand and continues drinking water	☐ (1) Yes	☐ (2) No
• Continues drinking water by having a bottle or glasses nearby	☐ (1) Yes	☐ (2) No
• Drinks water directly from the faucet	☐ (1) Yes	☐ (2) No
• Frequency and intake amount of coffee or soft drink are enormous	☐ (1) Yes	☐ (2) No
• Drinks water frequently within the day	☐ (1) Yes	☐ (2) No
• Continues drinking water by disregarding an order not to drink so much	☐ (1) Yes	☐ (2) No
• Gets angry and resists an order not to drink so much	☐ (1) Yes	☐ (2) No
• Drinks water secretly at places such as toilet or wash basin which are not normal drinking places	☐ (1) Yes	☐ (2) No
• Drinks a lot of water in one gulp	☐ (1) Yes	☐ (2) No
• Drinks soiled water from toilet, urine, or water from puddle	☐ (1) Yes	☐ (2) No
• Volunteers information that he/she is drinking lots of water including soft drinks	☐ (1) Yes	☐ (2) No
B. During the last six months, was prevented from drinking lots of water by having been forced to deposit the glass or bottle with the staff, was placed in an isolation ward, or was restrained the amount of drinking water	☐ (1) Yes	☐ (2) No
If <u>yes</u> → ☐ Check the amount of water drinking	☐ Restrain the amount of water drinking	
☐ Force to deposit the glass or bottle with staff	☐ Check the amount of urine	
☐ Place in the protective ward	☐ Others ( )	

organic psychotic disorders, 4% each had either of mental retardation, alcoholism, drug dependence, or maniac-depressive psychosis.

Twelve items regarding polydipsia behavior of the subjects were studied. As shown in Table 2, polydipsia was defined if a patient showed at least one of the 12 items of the Table 2.

2. Polydipsia and clinical factors

The study revealed approximately 20% of subjects ($n = 972$) were polydipsia. Polydipsia is found in significantly more men and smokers and that it is highly prevalent among patients of schizophrenia (21%), mental retardation (31%), and epilepsy (33%).

Since the definition of polydipsia is not necessarily consistent in previous studies, direct comparison with the present study is difficult. However, many studies cited "male gender", "smoking", "schizophrenia", and "mental retardation" as clinical factors related to polydipsia, which are similar to the result of the present study.

3. Polydipsia and psychotropics

Antipsychotic doses were expressed as chlorpromazine equivalent, and its relation with polydipsia was studied. In the high antipsychotic dose groups, polydipsia was observed at a high incidence. When the daily antipsychotic doses of the groups with and without polydipsia were compared, the dose was significantly higher in the polydipsia group (1,281 mg chlorpromazine equivalent) than in the non-polydipsia group (930 mg chlorpromazine equivalent). A similar result was obtained when the subjects were limited to schizophrenia patients (Fig. 1).

We then studied the relation between the types of psychotropics and polydipsia. There were significantly more polydipsia patients among those receiving anti-epileptic or anti-parkinsonism agents.

Because most of surveyed subjects were receiving plural psychotropics, logistic regres-

