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Japan's Clinical Training System
—Current Status and Future Directions—

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Developments in Clinical Training

In 1968, the so-called intern system under which unlicensed medical doctors were required to complete a year of internship as a medical trainee was abolished amidst controversy over the status of the trainees and other contentions. Almost 35 years have now elapsed since regulations were laid down under the Medical Practitioners Law targeting a two-year voluntary clinical training system to replace the compulsory internship.

With the inauguration of this clinical training system, the university department system came gradually to hold the field, and a straight training system that was beneficial to both the trainees and to the departments, and in a sense to regional health care, became mainstream. The system, which enabled students graduating from faculties of medicine to select a "department" from among the faculties of their alma mater and to receive focused training in a specialized field, undoubtedly played a role in supporting the then current system of supplying doctors, in the sense that it cultivated medical specialists, enabling them to reach *terminus ad quem* more rapidly. Many people will recall the way in which medical specialists were lionized in the regions. However, such misconceptions promptly forced us medical professionals to undergo major self-examination.

I asked a doctor from the generation that went through the internship about his experiences, and he recalled his impressions of the time with vivid clarity saying, "As a physician it was one of the most significant years of my life. It enabled me to gain a distinct awareness of the joys and thrills of medicine." For doctors like myself who went through the system after the period of internship was abolished, this emotion is one that we did not have the chance to experience. One hears such comments most frequently from the doctors who elected to undertake their one-year internship in a regional health care facility and not within their university. This is not merely nostalgia or a wistful longing for idyllic times past; as doctors we are now keenly aware of the need to heed the voices of these senior physicians.

Thereafter, a policy based on the vision of

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one prefecture one university, resulted in medical universities being newly constructed across the nation and the further deterioration of the situation. Medical universities in the regions were inundated with applications from the capital and the Kansai area, and graduating students targeted departments in the brand name medical universities in their home prefectures, making no contribution to the universities from which they had graduated. The result was the emergence of mammoth departments, and at the same time, the medical universities in the regions were left with insufficient incoming doctors even to operate their own hospitals.

As these circumstantial changes began to take shape, the detrimental effects of abolishing the intern system, together with those of the training system that replaced it, started to become apparent. Doctors who were unable to acquire the skills and knowledge to practice holistic medicine, what is known as primary care, so as to enable them to consistently undertake specialist training, diagnosis and treatment from the start of their careers, began to penetrate the ranks of medical professionals.

Such developments gave rise to concerns, and although guidance measures were repeatedly undertaken so as to introduce rotational training as opposed to straight training, after all the fanfare the undeniable impression is that the new system was a failure because universities have no emergency department infrastructure and the university doctors' office system, as the supply source for medical doctors, has become a major obstruction.

Japan Medical Association Efforts

I decided to look into the Japan Medical Association's assessment of the situation and discovered that the Association had early registered the problems with the training system and has undertaken measures to deal with them. In the decade spanning 1975 to 1985, reservations were already being expressed regarding the excessively specialized orientation of the training system, and specifically, in 1989 the Association compiled an "Interim Report from the Council for Clinical Training", which was followed in 1991 by the publication of the "Council for Clinical Training Report (I)".

This report contained an indication on "The importance of coordinating under- and postgraduate clinical training, specialist education, and lifelong education". It also pointed out the need to pay attention to both self-initiative and diversity over and above the decisions on the basic curriculum of clinical training, as being an important element in the collaboration between university hospitals and designated clinical training hospitals in the induction of trainees. Furthermore, the report advocated the promotion of open training hospitals in order to cultivate educational personnel, or so-called advisory doctors, recommending the participation of doctors in the field.

In addition, the report clearly spelled out "the need for government efforts in guaranteeing the status of trainee doctors and bringing about the necessary improvements in their working conditions so as to realize training without forcing the trainees to moonlight".

The "Council for Clinical Training Report (II)" was released in 1992. This report referred to a number of specific matters based on the content of the previous report. For example, it stated that "Training extending across a number of hospitals is effective. The content of training to be undertaken at each of the hospitals should be laid down as part of a planned curriculum where each of the components is mutually complementary from the outset". The report further outlined the need for clear-cut methods of evaluating the training and proposed that it would be effective to structure a training curriculum including achievement targets for postgraduate clinical training within the curriculum for licensing medical doctors under the medical society licensing system. In addition, it proposed the establishment of a joint committee (tentatively named the Clinical Training Education Committee) comprising

members from medical societies, medical associations, and other concerned parties, on the basis of the concept that the reciprocal convergence of facilities and advisors within groups of hospitals would be an effective means of improving training conditions.

Amazingly enough, these specific proposals were virtually identical to the matters contained in the "Interim Report (Draft)" of the "Medical Ethics Council, Medical Doctors Subcommittee Council on the Clinical Research System for Medical Doctors", organized by the Ministry of Health, Labor and Welfare, which was finalized in April 2002. Furthermore, the 6th Report of the Council to Promote Lifelong Education of the JMA, which was released in 1994, pointed out the necessity of advancing further concrete discussions to promote reform of the postgraduate clinical research system, and proposed that a study be undertaken to identify the actual situation of postgraduate clinical education. It also indicated the need for a review of the entire process of educating medical doctors in order to clarify the distinct responsibilities of faculty education and postgraduate clinical research within the process.

Furthermore, with regard to the content of the training, the report specified that only compulsory items and standards should be fixed and that the identity of the institutions should be respected, that they should be given freedom to determine other components of the research program. It further indicated the need to establish a third party organization to oversee the overall planning of the research, decide the programs, undertake trainee quota allocation, assessments, and other related matters.

Having heard the arguments for legislating postgraduate clinical research, a string of similar proposals have subsequently been made by the national organization of national, public, and private university-affiliated hospitals and by a committee of the Ministry of Education, Culture, Sports, Science and Technology (MEXT). These proposals included indications on the formulation of a concrete curriculum, the need for decisions on research institutions to be made by trainee doctors after they have gone through a process of public application and selection, in other words, a matching system so that trainee quotas are decided for individual institutions, fixing student allocation at a certain level in order to enhance exchanges with other universities, and it appeared that the universities were finally developing a burgeoning sense of crisis.

The Content of Compulsory Clinical Training

In the midst of these debates, the Medical Practitioners Law was revised in November 2000, so that as of 2004 medical students will be required to undergo two years of postgraduate clinical training.

The key points of the revisions are as follows. After the revisions are enforced, individuals who have obtained a medical doctor's license will be required (1) to undertake a minimum of 2 years training, in other words, to apply themselves to training either at their university hospital or at a designated clinical training hospital as defined by the Ministry of Health and Welfare (currently the Ministry of Health, Labor and Welfare); (2) to have this information recorded in the register of physicians upon completion of the training period, at which point they will be granted a "Completion of Clinical Training Registration Card". In addition, (3) those individuals who are not registered will be required to receive permission from a municipal governor in the event that they want to open a clinic; and (4) any individual who opens a practice (the hospital director) will be required to consign its management to a physician who holds a registration card.

In short, as of April 2004, a number of restrictions will be placed on medical doctors who have obtained a license to practice but fail to complete postgraduate training. Naturally enough, although such individuals have not undergone training they will still have a

doctor's license and will be qualified and authorized to treat patients covered by health insurance plans, they will also be able to open a practice by obtaining permission from a municipal governor. However, in reality it is assumed that close to 100 percent of doctors will receive the training, excluding a number who advance to the basic research course.

The Current Status of Clinical Training and Related Problems

University hospitals are designated as advanced treatment hospitals under the Medical Service Law. In terms of the spirit of the Medical Service Law, the essence of advanced treatment hospitals lies in the provision of progressive treatment and the undertaking of the research needed to do so, and moreover, in the provision of clinical training in advanced medicine. In consequence, severe limitations are imposed on the handling of those ailments with which hospital doctors are routinely confronted, which situation is inappropriate for implementing initial clinical training.

However, and regrettably, the fact of the matter is that at this time postgraduate clinical training is primarily being undertaken at university hospitals. According to the Ministry of Health, Labor and Welfare data, in 2000, a total of 15,554 doctors were receiving postgraduate clinical training, with students from the two years combined. A total of 13,489 doctors, or 86.7 percent, was actually receiving training in line with the current training system. Of these, 10,282 doctors were receiving their training at university hospitals, which in fact accounts for three-quarters of the total, or 76.2 percent.

The Japan Medical Association was given an opportunity to voice its opinions regarding the clinical training system at a debate set up by the Ministry of Health, Labor and Welfare, at which time they sparked controversy by stating that "In principle, postgraduate clinical training at university hospitals should be prohibited, in consideration of the fact that they are advanced treatment hospitals". I do not, however, think that this statement is invalid. University-affiliated hospitals have a considerable responsibility to teach more advanced medical techniques and knowledge to doctors who have completed their initial clinical training, and allow them to undertake more advanced research.

The results of a questionnaire survey relating to clinical training, which was undertaken by the Japan Medical Association in 2001, also indicate an awareness of the problems being caused by the disproportionate weighting of training at university hospitals. Of trainee doctors currently in the system who feel dissatisfied with their training, 43 percent are dissatisfied with training in emergency medicine, 38 percent are dissatisfied with training at regional health care facilities (clinics, geriatric facilities, etc.), and 31 percent expressed frustration with the system for dealing with consultations or complaints from trainee doctors.

Many trainee doctors also voiced dissatisfaction about their income. In fact, according to this survey, 80 percent of respondents receive less than 300,000 yen per month in salary and allowances. In connection with the working conditions at university hospitals in particular, the press has recently been making much of work-related deaths (*karoshi*, or death from overwork) among trainee doctors, and this has become something of a social issue. Trainee doctors are concentrated in a number of university hospitals located in metropolitan areas and are unable to receive sufficient training, or, due to circumstances, are engaged in providing treatment as part of the hospital's work force without adequate remuneration. The tone of the newspaper articles is understandable, given that these trainee doctors are fresh out of university and have their medical licenses but, due to circumstances, are being obliged to work for long hours whilst receiving only nominal training and insufficient pay.

The problem is also compounded by major regional differences, with only around 30 percent of graduates remaining at medical univer-

sities in the regions. Moreover, considered in terms of providing training in the regions, there are currently only around 400 hospitals nationwide that have been specified as designated clinical training hospitals. What's more, looked at in terms of the 363 secondary medical care zones, it becomes clear that even with university hospitals included there are approximately 176 medical care zones, or approximately half the total number, that are without a single training facility. These medical care zones include secondary medical care zones in medium-sized cities, and in many cases encompass sparsely-populated areas where the population is aging, and in no few instances, the shortage of doctors is a serious problem. How is this situation to be resolved? Unfortunately, neither the Ministry of Health, Labor and Welfare, nor the universities are currently able to specify any concrete ideas by way of resolving the problem.

Nevertheless, we at the Japan Medical Association, are assuming that it will be possible for medical institutions in the regions to form groups, independently and without being designated to do so, which would thus enable trainee doctors to receive training in a wide number of areas throughout the country. These expansions are an urgent task and we are attempting to have them realized at the earliest possible time.

Training Methods Advocated by the Japan Medical Association

It is evident that if regional medical institutions and related facilities can collaborate in the formation of institutional groups, even without being designated to do so, then it will become possible for trainee doctors to receive their training across sizeable areas of the country. It is considered that the best method of implementing training is under an organic alliance of distinctive medical facilities. To put it another way, the construction of a system under which senior physicians at the frontline of activities in the regions can provide direct guidance to trainees to replace the existing university hospital-centered training, is considered to be the most important task at this time. In order to give this proposition concrete shape, there are plans to actually implement a pilot (model) training program in the regions.

In specific terms, this would not take the form of contractual relationships between university hospitals, university departments, and designated medical facilities, instead the plans are for local associations of senior doctors, the medical associations, to become guardians so to speak, to utilize all available medical resources in the region, and to implement training whilst evaluating the results by feeding the opinions of the trainees back into the program, in other words, order-made training. As of 2002, preparations are being advanced, mainly within the Tochigi Medical Association and the Oita Medical Association, with the aim of accepting a number of medical trainees for a 2-year period.

The local medical associations have formed institutional groups in conjunction with medical universities. They have established training committees to formulate training programs and select the medical trainees and are appraising the training facilities and evaluating the results of the training. It is hoped that this will mark the first step towards the continuous quest for better training approaches, in other words, the spread of ideal training techniques. This is based on the concept that the doctors belonging to the local medical associations will worry about the medical trainees as if there were their own children and will view the task of raising the next generation of doctors as being one of paramount importance that merits the efforts of every member of the association. I would suggest that the fault of the current training system lies in the very fact that it is not possible for these senior doctors to be seen in action, to directly communicate the joys and thrills of medicine to the medical trainees.

It goes without saying that the practice of

teaching is a tough task. It may be that young medical trainees who are armed with the latest knowledge pose a kind of threat. Nonetheless, if senior doctors in the regions neglect to teach the young trainees and leave the task to universities and a limited number of hospitals, they cannot then lay the blame for their dissatisfaction with the results at the doors of university education. It is necessary for these doctors to take on a role in the process of communicating the attraction and thrill of regional health care within the two-year period. After the training is complete, when these young doctors come to choose their individual specialist paths, they will invariably recall this training period. If we, the doctors in the regions, can be enthusiastic in our contact with these trainees, then the memories of the intern generation that I cited earlier can again be given objective reality today.