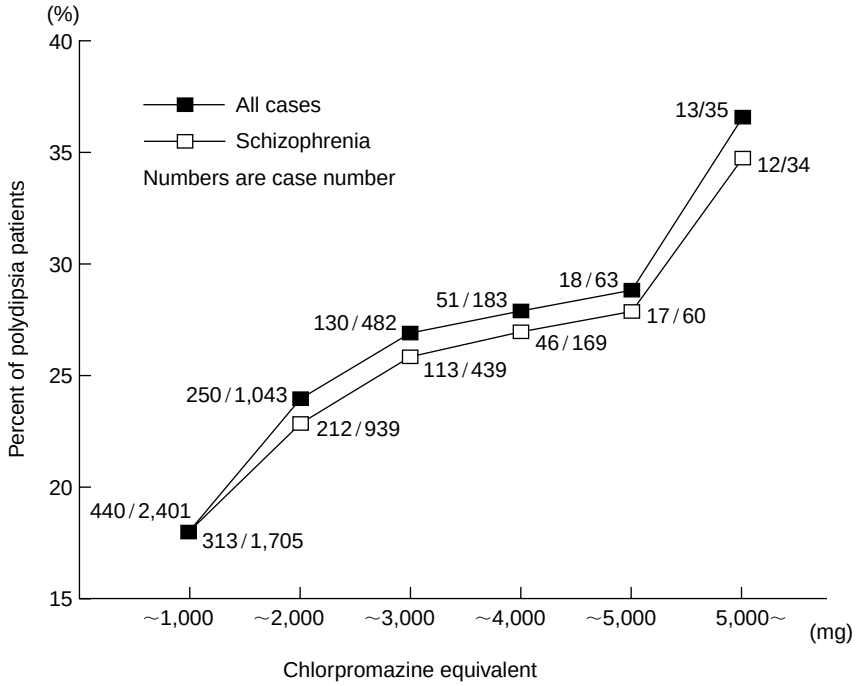

Fig. 1 Polydipsia and antipsychotic medication

sion analysis was conducted with psychotropic administration as a variable in order to evaluate effects of individual drugs. The result showed that polydipsia was likely to occur among significantly more of those receiving psychotropic medicine such as chlorpromazine, levomepromazine, propericyazine, perphenazine and zotepine, anti-epileptics such as phenytoin, anti-anxiety agents such as diazepam, hypnotics such as bromovalerylurea, and anti-parkinsonism agents such as promethazine.

No consistent conclusion has been drawn regarding the relation between polydipsia and drug therapies. While there are reports that psychotropic agents induce polydipsia and water intoxication, there are also studies that recognized the fact that polydipsia and water intoxication improved with improvement of psychiatric symptoms by the psychotropic therapy.

According to the present study, however, the incidence of polydipsia is higher if the antipsychotic dose is higher, and there is a significant relation between polydipsia and drugs such as phenothiazines. It is therefore desirable to reduce the psychotropic dose as much as possible by substitution with other drugs in order to prevent polydipsia, particularly that of phenothiazine with its intense sedation effect, during the chronic phase.

Although previous reports point out the risk of drugs other than psychotropics such as carbamazepine, thiazide, tolbutamide, no consistent view has been presented.

One of the mechanisms by which water intoxication develops by psychotropics is probably abnormal ADH secretion. There are reports that psychotropics such as chlorpromazine, fluphenazine, and thioridazine, anti-depressants such as imipramine and amitriptyline, and anti-epileptics such as phenytoin and carbamazepine promote ADH secretion. However, another report suggests that abnormality of the ADH regulation system is due to psychosis itself. While the effects of psychotropics on development of polydipsia and water intoxication cannot be denied, the morbid conditions *per se* of

the disease are believed to be relevant, warranting further studies.

4. Pathological polydipsia and water intoxication

As discussed above, 972 or approximately 20% of 4,882 psychosis patients were found with polydipsia.

Those who were observed to have gained at least 3 kg / day of bodyweight or to have developed polydipsia or incontinence, low specific gravity urea or hyponatremia in the six months previously were defined as "pathological polydipsia", and those whose polydipsia was accompanied with the CNS symptoms such as disturbance of consciousness, seizure or vomiting were defined as "water intoxication".

Pathological polydipsia was found in 45% of polydipsia patients and water intoxication in 3% of polydipsia patients. Compared to reports of other institutions, the incidence of water intoxication was rather low, but this may be attributable to the fact that only the serious cases were selected as water intoxication according to the definition employed in this study.

Polydipsia patients were then divided into two, pathological polydipsia and non-pathological polydipsia, and the relation between pathological polydipsia and clinical factors was studied. In comparison of pathological polydipsia patients and non-pathological polydipsia patients, no significant difference was seen in terms of gender or smoking. As for diagnosed disease entities, the incidence rose in the order of epilepsy, mental retardation, and schizophrenia.

We then studied the relation between the psychotropic therapy and pathological polydipsia. The daily dose of antipsychotics was significantly higher in the pathological polydipsia group than in non-pathological group. However, when a similar comparison was made among those administered antipsychotics in the pathological polydipsia group, the difference was not significant. By logistic regression analysis, the factors related to pathological polydipsia were sought. Significant explanatory variables were the age at the onset, smoking, schizophrenia and, amobarbital.

In view of the above result, it was concluded that while psychotropics are significantly related to development of "polydipsia", their effects are limited, suggesting that other factors do participate in serious or chronic polydipsia.

Countermeasures for Polydipsia and Water Intoxication

Because of the poor understanding of pathophysiology of polydipsia and water intoxication, we are currently compelled to rely on the nosotropic treatment. In absence of radical treatment, it is necessary to detect polydipsia early, to prevent progress to serious water intoxication, and to treat hyponatremia early if water intoxication is discovered, so that progression to grave, life-threatening conditions accompanying disturbance of consciousness or seizure may be prevented.

As for prevention of polydipsia, patients should be placed under surveillance by checking and controlling the amount of water they drink, having them deposit their glasses and bottles of water with the staff, measuring the amount of urine and restricting activities by the use of the seclusion room.

When polydipsia is detected by observation of the daily water drinking behavior and bodyweight measurement, serum sodium level and osmotic pressure, the specific gravity of urine and osmotic pressure should be measured frequently and the degree of water retention be learned. Patients whose diurnal bodyweight changes are excessive are likely to be ingesting excessive quantity of water, and if their water intake is adequately controlled, their chances of developing water intoxication may be prevented.

The CNS symptoms due to hyponatremia appear generally when the serum sodium level rapidly lowers. In the case of water intoxication patients, they often do not develop symptoms even when their serum sodium level has gone down below 120. If the CNS symptoms such as

seizure or disturbance of consciousness appear, drip infusion of physiological saline or hypertonic saline solution is necessary.

Such behavioral measures as well as the review of drug therapy are necessary for prevention of polydipsia and water intoxication. It is clear from our data mentioned above that various psychotropics are one of the causes that induce polydipsia. The psychotropic doses should be decreased as much as possible by considering the mental conditions of patients, and concurrent dosing of multiple drugs should be avoided so that water intoxication may be prevented.

In recent years, it is pointed out that some drugs may possibly be effective for treatment of polydipsia and water intoxication. There are reports that propranolol, naloxone, and angiotensin converting enzyme antagonists are effective for treatment of polydipsia as well as demeclocycline with its anti-ADH activity, and the combined use of lithium and phynytoin is also effective for hyponatremia. Clozapine, a antipsychotic for atypical psychosis, is also reported to be effective for hyponatremia. All these reports warrant further studies.

Conclusion

As polydipsia and water intoxication are often encountered in clinical psychiatry and could be sometimes life threatening, adequate diagnosis and countermeasures are necessary.

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Guidelines for the Use of Antimicrobial Drugs

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Key words: Antibiotics; Prophylactic drug; Therapeutic drug; Post operative infection

The Drugs Used for Prophylactic Purposes in Protection against Postoperative Infection

Antimicrobial drugs used in the field of general gastroenterological surgery are briefly classified into two groups according to the purposes: The drugs used for prophylactic purposes in protection against postoperative infection, i.e., they are administered for the purpose of preventing the occurrence of postoperative infection in the perioperative stage, and the drugs used for the treatment of postoperative infection, i.e., they are administered to the patients who develop infection postoperatively.

The drugs used for prophylactic purposes in protection against postoperative infection are administered for the purpose of preventing the occurrence of infection following clean surgery and semi-contaminated surgery. The drugs used for the treatment of infection are administered for the purpose of treating postoperative infection or infection developing after contaminated surgery. The use of antimicrobial drugs for the purpose of preventing and treating postoperative infection in gastroenterological surgery must be considered according to the distinctly classified two types of drugs, the drugs used for prophylactic purposes in protection against postoperative infection and the drugs used for the treatment of postoperative infection.