The treatment that trainees receive during the training period is also important. The trainees may be required to perform night duties and other tasks within the medical institutions in line with necessity, but it is hoped that they will be paid on a monthly basis so that they can afford to live without having to moonlight, that accommodation and social insurance costs will be kept to a minimum, and that their conditions will be on a par with doctors employed by local medical association, for example. Moreover, the medical trainees are being given membership of the medical associations and are required to take out doctors compensation responsibility insurance. It is hoped that the training system being proposed by the medical associations will meet with widespread approval.

I was recently discussing the training system with a close friend who commented, "Easy for you to say, but it is in fact very difficult to accept medical trainees. My hands are already full enough." No doubt, this is the reality of the matter. However, once I had explained the significance of this training over again, he admitted, "There is a definite need for the system. However, I worry as to how much cooperation it will actually be possible to obtain".

That said, when I discussed this matter with the key executive member of the Tochigi Medical Association, a doctor belonging to the Oita Medical Association, and the staff of Almeida Hospital, they voiced all-out approval of the concept and were convinced that it would be possible to gain the understanding of the majority of doctors. A related party at the medical association hospital also commented that "Much is expected from this training method as a new function for medical association hospitals".

The Impact on Medical Doctors

I would now like to consider the various impacts that the enforcement of postgraduate clinical training is expected to have from a number of perspectives. Health care will assuredly change, although I am sure that this will emerge as an important tool in the ongoing structural reforms of the health care system. In the first instance, if the matter is examined in terms of regional health care, this move will likely see young doctors fresh out of university entering hospitals and clinics that were previously unable to accept medical trainees independently. Seeing young trainees being taught in clinical settings will also furnish patients in the regions with the opportunity to discover new facets to their primary physicians. This is a new direction in the medical world, one that is not biased toward the advanced medicine available in cities and at large hospitals, nor does it give weight to such medicine alone, and one that is likely to change the consciousness and flow of patients. There is no doubt that it will produce closer ties between hospitals and clinics in the true sense of the word.

Next, I would like to discuss the impact on the activities of the medical associations. Medical association hospitals are utilized as joint use facilities, and as I mentioned earlier, they will play a significant role as the nucleus of the training system. It should also be possible for

the medical trainees to be taught by local doctors with their own practices in fields such as ambulatory medicine, which are not available in medical association hospitals. It will be possible for the trainees to give thought to collaborative health care and cooperation, and of the sharing of roles, from the first step of practical medicine onwards. It should also be feasible for them to gain an understanding of the activities of the medical associations *per se*. Research that is performed in the closeted environment of hospitals is cut off from the activities of the medical associations, and it is difficult to anticipate that this will afford trainees with the opportunity to apprehend the role that is actually being performed by regional health care.

The legislation of postgraduate training is likely to deal a major blow to medical universities and university hospitals. Recent inquiries have turned towards exploring the possibilities of limiting training at the graduating university, and I suspect that the department system and the doctor's office system are entering a major transitional phase. It is anticipated that these systems will no longer act as a supply source for physicians, but that they will become a part of the specialized activities that are the true role of universities. It is also hoped that research with a global reach will show exponential growth. Furthermore, the move is expected to have a major impact on faculty teaching in the universities in order that the recognition afforded to individual graduates can be fed back into the reputations of the universities.

To reiterate a matter I mentioned earlier, it is anticipated that enforcing postgraduate training will also link to the resolution of the problem of providing health care in underpopulated areas and medically underserved areas. Moreover, with graduates from a numerous universities pitting themselves against each other, any disparities in the system should be rectified. There should also be some consolidation in establishing a standard way of writing medical records and the style of ordering.

Conclusion

I believe that the introduction of a new training system will have a major impact on the shape of the doctors' office system of the departments in universities and regional health care approaches, and that this will extend to cover the role of the medical associations and faculty teaching in the universities.

As I have mentioned, the Japan Medical Association is of the belief that bringing the initial clinical training system up to scratch is indispensable for breeding good doctors, and specifically, is proposing a training model under which there will be cooperation among multiple health care institutions led by the regions. The legislation of the postgraduate clinical training system will offer a unique opportunity to return to the original approach to doctors training via which senior physicians working in the regions will take on the role of teaching and rearing the young doctors who will lead the next generation. However, it is necessary to be aware that the fate of this opportunity — whether it is to be optimized or extinguished — will come down to the attitudes of each and every one of the doctors currently in active service.

Community-Related Infection that Develops into Hospital Epidemics
—Influenza—

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Abstract: Influenza is an important in-hospital infection. The infection rate when influenza is prevalent exceeds 30% at peak periods. The number of patients with fever can increase markedly in a short period of time. When elderly inpatients contract influenza, about 20% become complicated with pneumonia. Accordingly, it is considered a serious disease that could easily result in death. The basis of any anti-influenza strategy is prevention by vaccination. The vaccine in current use induces favorable antibody reactions in the elderly, causes few adverse reactions and prevents infection. Surveillance to detect the prevalence of influenza is another important measure to prevent influenza. The sooner signs of prevalence are detected, the sooner appropriate measures can be taken. The quick diagnosis kits have recently become available with sufficient sensitivity and specificity. When an influenza outbreak occurs, it is desirable to isolate the patients in order to prevent further infection. Treatment with anti-influenza agents at an early stage is effective. An in-hospital infection countermeasure team should make effective use of vaccination, the quick diagnosis kit, and anti-influenza drugs to control outbreaks of influenza.

Key words: Influenza; Hospital epidemic; Influenza vaccine; Anti-influenza virus agents

Introduction

Influenza is a community-related infection that sometimes becomes epidemic and creates social disruption. Due to its potent infectivity, a large number of patients can contract this disease in a short period of time. Accordingly, it is also an important disease from the standpoint of hospital infection. When influenza epidemics occur, medical staff can be involved in and routine consultations and medical care are substantially influenced. Influenza is often also a cause of death among the elderly and inpatients with serious underlying diseases. This report describes the background of influenza infection in hospitals and its countermea-

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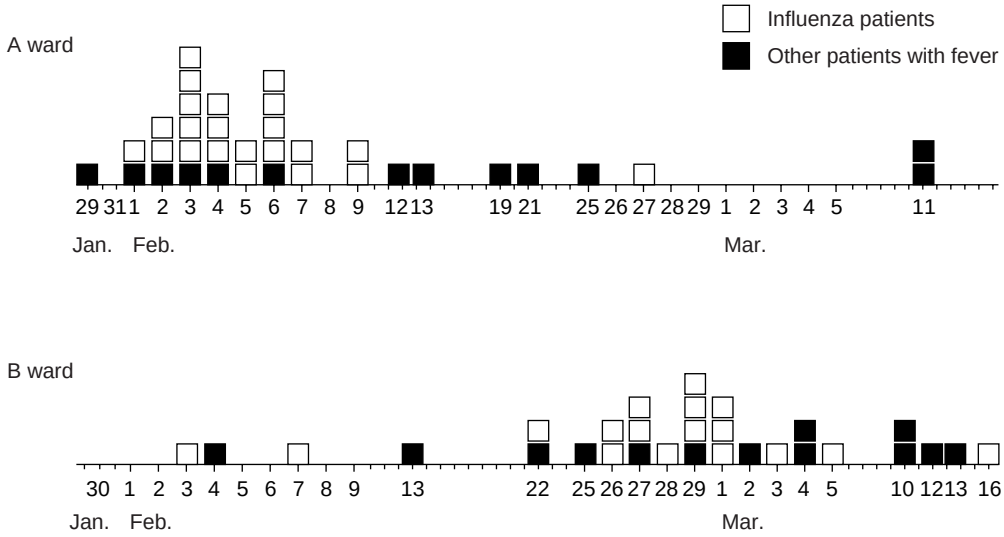

Fig. 1 Number of patients who came down with a fever when influenza was rampant in a hospital

Table 1 Infection Rate of Elderly Inpatients When Influenza Was Rampant in Hospitals

Year	Number of subjects investigated	Type	Infection rate (%)
1992–93	213	A/H3N2	10.8
1994–95	123	A/H3N2	31.7
		B	16.3
		A/H1N1	8.9
1995–96	148	A/H1N1	2.0
1996–97	104	A/H3N2	16.7
		B	8.7

Table 2 Complication Rate of Pneumonia from Influenza in Elderly Inpatients

Year	Number of patients	Number of pneumonia patients	Pneumonia complication rate
1985–86	133	32	24.1%
1991–92	39	10	25.6%
1992–93	23	5	21.7%
1994–95	92	16	17.4%

sures effective for controlling hospital outbreaks.

Influenza as a Hospital Epidemic

When influenza is rampant, the number of inpatients with fever markedly increases. Though the scale of prevalence differs each year, outbreaks are characterized by a sudden marked increase in febrile inpatients that grows to a sharp peak, followed by a gradual decrease in the number of new cases (Fig. 1).[1] The antibody titer of paired sera examined in a hospital showed an infection rate exceeding 30%,[2] indicating the substantial influence of influenza when it becomes rampant in hospitals, especially in hospitals with many elderly inpatients (Table 1).

Influenza is significant as a hospital epidemic because the disease constitutes a direct or indirect cause of death in high risk inpatients even though a spontaneous cure would be expected in general healthy people. Complications with pneumonia can become an especially serious problem. According to our survey, the pneumonia complication rate exceeds 20% when an influenza outbreak occurs among elderly inpatients (Table 2).[3] Accordingly, influenza is a serious disease that can cause death in the elderly with underlying respiratory and

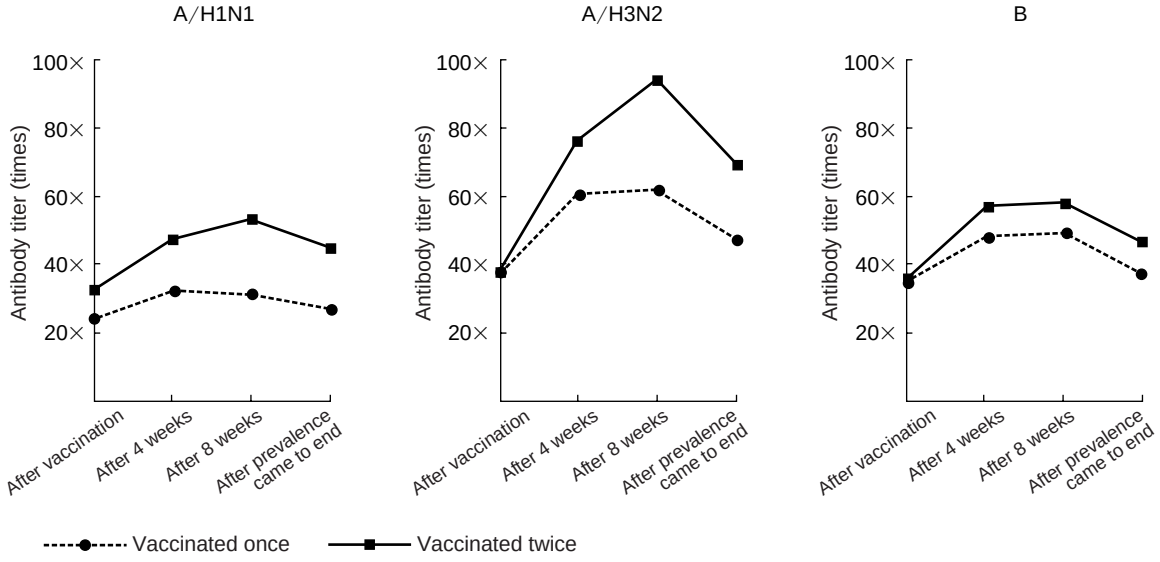

Fig. 2 Increase in HI antibody titer due to influenza vaccination in the elderly

circulatory diseases. In view of the aging of inpatient population, measures to counteract influenza are important.

Measures to Counteract Influenza

1. Surveillance

The first step in any plan to counteract influenza is early detection. Influenza in the community shows different patterns by seasonal outbreaks. Because hospital infection is related to infection outside the hospital, it is necessary to carefully monitor information on epidemics in the community.

Particular attention should be focused on the sudden onset of high fever, a clinical symptom of influenza. When an outbreak occurs, a number of patients with high fever can be found in certain wards. It is necessary to detect such signs as early as possible and to take appropriate measures. As many diseases cause fever, it is often difficult to differentiate influenza by clinical symptoms at the start of an epidemic. In such cases, quick diagnosis kits are very useful. There are several types now on the market. Though each has its own characteristics, all are clinically useful.[4] The diagnostic sensitivity of these kits in elderly inpatients is close to 70% if the kit is used within 3 days after onset. During influenza season, the kits are very useful for differentiating influenza from other influenza-like diseases.[5]

2. Influenza vaccine

Currently, an easy and effective method for preventing influenza is the influenza vaccination. Epidemiological investigation has reported that influenza vaccination can reduce the incidence of pneumonia caused by influenza, the number of patients hospitalized, and the number of deaths caused by this disease. Our long-term survey of elderly inpatients also suggested that vaccination could decrease the number of deaths. The vaccine in current use is considered safe because it favorably induces antibody reactions in the elderly, prevents infection, and causes less adverse reactions.[6]

A single vaccination is generally recommended for adults.[7] Unless the antigenicity of the vaccine strain used in the influenza vaccine is substantially changed, equivalent antibody increase and infection prevention rates have been observed in one and twice vaccinated elderly inpatients (Fig. 2).[8] In view of the cost and

effectiveness, a single vaccination is generally recommended for inpatients.

Vaccination not only alleviates the pain caused by contracting influenza but also prevents a decrease in ADL and curtails prolonged hospitalization due to the patient becoming bedridden as a result of influenza. The vaccination thus reduces medical costs. In Europe and the United States, vaccination is recommended for the elderly, who are regarded as a high risk group for contracting influenza. In Japan, financial aid for influenza vaccination for the elderly was officially introduced in 2001. Accordingly, aggressive vaccination of elderly inpatients is advisable. Physicians and others engaged in medical care should also receive vaccinations.

3. Anti-influenza virus agents

To counteract influenza, it is first of all desirable to isolate the patients to prevent further infection, because the influenza virus is highly infectious. Treatment with anti-influenza virus agents should start promptly in the initial stage of onset. These drugs are not very effective in patients after 48 hours from onset.

Anti-influenza virus agents available in Japan include amantadine and the neuraminidase-inhibitors, zanamivil and oseltamivil.[9] Amantadine is effective only against type A influenza viruses. Neuraminidase-inhibitors are effective against both type A and B influenza viruses. Since these drugs induce few adverse reactions, they can be safely administered to children as well as to the elderly.

The prophylactic use of anti-influenza virus agents is a possible countermeasure at the time of outbreaks. However, it has yet to be appraised. Furthermore, the prophylactic administration of these drugs is not covered by insurance in Japan. By inhibiting the proliferation of the viruses, anti-influenza drugs inhibit person to person transmission, reducing the scope of an epidemic. A study done when type A influenza (Hong Kong flu) was rampant in an institution for the elderly showed that the administration of amantadine to those with fever inhibited the spread of influenza (Fig. 3).[10] The treatment of patients with influenza with anti-influenza virus agents is useful as a measure to control the spread of influenza.

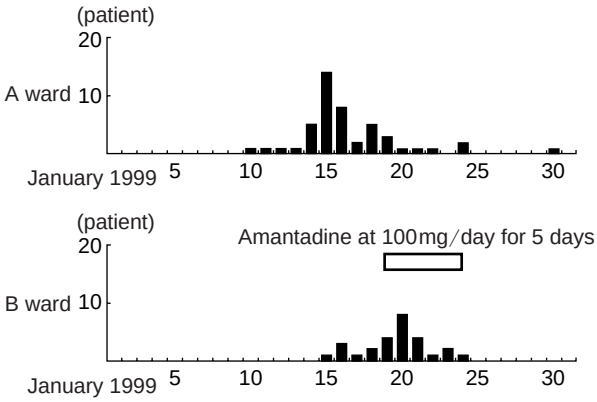

Fig. 3 Number of patients who came down with a fever during an outbreak of type A influenza (Hong Kong flu) in an institution for the elderly

In the prophylactic administration of drugs, the problem is how to determine the best candidates. Who should take the drug first? Should it be patients in the same room, the same ward, high risk patients or medical staff? The use of anti-influenza virus agents at the time of influenza outbreaks requires further investigation. Since the appearance of a new type A influenza virus has recently been suspected, strategies for the appropriate use of anti-influenza virus agents should be planned in advance for cases in which the current influenza vaccine cannot be used or its efficacy cannot be guaranteed.

Conclusion

Remarkable progress has been made in the field of influenza research and treatment. Measures such as maintaining a global surveillance system for the influenza virus, the marketing of quick diagnosis kits, and neuraminidase-inhibitors have contributed much to the suppression of in-hospital influenza infection. Hospital infection countermeasure teams should take advantage of these new tools for controlling influenza.

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Blood Transfusion and Infectious Diseases

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Abstract: In Japan, drawing a lesson from the spread of AIDS and hepatitis C transmitted through blood transfusion, antibody screening was established, followed by the introduction of nucleic acid amplification testing for HIV, hepatitis B virus, and hepatitis C virus. The safety of donated blood has increased dramatically, but there remains the threat of a new variant Creutzfeldt-Jakob disease while bacterial infection is the most urgent practical issue. Management of in-hospital collection of allogeneic blood components and storage of autologous blood is left to each facility, and the risk of transmission of infectious diseases exists. As professionals dealing with blood, which can cause infectious diseases at any time, we should be fully aware of the risks involved and exercise constant caution.

Key words: Blood transfusion; Posttransfusion hepatitis; HIV; Bovine spongiform encephalopathy

Introduction

Many pathogens and pathogenic agents are transmitted via blood, causing infection. Because infusion of blood or its components into the body, or blood transfusion, imports a much greater amount of infectious agents into blood vessels compared with an accidental needle prick, it is one of the medical activities involving the highest risk of infection (Fig. 1). Major disasters such as drug-induced AIDS and hepatitis C have been caused by blood transfusion at the hospital. Thus medical professionals must always question the safety of donated blood, which is medical society's fundamental resource affecting the nation's health and welfare significantly. Blood transfusion should be considered a daily medical activity containing the risk of nosocomial infection.

Transfusion-Transmitted Infectious Diseases

Infectious agents transmitted by blood include hepatitis viruses; syphilitic spirochete; retroviruses such as adult T cell leukemia viruses (HTLV-I/II) and AIDS viruses (HIV-1/2); viruses found in the ordinary environment such as EB virus and cytomegalovirus, which cause asymptomatic infection in many humans; and emerging infectious disease pathogens found in certain areas of some countries other than

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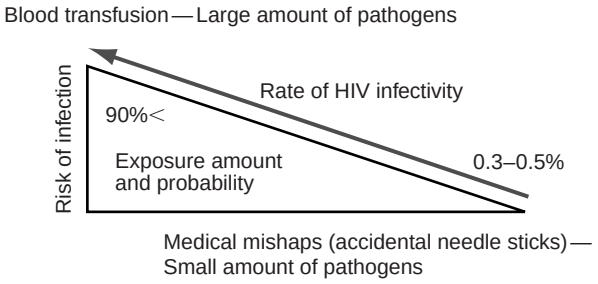

Fig. 1 Nosocomial infection through blood transfusion

Table 1 Infectious Diseases and Pathogens Transmitted Through Blood Transfusion

1. Certain
   - Hepatitis viruses: HAV, HBV, HCV, HDV, HGV
   - HIV-1/2 • HTLV-I/II • HHV-8
   - Cytomegalovirus • EB virus • Babesiosis
   - Parvovirus B19 • Syphilis
   - Bacteria (*Yersinia enterocolitica*)
   - Malaria • Chagas' disease
2. Theoretically possible
   - Lyme disease • Borna disease
   - Crimean-Congo hemorrhagic fever
   - Lassa fever • Ebola hemorrhagic fever
3. Under investigation
   - New variant Creutzfeldt-Jakob disease

CDC, 1996. Items added.

Japan, such as malaria parasite and *Trypanosoma cruzi*, which causes Chagas' disease (Table 1).

Although not definitely reported, the following organisms are also highly likely to cause infection through blood: tropical hemorrhagic fever viruses such as Ebola virus; Borna disease virus, which is an animal encephalitis virus often found in patients with schizophrenia or depression; and Lyme disease-inducing spirochete (*Borrelia*) transmitted by mites.

New variant Creutzfeldt-Jakob disease (nvCJD) resembling bovine spongiform encephalopathy (BSE), which caused panic in Britain and other European countries and has recently been a significant problem in Japan as well, may be transmitted by abnormal prion proteins, the causative agents of the disease, through blood transfusion. The possibility is now being studied.

1. Hepatitis

Japan's transfusion medicine has been a battle against hepatitis. Surprisingly, half of the transfusion recipients had contracted hepatitis because of paid blood donation before a blood donation system was introduced in 1964. Blood came to be supplied totally by donation in 1969 after a six-year transition period, when the incidence rate of posttransfusion hepatitis dropped to 16.2 percent. Then examination of the hepatic function by GOT and GPT and detection for HBs antigen of hepatitis B virus (HBV) were included in the screening of donated blood, reducing the rate to 14.3 percent. After 400 m*l* blood donation and blood component collection started under the revised standards for blood collection in 1986, the rate further dropped to 8.7 percent. In 1989, detection for anti-HBc and anti-hepatitis C virus (HCV) antibodies started, lowering the rate to 2.1 percent. Finally, the rate dropped below 0.48 percent after the initiation of the second generation of tests for anti-HCV antibody in 1992.[1–3)]

However, because of the nature inherent in antibody detection, a few cases were still reported of the development of hepatitises B and C caused by blood donated during the period between infection and antibody development (the window period). Then a screening technique for detecting the viruses themselves at a high sensitivity using nucleic acid amplification testing (NAT) was developed in Japan. This was applied first to mini-pools of samples of plasma derivatives for fractionation along with testing for HIV in 1997; then to 500-sample mini-pools of blood preparations for transfusion in October 1999; and to 50-sample mini-pools in February 2000.[3–5)]

As a result, of the 11,488,868 units of donated blood having passed biochemical and serological tests, 200 were found HBV-positive, 41 HCV-positive, and 4 HIV-positive by October 2001. This translates to the prevention of infec-

tion by the introduction of NAT in 20 cases, 5 cases, and 2 cases, respectively, of the estimated 1.29 million patients receiving blood transfusions annually.[5] This indicates the safety level of the blood preparations for transfusion currently used.

Despite these efforts, cases of posttransfusion hepatitis not of the type A, B, or C occur. Some may be caused by liver-affinitive viruses such as hepatitis G virus (HGV or GBV) or TT virus.[6,7] Ten to twenty percent of patients receiving frequent blood transfusions or chronic dialysis possess anti-hepatitis G virus antibody compared to 1.7 percent for healthy blood donors. Thus, it seems certain that the virus is transmitted by blood. However, the pathogenicity is still unclear.

2. Retroviruses

Testing for anti-HTLV-I and anti-HIV-1 antibodies was included in the screening of donated blood in 1986, and testing for anti-HIV-2 antibody was added in 1994. In western Japan, the proportion of HTLV-I carriers was as large as 1 percent of the population and the rate of infection due to blood transfusion was nearly 10 percent. However, the horizontally infected through blood transfusion rarely develop viral diseases such as leukemia, lymphoma, or neurological symptoms, suggesting that the introduction of antibody detection has assured an almost satisfactory level of safety.[2]

HIV infections have a great impact on society partly because of the poor prognoses for the infected. As stated above, multiple reports of HIV infection through blood donated during the window period led to the introduction of NAT for HIV along with two types of hepatitis viruses.[5] However, it should be noted that the window period exists even with NAT.

3. Parvovirus B19

Parvovirus B19, the cause of epidemic erythema infectiosum, has affinity for red blood cells and causes pure red cell anemia. In patients with chronic anemia such as congenital hemolytic disease, this virus may aggravate the condition. It may also have significant effects on embryos and newborn infants. A large proportion of adults have acquired the antibody to this virus through asymptomatic infection. Therefore screening for the antigen of this virus was introduced to blood donation in 1997, thus assuring safety almost completely.

Because it has no envelope, this virus is resistant to inactivation treatment by heating or solubilizers. Therefore, it can be transmitted by plasma derivatives.[2] Actually, imported derivatives not made from blood donated in Japan were recently found to cause infection at a high rate. In a prospective study of 85 pneumectomy patients receiving local treatment with imported fibrin sealant, viral DNA was detected and transient reticulocytopenia was observed postoperatively in 6 out of 29 patients (20.7 percent) preoperatively antibody negative.[8] This suggests that the establishment of safety standards for imported derivatives is imperative and that those derivatives must be used with caution.

4. New variant Creutzfeldt-Jakob Disease (nvCJD)

Since the first case of nvCJD was found in Britain in 1994, more than 100 cases in Britain, 3 in France, and 1 in Ireland have been observed. This disease bears striking clinical and pathological similarities to BSE (mad cow disease), which occurred explosively in Britain prior to nvCJD, and characteristically develops in the young generation. Thus, this was named nvCJD in order to distinguish it from the original isolated CJD. Like scrapie in sheep or kuru stemming from the cannibalism of the aboriginal people of New Guinea, the body of infection of nvCJD is abnormal prion agents. An epidemiological study strongly suggested that patients had been infected with this disease across the species barrier by ingesting tissues of BSE-infected cows. Infection is completed in the lymphatic tissue of the intestinal tract. The possibility has been shown that prion agents may

be accumulated in lymphocytes, particularly the dendritic cells of lymph follicles, and travel all over the body.[9)]

By 2000, the British government took measures to remove white blood cells from all donated blood before storage while importing all plasma derivatives, for which removal and inactivation of prion agents are difficult, from other countries. Yet whether nvCJD is transmitted by blood remains unclear. Because the incubation period for this disease lasts long, it is possible that many people in the period donate blood. Then immeasurable damage to the nation by blood transfusions is anticipated. Therefore, other European and American countries employed similar policies on the handling of blood. In fact, when sheep were transfused with blood from other sheep that had ingested brain tissues of BSE-infected cows, one sheep developed encephalopathy similar to mad cow disease.[10)] This result strongly suggests the possibility of infection of this disease through blood transfusion, and accumulation of stronger evidence is expected.

In Japan, would-be blood donors are interviewed to exclude people who have spent a certain period of time in European countries, such as Britain or France, where nvCJD and BSE are occurring. However, if BSE goes widespread, Japan may also have to consider adopting those measures that European countries were quick to employ.