Classification of Postoperative Infectious Diseases

Postoperative infectious diseases are classified into surgical site infection (SSI) and remote infection (Table 1). Since remote infection is highly likely to be exogenous, the drugs used for prophylactic purposes in protection against postoperative infection are usually administered for the purpose of preventing SSI. The incidence of SSI varies with the degree of surgical contamination.[1)]

The Basic Policy on Selection of the Drugs Used for Prophylactic Purposes in Protection Against Postoperative Infection

The use of the drugs with broad antibacterial spectra as the drugs used for prophylactic purposes in protection against postoperative infection makes indigenous bacterial flora to become

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Table 1 Classification and Pathogenic Bacteria of Postoperative Infectious Diseases

Classification of infectious diseases		Pathogenic bacteria
SSI	Infection at the site directly influenced by surgical procedures (surgical site infection: SSI) Wound infection (in a narrow sense), Intraperitoneal abscess, Mediastinal abscess, Pyothorax	Indigenous bacteria in the digestive ≒ Endogenous infection
Remote infection	Infection at the site that is not directly influenced by surgical procedures (remote infection) Respiratory infection, Catheter infection, Urinary tract infection, Drain infection	Contaminated bacteria in a hospital environment ≒ Exogenous infection

*The drugs used for prophylactic purposes in protection against postoperative infection are usually designed to prevent SSI.

Table 2 Practical Selection of Antimicrobial Drugs Used in Perioperative Stage

	The drugs used for prophylactic purposes in protection against postoperative infection	The drugs used for therapeutic purposes against postoperative infection
Semi-contaminated surgery		
Surgery for the upper digestive tract	First generation cephems (CEZ)	Second generation cephems (CTM, CMZ) Third and a half generation cephems (FMOX, CPR, CZOP) ↓ Carbapenem antimicrobial drugs (IPM/CS, PAPM/BP)
Surgery for the lower digestive tract	Second generation cephems (CMZ, CTM)	Third and a half generation cephems (FMOX, CPR, CZOP) ↓ Carbapenem antimicrobial drugs (IPM/CS, PAPM/BP)
Contaminated surgery		
Mild case·Early stage	Second generation cephems (CMZ, CTM)	Third and a half generation cephems (FMOX, CPR, CZOP) ↓ Carbapenem antimicrobial drugs (IPM/CS, PAPM/BP)
Severe case and Shock	Carbapenem antimicrobial drugs (IPM/CS, PAPM/BP)	

irregular and accelerates colonization of exogenous pathogenic bacteria. For this reason, the targets for the prophylactic antimicrobial drugs used in semi-contaminated surgery include one or two species of contaminated bacteria of the surgical site. The antimicrobial drugs are not changed only for the reason including surgical stress, patient's age, or underlying disease.[2)] The antimicrobial drugs used in contaminated surgery, however, are selected in view of perforated organs, the course after the occurrence of infection, and the severity of the infection. The antimicrobial drugs selected for contaminated surgery should have broad antibacterial spectra, because the lifesaving factor is the most important for administration of these drugs.

Timing and Period of Administration

The ideal condition about timing of the start of administration of the drugs used for prophylactic purposes in protection against postoperative infection is that the patient's blood level is high when surgical site is most contaminated. In other words, it is ideal for drip infusion to have been initiated one hour before open sur-

gery for the digestive tract, because the surgical site is most contaminated when the digestive tract is exposed in surgery.[3] When it takes a long time for surgery, the drugs are administered again during surgery. Therefore, these drugs may be administered even preoperatively in case of short-time surgery, and they are administered every 3 hours in case of long-time surgery. Antimicrobial drugs for prophylactic purposes in protection against postoperative infection should be administered within 3–4 days including the day of surgery, based on the fact that antimicrobial drugs administered for 3–4 days generally induce the bacteria resistant to the drugs. When signs of infection persist, the drugs must be switched to the drugs used for the treatment of postoperative infection at this time point.

Practical Selection of the Antimicrobial Drugs Applied in the Perioperative Stage

Based on the above description, practical selection of the antimicrobial drugs applied in the perioperative stage is shown below (Table 2).

There are some differences in surgery between Japan and Western countries; the frequency of surgery for esophageal cancer and gastric cancer is high in Japan, as compared to that in Western countries, dissection of the lymph nodes in cancer operation is wide-ranging, and the Japanese people have a hemorrhagic tendency. As shown in Table 2, however, it is noteworthy that the guidelines established by the authors are consistent with the guidelines of SSI prevention, which were established by CDC in U.S. and reported in 1999,[3] in terms of many points about the drugs used for prophylactic purposes in protection against postoperative infection. Further studies may be conducted by surveillance based on these guidelines.

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