5. Bacterial Infection

The safety of blood preparations now seems to be almost perfect against known pathogens that can be detected by screening. Currently the most worrying type of infection is infection with bacteria mixed into blood preparations. Nevertheless, this problem is overlooked or underestimated in Japan. Actually, 1 out of 2,000 units of platelet preparations stored at room temperature is contaminated with bacteria, and it is estimated that more than 150 deaths resulting from those contaminated preparations occur annually in the United States.[11)]

For red blood cell (RBC) preparations, which are stored at low temperature, the psychrophilic bacteria *Yersinia enterocolitica* and *Serratia* pose a threat while for platelet preparations stored at room temperature, indigenous bacteria on the skin including *Staphylococcus epidermidis* are a problem. The highly deadly *Yersinia enterocolitica* contamination is caused by blood from donors with transient bacteremia. It is considered to take three weeks or more of storage for the bacterium concentrations to reach a noxious level. In consideration of the risk, storage of RBC preparations (RBC MAP) is limited to three weeks in Japan though they could be stored for six weeks. Cases of posttransfusion sepsis from platelet preparations are sporadically reported in Japan, and investigation of the conditions is imperative. Depending on the results, manufacturers may be required to perform screening, as some of their European and American counterparts do now.

Problems

1. In-hospital allogeneic blood collection

As stated earlier, blood preparations derived from donated blood collected and processed by the Japanese Red Cross Blood Center for general use are satisfactorily safe thanks to their great efforts. However, many medical facilities still use allogeneic blood collected at the site. Such blood should not be used except in a disaster emergency or when the stock of blood has run out, because blood collected at the hospital can never be guaranteed the safety comparable with the safety of donated blood due to the capability of performing infection screening tests such as NAT. There is no doubt about the relative benefits of using donated blood to the recipient. It should not be allowed if consent to blood transfusion is obtained without informing the patient of this point.

Recently the Japan Society of Blood Transfusion submitted "Guidelines on Collection, Process, and Use of Blood and Its Components

Intended for Treatment at Medical Facilities" to the Ministry of Health, Welfare and Labour. Guidelines on the handling of blood and its components at medical facilities will be published soon.

2. Autologous blood and nosocomial infection

Informed consent to blood transfusion has become required, and use of autologous blood during elective surgery has become common. The duration of preoperative blood storage sometimes extends to six weeks, and there is concern about contamination with bacteria such as *Yersinia enterocolitica*. Therefore, special caution should be exercised to prevent nosocomial infection. The present conditions need to be reviewed and autologous blood should be collected and stored at a dedicated administrative section following the procedures prescribed in the Guidelines on Autologous Transfusion (the Japan Society of Blood Transfusion and the Japan Society of Autologous Transfusion, revised in January 2001). Autologous blood transfusion, which should be far safer than allogeneic blood transfusion, should be re-evaluated. Of course, medical professionals should be careful in handling autologous blood of patients with infectious disease in order to protect themselves.

Conclusion

Blood preparations for transfusion made from donated blood; plasma derivatives such as albumin; allogeneic blood, and autologous blood collected at the hospital; and blood components such as hematopoietic stem cells also collected at the hospital — any of these materials is not free from the risk of infection. As professionals dealing with them, we should be always cautious, understanding the level of the risk. Blood could cause infectious diseases at any time and it is an important object of risk management in the hospital. It is important to implement blood management centered around the director of a dedicated administrative section under consensus of the whole facility (the committee on transfusion therapy).

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Prevention of and Measures against Needlestick Accidents

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Abstract: Needlestick accident is a term that symbolically expresses blood-related infections seen among healthcare workers. Healthcare workers must understand the nature of such infections, and learn how to prevent and deal with needlestick accidents if they are to protect themselves from such infections. The background and specific preventive measures against HBV, HCV, and HIV infections are herein provided, along with daily measures to be taken so that, more importantly, healthcare workers will become aware that all blood and anything possibly contaminated by blood are potential source of infection.

Key words: HBV infection; HCV infection; HIV infection; Needlestick accidents

Introduction

Needlestick accident is a term that is used to represent injury that is incurred by the handling of instruments with a patient's blood.

Although such injuries are always likely to occur during daily medical practice, this is the type of accident that can certainly be reduced if each healthcare worker is careful with himself/herself and others.

While HBV (hepatitis B virus) initially drew attention as the cause of infections caused by such injuries, followed by HIV (human immunodeficiency virus) and HCV (hepatitis C virus), it must be recognize that, in reality, infection can be caused not only by these viruses but by any pathogen in a patient's blood. Although patients with HBV, HCV, and HIV infections tend to get the greatest attention, and the attempts to identify only such patients are prevalent, not all patients can be actually identified since there are patients who have not been tested for these three diseases and unknown carrier of these diseases. The most important thing, therefore, is to consider all blood as a source of infection.

General preventive measures and measures used to deal with accidents caused by the three aforementioned infections are herein discussed.

General Measures for Prevention of Accidents

General measures for prevention of accidents

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have been widely taught in the past 20 years, since guidelines for measures against nosocomial infections, such as HBV infection that became a problem first, were prepared and publicized by the Hepatitis B Research Team of the Hepatitis Research and Liaison Council Division of the Health and Welfare Ministry at the time in 1982.[1] The guidelines also became the bases for guidelines for HIV infection and HCV infection.

They can be summarized as follows:

- Healthcare workers should prepare for invasive medical practice by protecting themselves with gloves, protective gown, and protective glasses.
- Fingers should not touch the tip of an edged instrument during surgery to the extent possible.
- Edged instruments should be used with the utmost care.
- Edged instruments should not be handled carelessly.
- Instruments that have been used should be immediately rinsed with water or soaked in antiseptic solution or water.
- Disposable needles and edged instruments should be disposed into a special container in accordance with specified methods.

However, even if these acts were carried out very carefully, it is difficult to avoid accidents of irresistible force during medical practice. Be that as it may, as a specialist in the field of viral hepatitis, on an average, I still annually encounter at least one case of hepatitis C that have occurred within 2 to 3 months of receiving medical care. This is solid evidence that healthcare workers mediate HCV infection from patient to patient, and shows that the basic daily preventive measures mentioned earlier have still not been thoroughly implemented. The fact that such situations still remain suggests the necessity for healthcare workers to be aware that the risks are rising.

It is necessary for hospitals to make an effort to maintain awareness of infections among healthcare workers by running workshops from time to time through something like a committee especially set up for prevention of nosocomial infections.

At medical institutions, people are commonly seen eating or drinking with their preventive gowns still on. The first step in preventing nosocomial infections may be to correct the daily habits of healthcare workers by encouraging them to wash their hands, wash their faces, and take off their preventive gowns after work and before eating or drinking.

Response to Needlestick Accidents

There is a need to check the presence of new HBV or HCV infection during regular medical checkups, and to see the changes in HBs antibody titer for HBV infection. While the aforementioned guidelines previously stated that, depending on the department, tests should be conducted every two to three months for HBV, once a year seems sufficient now that the incidence of actual infections has decreased thanks to various responses.

Next, as something common to all needlestick accidents, wounds should be washed under running water and blood should be squeezed out as soon as it is discovered. The wound must also be disinfected with a disinfectant. At the same time, it should be verified whether or not the patient has been infected with HBV, HCV, or HIV, and the following measures should be taken once it is confirmed that the patient was infected. In this case, it is important to contact the person in charge of a task force for nosocomial infections, and to record the details.

1. Prevention of HBV infection

At least 15 years have past since HB vaccine came onto the market, and all healthcare workers under the age of 31 have supposedly received HB vaccine.

If they had received HB vaccine before or when they started working as healthcare workers, most of such people would have been in their 20s. Therefore, since the HBs antibody

Table 1 Changes in the Ratio of Positive HBs Antibody Test and the Geometric Mean Antibody Titer Following rHB Vaccination in Different Age Groups[2)]

Age group (years)	Item	Months after vaccination			
		Before inoculation	1 month later	6 months later	7 months later
>10	Positive ratio	0/144*	49/144 (34.0)	137/142 (96.5)	130/132 (98.5)
	Antibody titer	<0.6**	4.0	60.1	420.7
10–19	Positive ratio	0/197	42/197 (21.3)	192/197 (97.5)	193/194 (99.5)
	Antibody titer	<0.6	5.1	33.9	363.1
20–29	Positive ratio	0/703	113/703 (16.1)	614/696 (88.2)	651/668 (97.5)
	Antibody titer	<0.6	2.6	19.5	158.5
30–39	Positive ratio	0/406	38/406 (9.4)	308/401 (76.8)	368/386 (95.3)
	Antibody titer	<0.6	2.5	13.5	64.6
40≦	Positive ratio	0/281	28/281 (9.9)	194/279 (69.5)	261/273 (95.6)
	Antibody titer	<0.6	2.3	9.1	36.3
Total	Positi ve ratio	0/1,731	270/1,731 (15.6)	1,445/1,715 (84.3)	1,603/1,653 (97.0)
	Antibody titer	<0.6	3.1	19.6	117.3

* Number of positive cases/Number of cases from whom blood was collected
** Geometric mean antibody titer: mlU/m*l* ( ): Percentage of positive antibody

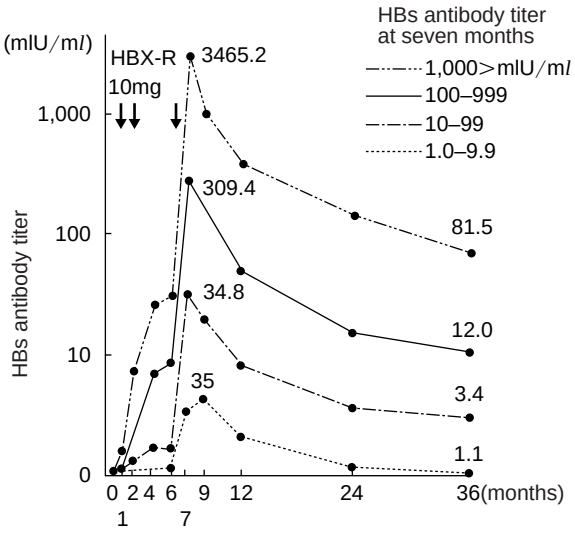

Fig. 1 Changes in the antibody titer based on HBs titer seven months following the initial inoculation[3)]

acquisition rate has been at least 98% in all vaccine-related trials, and cases without positive HBs antibody include cases with positive HBc antibody, which show that a person has been infected with HBV, approximately 100% of them are thought to have acquired HBs antibody. In particular, since recombinant vaccines have started to be used, the rate of positive HBs antibody continues to improve even with age,[2)] as shown in Table 1, and it is speculated that HBs antibody emerges at least once in vaccinated individuals.

However, since HBs antibody that has been acquired through vaccination decreases with time, as shown in Fig. 1, it may be necessary to get additional vaccinations.[3)] On the other hand, however, some have recently reported

that there is no such need, based on the fact that results of a long-term follow-up study on people who received vaccinations during early childhood show that they did not get infected even without additional inoculation when HBs antibody had turned negative. However, the data in these reports may not be credible as to whether or not infection was truly prevented if circumstance made it difficult for infection to occur, such as through improvement in environmental conditions.

Therefore, in response to specific HBV needlestick accidents, additional inoculation (once) of HB vaccine may be sufficient whether a patient is HBe antigen positive or HBe antibody positive. However, when HB vaccine has never been given, HB vaccine inoculation (three inoculations: at the time of the accident, 1 month later, and 3 months later) and intramuscular injection of HBIG (high-strength HBs immunoglobulin) should be given as soon as possible following the accident (without being restricted to the timeframe of 48 hours), as it has always been recommended. For post-accident follow-up, HBs antigen and ALT (GPT) should be tested once a month until six months following the accident.

2. Prevention of HCV infection

Several percent of the elderly population at least 60 years of age are HCV carriers, and only some of them have been identified as carriers. It is necessary to consider HCV to be present in the blood of the elderly.

There are no specific methods to prevent HCV infection as HBV infection is by HBIG or HB vaccines. However, it is a relief to know that HCV is less infectious than HBV.

Kiyosawa *et al.* were the first ones to report HCV infection caused by needlestick accidents.[4] Out of 200 needlestick accidents that happened to 196 healthcare workers, 107 cases of HCV infection were involved. Out of 110 accidents, three healthcare workers developed acute hepatitis (2.7%), and two other workers developed non-B non-C hepatitis. Since first generation HCV antibody tests were used at the time, it is possible that all five cases (4.5%) had acute hepatitis C.

Mitsui *et al.* have reported on HCV infection in healthcare workers that was caused by needlestick accidents in a dialysis center.[5] Out of 68 cases of accidents, seven cases (10%) developed acute hepatitis. Except for one case, they turned out to be a temporary infection.

Although there are many other reports on HCV infection caused by needlestick accidents, the incidence of the disease and the infection rate in HCV-exposed cases are not clear because not all of the needlestick accidents have been reported. The incidence of the disease is, therefore, assumed to be higher than the actual figures. An investigation in England has shown that only 1/3 of accidents is reported.

The low incidence of the actual establishment of HCV infection caused by needlestick accidents can also be surmised from many reports from various countries that show that there are no differences between the rate of positive HCV antibody among healthcare workers and that among blood donors.

As in the case of HBV infection, the use of commercially available immunoglobulin has been considered as a treatment option following needlestick accidents that may cause infection. Although administration of immunoglobulin was ineffective for prevention of the onset of HBV infection, prevention has become possible through immunoglobulin preparations containing a large quantity of HBs antibody. As for HCV, although there are antibodies that would prevent HCV infection, the protective antibody titer is expected to be much smaller compared with HBV. Therefore, a more condensed and specific immunoglobulin preparation needs to be developed.

Administration of interferon (INF) has also been attempted, but turned out to be ineffective. Since there is a several-hour timeframe before INF can manifest its effects in the body, there is a strong possibility that HCV that had slipped in during that time are attached to

hepatocytes. The rate for HCV infection to be established is low, and considering the adverse effects of INF, INF should not be used. In addition, even if acute hepatitis should occur, the possibility that it would heal is 30 to 40%. Moreover, if it is within one year of the onset of acute hepatitis, HCV can be successfully eliminated by INF at a high rate. [6)]

Following HCV needlestick accidents, ALT and at times HC-RNA (qualitative) should be tested once a month for six months.

3. Prevention of HIV infection

The chances of getting infected with viruses as a result of needlestick accidents are found to be in the order of HBV, HCV, and HIV; the possibility of getting infected with HIV as a result of needlestick accidents is approximately 0.4%, the lowest of the three viruses. If the following preventive administration is started within 1–2 hours following the accident, the probability of infection reportedly drops to 1/5.[7)]

When there is a possibility that the patient is an HIV carrier, the first preventive administration should be started even before it is confirmed by test results. When the patient is an HIV carrier or if test results have confirmed that this is the case, preventive administration should be started in both cases.

The following three drugs are used for preventive administration: Retrovir® 600 mg/day tid (after every meal), Epivir® 300 mg/day bid (after breakfast and supper), and Viracept® 2,250 mg/day tid (after every meal). After this preventive administration has been continued for four weeks, during which any adverse drug events should be carefully monitored, discontinue the administration. Verify that there is no HIV infection by conducting tests on the 6th week, the 12th week, the 6th month, and the 12th month. If HIV infection has been verified, begin treatment for HIV.

The primary adverse drug events of the three drugs are as follows:

- Retrovir®: Anemia, headache, malaise, fever, urticaria, gastrointestinal symptoms such as loss of appetite and nausea, mental symptoms such as dizziness and anxiety, respiratory symptoms, renal dysfunction, etc.
- Epivir®: Anemia, pancreatitis, neuropathy, confusion, seizure, heart failure, digestive symptoms, rash, etc.
- Viracept®: Diarrhea, rash, etc.

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Nosocomial Infection of Tuberculosis

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Abstract: In the midst of increasing outbreaks of tuberculosis (TB) in recent years, the increase of TB infection within medical facilities has also been concerned. Among recent reported cases of TB outbreaks, 20% are related to medical facilities. One recent observation indicates that the TB case rate of female nurse is almost twice as high as that of the average female population. The main cause for this is that while the proportion of the health staff that have never been previously infected with TB is on the increase, the risk of developing the disease among the mid-aged or elderly patients that they contact with is still persistent. Other factors may include; the delay in diagnosing TB, the relative increase in TB patients with serious disease at onset, and the increase in medical procedures inducing coughing. In addition, it has to be pointed out that there has not been more attention paid to this problem in Japan. A research team of the Ministry of Health, Labor & Welfare has recently announced the guidelines for its prevention in 2001. We have much to learn from the experience of the US where attempts have been made to address this issue much earlier.

Key words: Tuberculosis; Nosocomial infection; Epidemiology; Prevention; Hospital

Increase of Nosocomial Infection

In the midst of the increasing outbreaks of small epidemics of TB in recent years, the increase of nosocomial TB infections, i.e. TB infection that takes place in medical facilities, has also been concerned. Figure 1 illustrates the main sites of TB outbreaks (defined as a case where 20 or more persons are infected from a single source of infection, development of a patient being counted as equivalent to 6 infections) out of 156 cases reported to the Ministry of Health, Labor and Welfare during 1998–2001.[1] While many cases are observed in schools and business offices as have been in the past, "general hospitals" and "mental hospitals" are also among the common sites of TB outbreaks. Several examples from these are shown below.

1. Maternity hospitals[2]: The source of infection was a 22 year-old pregnant woman who was sent to two hospitals (X and Y) succes-

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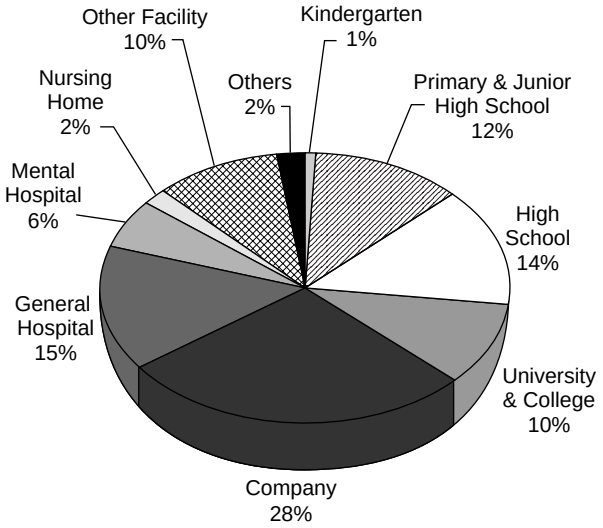

Fig. 1 Recent outbreaks of small TB epidemics (1998–2001, Total = 156)

sively. A total of 13 people including inpatients in the same room and in the adjacent rooms, visitors, and hospital personnel were infected and developed disease. The source of infection had had coughing for a long time but it was not until after her childbirth at Y hospital that she was finally diagnosed as smear-positive TB. Two babies in the adjacent room that had no direct contact with her were also infected from her. They both developed miliary TB with meningitis, due to identical TB strains as proved by RFLP. The source patient was hospitalized in X hospital for 17 days and 5 days in Y hospital 2 months later, infecting 11 people at X hospital, and 2 at Y hospital.

2. Clinic with beds[3]: A clinic with beds reported 3 new TB cases within a week, followed by another 2 new cases in the next 2 months (bacteriologically all smear positive). As a result of an investigation, it turned out that there had been another patient 2 months previously who was diagnosed as heavily smear-positive and died shortly later. From RFLP analysis, the latter two patients were confirmed to have had strains of the same pattern.

3. Mental hospital[4]: There were 18 cases of TB infection among inpatients at a mental hospital in 3 years. The RFLP patterns of the isolates from 4 patients from whom strains were obtainable were proved as identical. Although the infection of these patients were reported to the public health centers of the patients' residence following the TB Control Law, since they had been in hospital, the public health center of the hospital's district was not able to recognize the outbreak of TB at an early state.

4. ENT clinic[5]: A private ENT clinic had among its patients 15 cases of TB otitis media and 4 cases of pulmonary TB (including 1 doctor of the clinic). The doctor and 8 of the TB otitis patients had the TB bacilli with an identical RFLP pattern. The ages of the patients ranged from 5 to 74 for otitis patients, and 2 to 32 for pulmonary cases. Regarding the pulmonary cases, the suspicious source of the infection was the doctor with the smear positive pulmonary TB. However, the source of the infection for the doctor and the otitis cases is unknown, though assumed to be as one of the otitis cases.

These examples are of relatively large scale. In some other cases of particularly large-scale outbreaks, the numbers of the secondary disease patients were 17, 15, and 12 in general hospitals, and 23, 19, and 18 in mental hospitals.

Increase of TB Risk in Health Care Providers

We should not overlook small-scale outbreaks or transmissions of infection with only a few infected cases. These cases are not recorded in the statistics, but have occurred sporadically over the nation and are on the increase. Figure 2 shows the changes in the numbers of TB case notifications since 1987 among female nurses (more accurately, including public health nurses, midwives, and nurses), and teachers and doctors (including physicians, dentists, and physiotherapists).[6] Generally speaking, while the number is on the decrease for the occupation category of "teachers and doctors" (the majority in this category are teachers), the risk

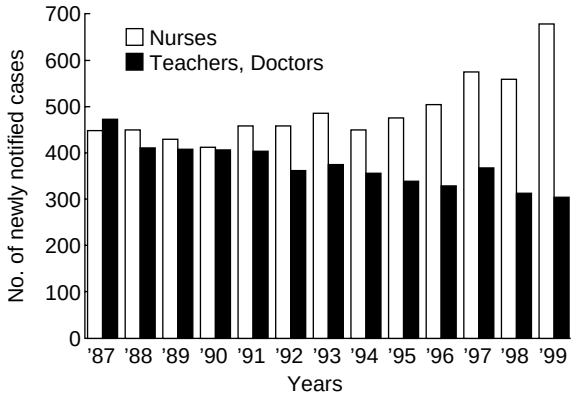

Fig. 2 Trend of number of new TB cases for select occupation groups (all forms of TB)

of TB among female nurses shows an increasing tendency.

What would be the reasons for this tendency? First and foremost, the gap in the proportion of those who have been infected with TB between the elderly people and the younger ages has been widening. Among current health care providers in their 20's and 30's, only 2 or 3% have been TB-infected. On the other hand, over 70% of the aged patients that they take care of have been infected and can develop clinical TB any time. This gap had not been as wide in the past. This is an epidemiological background for the increase in TB outbreaks in general settings, but is particularly the case in a more extreme form in medical facilities.

The situation has been further worsened by the increase of TB patients in severe conditions. The annual incidence of smear-positive patients increased from 12,291 in 1980 to 17,242 in 1999. Especially among those aged 70 years or over, the number increased threefold. Also, the delay in case detection of TB has to be thought of as the other side of the same coin. This is attributed to the increase of such cases as follows; atypical cases where diagnosis is difficult, acutely progressing types of disease (e.g. when associated with underlying disease); and cases who seek for medical care too late (e.g. as in case of socio-economically disadvantaged people). In addition, the diagnosis of TB has been perhaps further delayed due to the inadequate awareness of TB among medical professions.

Inadequate Preventive Measure of Nosocomial Infection

It is also important to remember that the preventive measures taken in Japan for nosocomial tuberculosis have been almost premodern. In other words, possible TB patients are taken care of by the personnel as if in the old days, when the majority of the hospital personnel had been infected with TB already.

A recent questionnaire survey shows the actual condition of medical facilities as shown below.[7] The survey refers to the period prior to the Japan Tuberculosis Society's recommendation for the prevention of nosocomial infection[8] and "Guidelines for the prevention of nosocomial infection of TB" by the research team of the Ministry of Health and Welfare.[9] Therefore, the current conditions are expected to have improved since then. As seen in Table 1, the result reflects the "pre-modernity" of the state of affairs in Japan of the recent past. This should be regarded as one of the important factors for the increase and complexity of incidence of nosocomial infection in the recent years.

Guidelines for Preventing Nosocomial TB

Below is a general summary of the preventive measures described in "Guidelines" mentioned above.

1. Administrative prevention

Each hospital, with its responsibility to take preventive actions, must develop its own manual for the prevention of nosocomial infection. The manual mandates the establishment and effective management of the committee

Table 1 Preventive Measures for Nosocomial Infection of Tuberculosis Taken by Japanese Hospitals with and without TB Beds (1997, Shishido *et al.*[7])

	With TB beds ($n=179$)	No TB beds ($n=170$)
Health check on employment		
Inquiry on TB history	77%	7%
Tuberculin testing	58%	23%
BCG vaccination	43%	12%
Health engineering of TB ward		
Separate ward building	73%	—
Independent air cond. system	27%	—
Negative pressure bed room	8%	—
Use of safety cabinet in TB laboratory	47%	29%
Use of mask		
Obligatory to doctors	53%	—
Obligatory to nurses	73%	—

for this issue and the training of hospital employees. In the latter, it is most relevant to keep them more alert to the notion that 'TB is still around!' and to thoroughly instruct how to manage a case when it occurs. In addition, the health surveillance with periodic health checkup for TB needs to be provided to the employees, as follows.

1) Health surveillance

The key point is to conduct two-step tuberculin testing in the medical check at the time of employment. If the result is negative, BCG vaccination should be considered. The result of two-step test is an important baseline finding for the interpretation of the tuberculin test result on the occasion of a contact examination in the future. Periodic medical checks including chest X-ray should be obligatory. When a patient in contact with personnel is diagnosed as TB, a special (extraordinary) health examination should be conducted in co-operation with the health center. Tuberculin testing should be included in this examination for those under 40 years of age (as a standard) and the reaction size should be compared with that of the baseline result in the previous two-step test. In addition to the chest X-ray examination right after the contact, follow-up X-ray examination should be done at 6 month interval, during, say, two years.

2) In-patient and outpatient service

Triage of outpatients, i.e. selection of patients who have greater likeliness of having TB and separation of them from other patients, in the outpatient department areas, and isolation of such inpatients into an isolation room. This should be adapted to the conditions of the hospitals, such as its size and the level of risk of TB. Also it is relevant to define the actions to be taken when the examination result of a patient turns out as smear positive, the way of transportation of infectious patient to/from other facilities, etc.

2. Health engineering prevention

The guidelines discuss the ventilation of bed rooms of a hospital, air conditioning, use of filters for cleaning air, etc. It also concerns the plan and the use of such facilities as sputum collection booth and the room for bronchoscopy, and patients' activities outside the bed room or ward.

3. Personal protections

To instruct patients to wear masks (gauze masks), and hospital staff and patients' visitors

Table 2 Comparisons of PCP Hospitals and Other US Hospitals by Use of Engineering Controls and Respiratory Protection of HCWs, 1992 and 1996 (Manangan *et al.*[13])

	PCP hospitals (27)		Other US hospitals (103)	
	1992	1996	1992	1996
Use of engineering controls				
AFB isolation rooms	63%	100%	64%	96%
UV-gemicidal irradiation	4	17	13	18
Portable HEPA filter	27	67	27	43
Routinen check of pressure	61	90	49	97
Respiratory protection HCWs				
Surgical, non-fitteted mask	60	0	68	1
Soft, molded or fitted	8	NA	8	39
Dust, mist or fume	NA	0	NA	4
HEPA filter	NA	26	NA	35
N95	NA	90	NA	83

PCP Hospitals: Hospitals providing care to patients with HIV-related pneumocystis carinii pnuemonia.

to wear masks of N95 type.

Situation in the United States

The case rate and mortality rate of TB in the United States are approximately a fifth or sixth of those of Japan. However, in the early 1990s the US experienced a reversal of the TB trend, accompanied by outbreaks of nosocomial TB infections, often combined with HIV. Under these circumstances, the prevention of nosocomial infection was prudently reviewed. In 1990, the guidelines for preventing nosocomial infection of TB with HIV[10] were issued and in 1994 for preventing nosocomial infection of TB in general.[11] Although these are basically comparable to the Japanese counterparts, they are far more concrete and in detail. Both general hospitals and HIV-related hospitals in the United States seem to have shown rather sensitive responses to such recommendations. Manangan *et al.* observed dramatic changes in hospitals' schemes on TB prevention (Table 2).[12] A direct observation at a hospital conducted by Maloney *et al.* has also revealed the same effect.[13]

The other unique practice in the US is the repeated tuberculin testing followed by chemoprophylaxis among health care providers. This has a subsidiary advantage of enabling to evaluate the risk of the facility as shown in Table 2 since BCG vaccination is not used in the United States. However, some have argued that BCG vaccination is clearly more useful because chemoprophylaxis bears a problem of low compliance with the scheme and also because INH is ineffective to infection with multi-drug resistant strain.[14]

While the American experience is not immediately comparable to the situation in Japan, we seriously need to consider the differences in the responses to the problem in the two nations; they have been too imprudent in Japan.

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An Overview of Gamma Knife Radiosurgery: Focusing on Brain Metastasis

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Abstract: The gamma knife (GK) focally irradiates targeted volumes, within the brain as well as its adjacent structures such as the orbit, the paranasal sinus and so on, in a highly conformal stereotactic manner. Frame fixation for head immobilization is employed during imaging and treatment, 3-D imaging and computer simulation during treatment planning, and target-focused beams from 201 cobalt-60 radiation sources during treatment. GK radiosurgery is relatively non-invasive and all procedures are completed within several hours in most patients. Already widely accepted as an alternative to microsurgical resection for brain tumors and vascular malformations, GK radiosurgery is now increasingly being used as the primary management or as a booster treatment with whole brain radiotherapy (WBRT) in patients with metastatic cancers, whether radio-sensitive or resistant, single or multiple. GK radiosurgery has recently been shown to be effective for cerebral metastases, achieving results comparable to those of surgery combined with WBRT. Tumor control rates are high and symptom palliation is achieved quickly. Approximately 80–90% of patients maintain good brain condition until death due to non-brain causes.

Key words: Gamma knife; Brain metastases; Radiosurgery

Introduction

The late Professor Lars Leksell initially used the GK to treat functional neurosurgical disorders, e.g., Parkinson's disease and intractable pain.[1)] However, in the three decades since, arteriovenous malformations (AVMs) have become the most common indication for GK radiosurgery. The last decade of the 20th century witnessed a remarkable expansion of GK radiosurgery, which is now used worldwide, as well as some innovative improvements in this technology.

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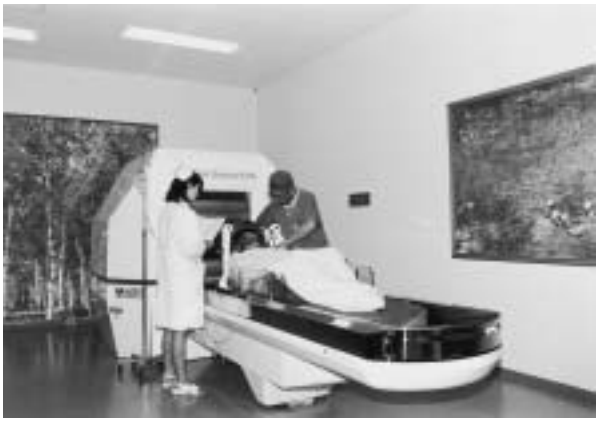

Fig. 1 The gamma knife system at the Katsuta Hospital Mito GammaHouse

Technology

The GK has undergone little modification since its introduction, as described in detail by Steiner.[2] The major recent innovation is the GammaPlan (Leksell GammaPlan, Elekta Instruments AB, Sweden), a dose planning computer system for which the hardware and software both continue to advance remarkably. Dose planning is based on three-dimensional computer tomography (CT) and/or magnetic resonance (MR) images which, along with digital subtraction angiography (DSA), are quickly transferred to a workstation via an online network. In addition, multiple isocenter treatments assure better conformity between lesion size/shape and the dose distribution. We can thus look forward to more precise, safer treatment, and thereby to lower morbidity and perhaps even better results.

Gamma knife

The three GK models, U (model U, used only in the USA), B, and C, all have 201 ^{60}Co radiation sources and four collimator sizes, 4, 8, 14, and 18 mm (Leksell Gamma Unit, Elekta Instruments). Model B, generally used outside the USA, is relatively simple and has an opening in the helmet at a right angle to the long axis of the bed of the machine. The patient is only moved horizontally into the machine, not up and down as in Model U. The model B gamma unit has also recently been installed in U.S. facilities. Model C, which recently became available, has no significant structural differences from Model B but, once a patient's head is fixed, subsequent target points are fixed by means of an automatic positioning system. This reduces the probability of human error, increases comfort for patient and doctor, and reduces treatment time.

Frame fixation

The stereotactic coordinate frame (Leksell Model G, Elekta Instruments) routinely used for GK radiosurgery has undergone little change in recent years. Frame fixation techniques are basically unchanged though MR imaging and DSA have become increasingly important. Given the anatomical distortions which are essentially inherent to all types of MR and DSA units, the target must be placed as near the center of the frame, i.e., X-, Y-, and Z-coordinate values of 100 each, as is feasible.

The authors generally perform this procedure with the patient supine using a specially designed adapter firmly fixed to the operating table.[3] This avoids the unwanted surprise of the coordinate box not fitting on the frame. This method has several advantages over the sitting position.

1. Patient condition, i.e., psychological state, nausea/vomiting, headache, dizziness, blood pressure instability, etc., can more easily be controlled.
2. Sedation or general anesthesia can be administered without complex procedures, which is crucial for AVM patients as bleeding can occur just as the frame is placed.
3. Adequate head positioning within the frame is achieved with earplugs or an experienced assistant. The latter is needed to support the frame during the procedure when the sitting position is used.
4. The patient can maintain a comfortable neck position during imaging studies.

Table 1 Indications for Treatment (Japan)

	Cumulative (as of Dec. 2001)	1 year/2001
Vascular diseases	**6,629 (15.0%)**	**763 (8.6%)**
AVM (including AOVM)	6,342 (14.3%)	694 (7.8%)
Others	287 (0.6%)	49 (0.6%)
Tumors	**36,714 (83.0%)**	**7,834 (88.0%)**
Acoustic neurinoma	4,276 (9.7%)	590 (6.6%)
Meningioma	4,405 (10.0%)	689 (7.7%)
Pituitary tumor	1,804 (4.1%)	297 (3.3%)
Pineal tumor	195 (0.4%)	24 (0.3%)
Craniopharyngioma	532 (1.2%)	91 (1.0%)
Other primary tumors	4,976 (11.3%)	840 (9.4%)
Metastasis	20,526 (46.4%)	5,303 (59.6%)
Functional diseases	**876 (2.0%)**	**302 (3.4%)**
Total	**44,219**	**8,899**

5. Pin positions can be selected precisely, especially in non-craniotomy patients, as there is no time pressure.

Imaging studies and dose planning

Dose planning for AVMs using the Leksell GammaPlan is always performed three-dimensionally employing CT, DSA, and/or MR imaging. With this system, all three or two imaging techniques can be used simultaneously. In the event of CT and MR images being incongruent, the former is more likely to be accurate. Either way, an axial image, which is less prone to distortion than coronal and sagittal images, with a slice thickness of no more than 2 mm, is recommended.

Clinical Applications

GK radiosurgery has recently been used as an alternative to, or in combination with, surgical procedures or intravascular treatment in an increasing number of patients with various intracranial diseases. More than 165,000 patients worldwide had reportedly undergone GK radiosurgery as of June of 2001 and more than 44,000 in Japan as of the end of 2001. Indications for treatment are listed in Table 1.

Vascular malformations

AVMs were the most common indication for this treatment through the beginning of the 1990s; nearly 50% of patients who underwent GK radiosurgery had cerebral AVMs. However, more patients with metastases or glial tumors have been undergoing this treatment in recent years. During the one year period between July of 2000 and June of 2001, only 12% of patients who underwent GK radiosurgery worldwide had AVMs. Although the relative annual percentage of treated cases is decreasing, AVMs constitute a very important indication as these lesions are benign in nature and tend to develop in adolescent and young adult populations. It is clear that angiographic nidus obliteration, which eliminates the risk of hemorrhage, can be achieved in 80–90% of cases with a two–three year latency period for small AVMs ($<2\,cm^3$) treated with an optimal irradiation dose (>20 Gy) at the nidus margin. In such cases, the risk of irradiation-related complications is acceptably low ($<3.0\%$).[4–5]

Angiographically occult vascular malformations (AOVMs) comprise a group of congenital

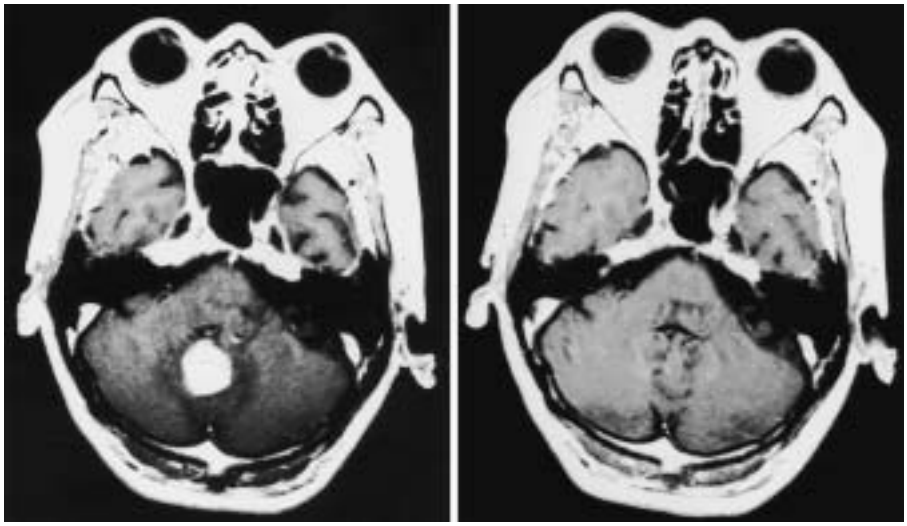

Fig. 2 A patient with a solitary brain metastasis, before (left) and two months after gamma knife radiosurgery (right). The original tumor was a pulmonary small cell carcinoma.

vascular abnormalities including cavernous malformations, thrombosed AVMs, capillary telangiectasias, and so on. Among AOVMs, only cavernous malformation can be treated with GK. Venous angioma is a different clinical entity, for which radiosurgery is not indicated. Several investigations focusing on radiosurgical treatment for cavernous angiomas have been published.[7–9] However, to date, it remains controversial, from the aspects of hemorrhage and seizure prevention, whether patients with cavernous angiomas are good candidates for GK radiosurgery.

Acoustic schwannoma

GK radiosurgeons have argued with microscopic neurosurgeons as to which treatment, radiosurgery or microscopic resection, is preferable for a patient with a relatively small tumor (<3 cm) that is accessible utilizing either procedure. Most neurosurgeons and otolaryngologists have been constrained by the notion that only patients whose tumors are inaccessible to surgical treatment, for whatever reasons, should be treated radiosurgically. However, in the real world, increasing numbers of patients with operable acoustic schwannomas are undergoing radiosurgery as a matter preference following the provision of sufficient information about the two treatment procedures. The vast majority of patients will choose the less invasive, less expensive, and less time-consuming procedure, if the treatment results are very similar. Nowadays, there are no significant differences in treatment results, including the long-term growth control rate (90% or more), hearing preservation rate (70% or more), and incidences of postoperative cranial nerve disturbance (far less than 3%), between GK radiosurgery and microsurgery performed by neurosurgeons with excellent (not average or better) surgical skills.[10–13]

Meningiomas

It is generally accepted that, based on long-term follow-up results, tumor growth control is achieved in 80–90% of meningiomas many years after radiosurgical treatment, and in approximately 50% of these tumors, remarkable shrinkage has been observed with an acceptably low complication rate.[14,15] However, in general, low risk microsurgery is still the treatment of choice for surgically accessible meningiomas such as convexity, parasagittal, falx

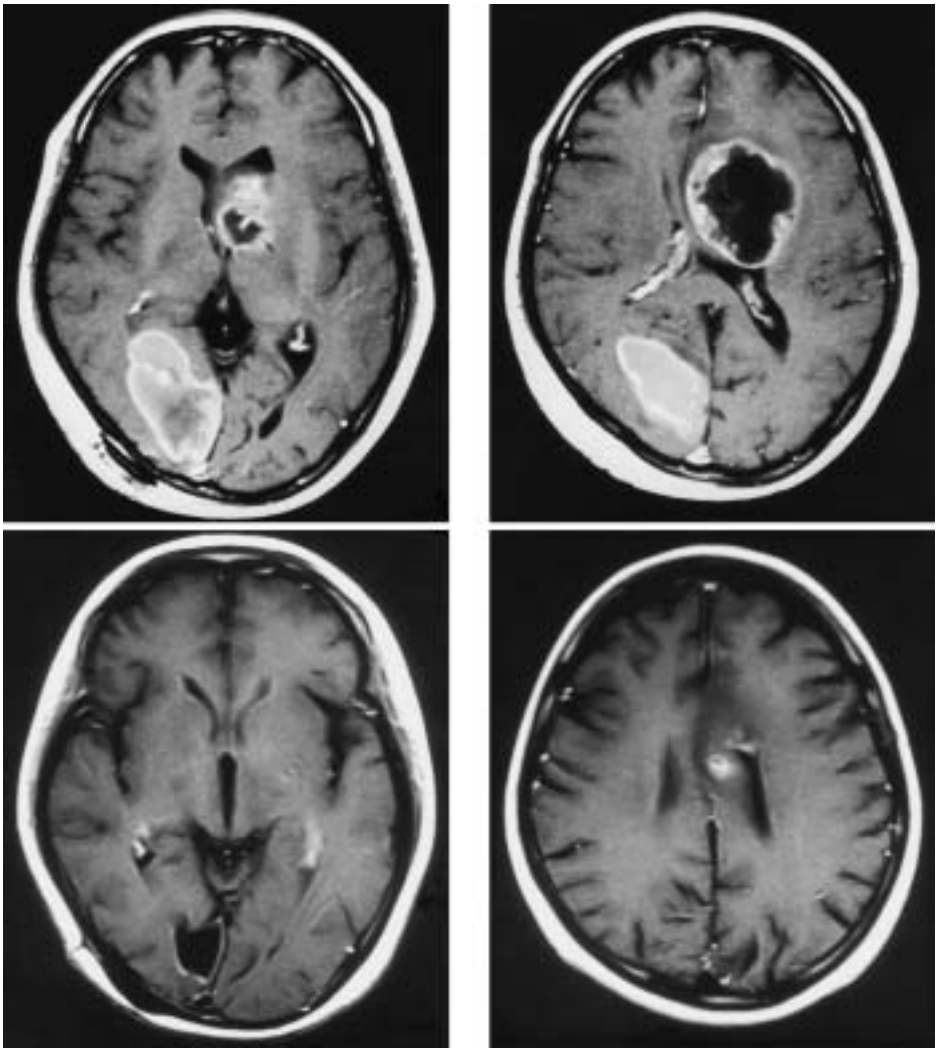

Fig. 3 A patient with two large brain metastases, before (upper) and six months after gamma knife radiosurgery (lower). The original tumor was a uterine carcinoma.

or falco-tentorial meningiomas, in which unexpectedly severe brain edema can develop several months after radiosurgical treatment, with a higher incidence than in skull base meningioma radiosurgery.[16] In contrast, patients with skull base meningiomas, in which total microsurgical excision with no additional neurological deficits cannot be achieved, are good candidates for radiosurgery as the primary treatment if the maximum tumor diameter does not exceed 3 cm, or following extirpation of the major tumor bulk when the maximum tumor diameter exceeds 3 cm.[14,15]

Pituitary adenomas

In the early history of radiosurgery using a particle beam unit as well as a GK, given the lack of satisfactory surgical treatment for, in particular, hormone-secreting adenomas, a considerable number of patients underwent radiosurgery. However, in contemporary treatment of pituitary adenomas, regardless of whether the tumor is secreting or non-secreting, or a macro- or micro-adenoma, GK radiosurgery is not the treatment of first choice. Notably, because radiosurgery cannot achieve a rapid and consistent reduction of tumor

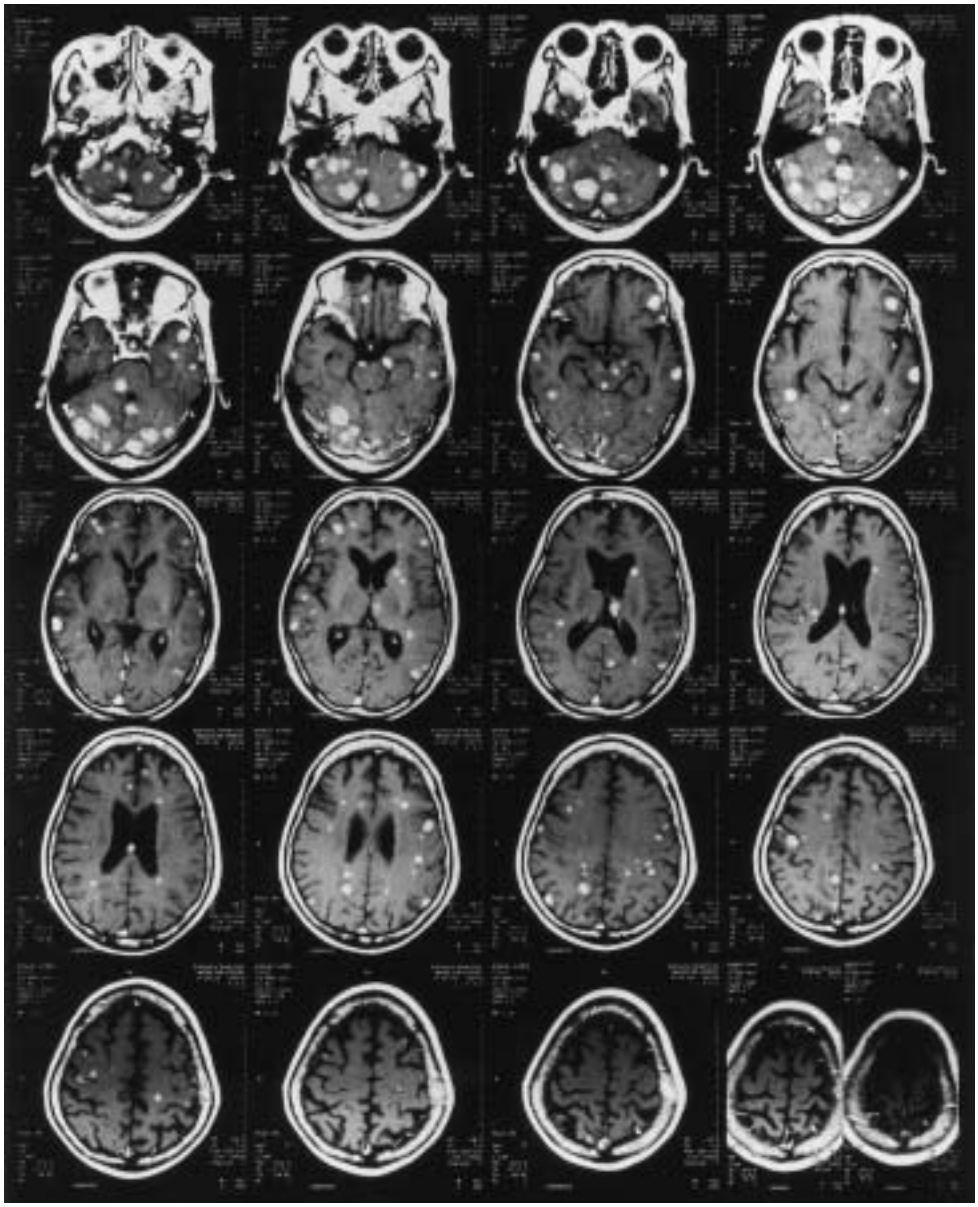

Fig. 4-a

Fig. 4 A patient with 48 brain metastases, before (Fig. 4-a) and six months after gamma knife radiosurgery (Fig. 4-b). The original tumor was a breast carcinoma.

volume, decompression of the visual pathway resulting in improvement of visual function cannot be expected in employing this technique for macroadenomas. The best indication for GK treatment is probably as an adjuvant to microsurgery for macroadenomas; especially postoperative residual tumor extending into the cavernous sinus.[17,18] Also, in the case of microadenomas, radiosurgery does not have a major role in primary treatment. The effective minimum dose needed to control serum hormone levels is considered to be about 35 Gy at the tumor margin. This high dose is difficult to deliver in most cases without damaging the visual pathway.

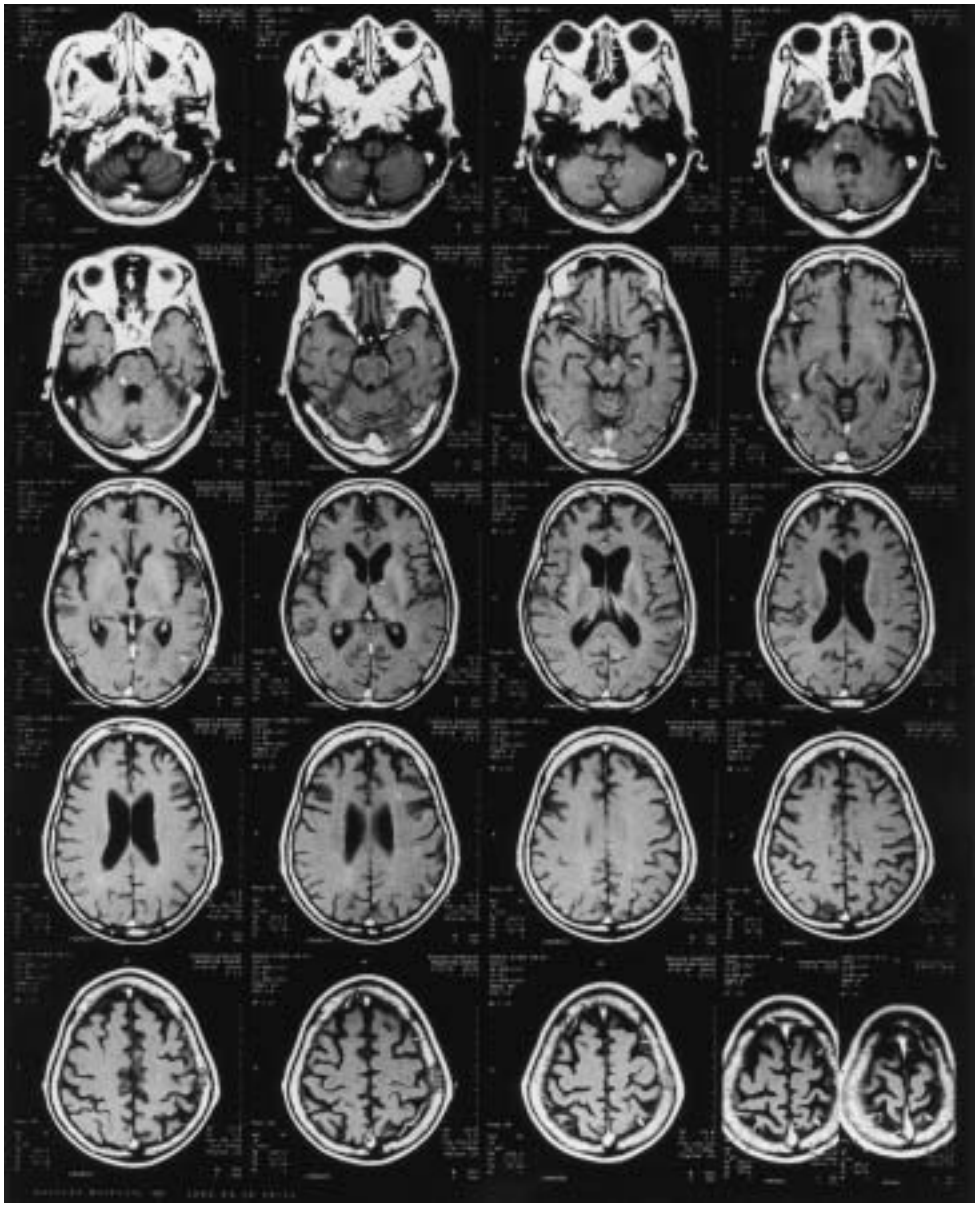

Fig. 4-b

Glial tumors

GK radiosurgery is increasingly being used for the treatment of glial tumors as an adjuvant to surgical resection, fractionated radiation and/or chemotherapy. Modest clinical efficacy has been reported sporadically.[19–21] However, the use of a highly focused beam appears to be conceptually difficult for infiltrating tumors, such as malignant gliomas, given the spread of tumor cells as part of the evolution of such tumors. Low grade gliomas may benefit from radiosurgical treatment if the pathologically enhanced area on MR images is limited to a small volume. Nevertheless, another fundamental controversy exists as to whether radiation treatment itself is required for benign gliomas. Therefore, the authors accept glioma patients for GK radiosurgery only when neuroimaging examinations demonstrate a small area of recurrence after multiple surgical proce-

dures with full dose irradiation. Clearly, to fully realize the potential of this technique for all types of glial tumors, further accumulation of cases, including multi-institutional randomized studies, is required.

Other primary tumors

Despite sporadic reports of good results, the appropriateness of radiosurgically treating other primary tumors, e.g. craniopharyngiomas, hemangioblastomas, chordomas, and glomus jugulare tumors, remains controversial. Study sample sizes and the duration of follow-up are not yet sufficient to allow conclusions to be drawn as to the efficacy of radiosurgery for these tumors.

Brain metastases

The successful use of GK radiosurgery to treat brain metastasis, a recurrent hypernephroma, was first reported in 1989.[22] GK radiosurgery has since been used as a primary or booster, with whole brain radiation therapy (WBRT), treatment for increasing numbers of metastatic cancer patients. Many tumors, whether radio-sensitive or resistant, single or multiple, can be managed with GK radiosurgery. This technique is particularly suitable because many metastatic lesions are well-circumscribed. For single metastases, stereotactic radiosurgery, with or without WBRT, achieves results comparable to those of conventional surgery combined with WBRT.[23–27] GK radiosurgery for multiple metastases reportedly produces survival rates similar to those achieved using this technique for single metastases.[28,29] A comprehensive review found no correlation between lesion number, even in patients with eight or more lesions, and survival.[24] Our group and others have demonstrated radiosurgery to be beneficial for carefully selected end-stage patients with intracranially disseminated metastatic tumors.[30–32] Even a patient with 20–50 such tumors can maintain good performance status for a major portion of his/her remaining life.[32] We also determined cumulative radiation doses to the whole brain in a phantom experiment, using numerous radiosurgical targets, and found that the whole brain had not been irradiated with dangerously high doses.[33] As we reported elsewhere[31] based on a phantom experiment as well as an analysis using a dose-planning computer system, the cumulative whole brain irradiation doses for patients with numerous radiosurgical targets were not considered to exceed the threshold level of normal brain necrosis.

In discussing GK radiosurgical indications for individual cases, while well-recognized factors such as age, performance status, and active extracranial diseases deserve consideration, the only limitation is lesion size. Maximal lesion diameter is less than 3 cm in patients with one to several lesions, and less than 2 cm in those with more numerous lesions. The number of lesions is not a limitation. In the setting of brain metastasis, it appears that total intracranial volume has greater prognostic significance than the actual number of lesions irradiated.

The main goal of radiosurgery for brain metastases is local tumor control. Radiosurgery alone achieves this goal for more than 90% of lesions. Rapid symptom palliation ensues and most patients maintain good performance status. The duration of survival, however, depends primarily on the state (including origin) of extracranial lesions. Controversy persists as to whether radiosurgery should be combined with WBRT. As most visible small metastases can be controlled with radiosurgery alone, the function of WBRT is solely to irradiate undetectable foci and thereby prevent new lesions from developing. An alternative to WBRT is to meticulously follow-up with MR imaging, which can detect new lesions before they become too large for radiosurgical treatment. As retreatment with GK radiosurgery can control all such lesions, the number of metastases is not, as described above, a consideration. We thus advocate MR imaging, at intervals of no more 12 weeks after radiosurgery, rather than WBRT. This spares the patient the physical and

economic burden of WBRT, the benefits of which are doubtful, allowing optimization of any remaining time with his/her family.

GK radiosurgery is feasible for skull base malignancies and intraorbital tumors, including primary and recurrent nasopharyngeal carcinomas and tumors showing intracranial expansion.

Functional disorders

The original use of GK radiosurgery for functional diseases has diminished as pharmacotherapy has improved. Chronic pain, Parkinson's disease, cluster headache, certain forms of epilepsy, some psychoneuroses, and trigeminal neuralgia may, however, be radiosurgically treatable. The latter is the best established indication for GK radiosurgery, with 56% to 72% of patients reportedly experiencing pain relief.[34,35] Parkinson's disease is the second most common indication. While the GK can provide relief from tremor, bradykinesia, dyskinesia, and rigidity for some patients who are poor candidates for open surgery, it is apparently no more and possibly even less effective than other stereotactic techniques.[36,37] The authors believe that further multi-center trials, with longer follow-up and collaboration with other medical specialists, are needed before the indications for radiosurgery as a treatment for functional diseases can be established.

Future Directions

GK radiosurgeons will unquestionably continue to strive for more reliable and safer treatment technology, including new imaging techniques, lesion-specific enhancement substances, and dose-planning computer systems. Imaging innovations have already been made available and will come into general use when costs are markedly reduced, procedures simplified, and spatial resolution greatly enhanced.

A major criticism of GK radiosurgery, particularly for the treatment of nonmalignant disorders, is the lack of information about the pathological, pathophysiological and radiobiological mechanisms of its operation. Though several publications have focused on these issues, most of our knowledge comes from the ever-expanding use of and experience with GK radiosurgery. Larger lesions are now being treated using various modified techniques. Another concern is the use of radiosurgery to treat benign lesions in young patients. Only long term follow-up, perhaps 10–20 years, can determine the incidences of serious complications such as tumor neogenesis, cyst formation, major vessel obliteration, and radionecrosis. It is also important to detect lesions before they enlarge and/or become symptomatic. MR imaging is now widely used to detect pre-symptomatic brain lesions, as part of a system called *Brain Dock* in Japan. MR imaging is also essential for detecting metastases in patients with extracranial malignancies, as timely radiosurgery offers hope of better-quality survival.

With the research and development now underway, GK radiosurgery has a promising future. We anticipate being able to treat more patients with a wider variety of diseases, with ever-improving results.

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Discovery of New Functions of Sugar Chains and Glycosyltransferase Genes

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Abstract: The draft sequence of human genome which has now been reported provides us with a blue print of the human body. The human genome contains approximately 30,000 to 34,000 genes. On the other hand, translated proteins from the genome comprise at least 70,000–80,000 proteins and almost 50% of those proteins are glycosylated. As a result, their functions cannot be predicted simply by genome sequences. This indicates that much information is hidden in human bodies, and cannot be revealed in terms of genome research. It is clear that sugar chains contain additional information that extends beyond the genome. Sugar chains play an important role in cancer metastasis, development, differentiation, and immunology. However even though most of the disease-related genes are now evident, the development of real therapeutic strategies remain unknown. It is clear that this type of information is not directly linked to genomic data. It is likely that research related to genome information will not be directly linked to the treatment of human diseases. One of the major areas of interest in the post genomic area of research is glycobiology and it is hoped that advances in this area will lead to many societal benefits.

Key words: Sugar chains and glycogenes; Glycosyltransferase; Suppression of cancer metastasis; Xenotransplantation

Introduction

Sugars are an important component of glycoproteins, glycolipids, and proteoglycans. Most of serum proteins and membrane proteins undergo glycosylation and almost over 50% of the proteins known thus far have been found to be glycosylated. Biosynthesis and regulation of sugar chains do not take place on a one to one basis as is observed in the case of a protein to a gene. The biosynthesis of each sugar on a sugar chain, is regulated by a specific glycosyltransferase activity and its expression. Namely, glycosyltransferase is a protein and a gene product of the glycosyltransferase gene designated as a "glycogene," and therefore sugar

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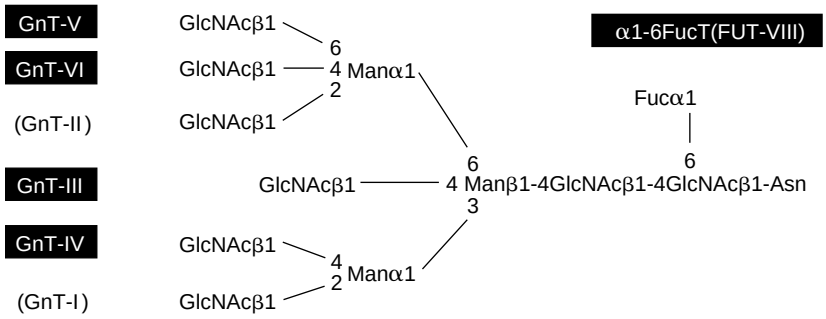

Fig. 1 Five glycosyltransferases which our group purified and for which their genes were cloned

These enzymes determine branching structures of *N*-linked sugar chains and therefore affect all of the structures that will be further biosynthesized.

chains biosynthesized are considered to be a secondary gene product produced by a glycosyltransferase enzyme.

Sugar chains are heterogeneous and composed of a variety of molecular species. Major posttranslational modifications of proteins involve glycosylation by glycosyltransferases and this, therefore, is the reason why glycobiology is called "third molecular biology." This area has the potential to reveal many facts in life science that cellular biology and molecular biology alone were not able to accomplish. Recently a number of CDGs (congenital disorders of glycosylation) that lack a specific glycosyltransferase gene have been found. In patients with CDG, severe symptoms were typically observed and it is known that some of the glycosyltransferase gene-deleted mice are embryonically fatal. Therefore, sugar chains are critical and necessary in the development and differentiation in animals.

The main focus of research on sugar chains has been on structural analyses and alterations in sugar structures at the stage of development, differentiation, and carcinogenesis and have been reported to be involved in cell adhesion and intracellular transport. In this research field, many leading Japanese scientists have contributed to the international research community. However, the issue of whether these changes in sugar structures are simply due to cause or consequence remains unclear. Unless cloning of the glycosyltransferase genes were to be carried out, it would be impossible to clarify the actual functions of sugar chains.

The authors' group has successfully purified five important glycosyltransferases, which are involved in *N*-glycan biosynthesis and cloned their genes. Here we show the discovery of new functions of sugar chains by a cell biological approach utilizing these cloned genes.

Cloning of Glycogenes

The authors' group has investigated protein chemistry and enzyme chemistry involving glutathione and enzymes related to reactive oxygen species.[1] In particular, we purified various γ-glutamyltranspeptidases, an enzyme that degrades glutathione from various tumor tissues and reported that this enzyme is highly activated in hepatocarcinoma and found that a purified enzyme from hepatoma tissues contains a unique structure designated as a bisecting GlcNAc. This was accomplished in collaboration with Dr. Akira Kobata's group.[2] After this report was published unique cancer specific glycosylation patterns became of interest for many researchers and a number of reports have been published. Among those, the α1-6 fucosylation of α-fetoprotein (AFP), a well known clinical tumor marker, is a good ex-

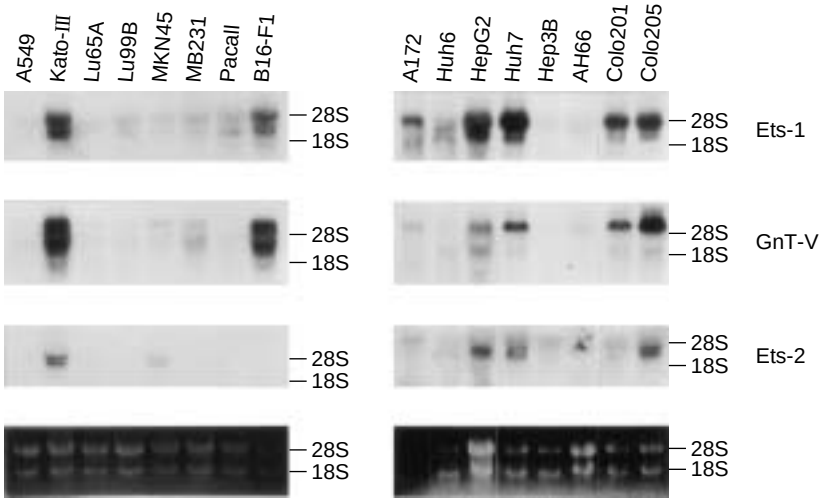

Fig. 2 Expression of the Ets- and GnT-V gene. Cooperative gene expression of both genes was found in various tumor tissues.

ample. In fact most of the currently applicable clinical tumor markers contain specific sugar chain structures. The mechanism underlying the nature of sugar chains in carcinogenesis is considered to be due to the specific activation of a glycosyltransferase, which adds sugar chains to the tumor maker glycoprotein. However, the purification of glycosyltransferase is difficult because the enzymes are tightly bound to the Golgi apparatus and, in addition the enzyme is unstable and is present at extremely low levels in the tissues.

We successfully purified *N*-acetylglucosaminyltransferase III (GnT-III) which is implicated with cancer-associated changes in the sugar chains of γ-glutamyltranspeptidase,[3] α1-6 fucosyltransferase (α1-6FucT),[4] which is implicated with cancer-associated changes of AFP, and then *N*-acetylglucosaminyltransferases IV, V, and VI, some of which may play a role in cancer metastasis.

We synthesized *in vivo* or *in vitro* substrates for these enzymes and using these substrates as a ligand, we developed columns for affinity chromatography and succeeded in purifying them to homogeneity and using partial amino acid sequence data, we were able to clone the cDNAs.[5–7] Before and after our cloning of these genes, many glycosyltransferase genes have been also cloned and, as of this writing over 110 genes have been cloned.[8]

Studies on Cancer and Cancer Metastasis Utilizing Glycosyltransferase Genes

Five glycosyltransferase genes, cloned by us all have a type II transmembrane topology and are tightly bound to the Golgi apparatus and their genes have multiple promoters and are expressed in an organ and tissue specific manner. As a result, they provide diversity in terms of sugar structures. In the case of a spontaneous hepatocarcinoma of a rat hepatoma model designated as LEC rats, we reported that, at the initial stage of the primary hepatoma, mRNAs of both GnT-III and V are expressed and sugar structures were altered. Moreover, at the metastatic foci, GnT-V mRNA expressions were found to be prominent. A highly degree of association between GnT-V and cancer metastasis has been reported by Dr. Dennis and Dr. Kobata as judged by lectin reactivity and structure analyses.[9,10] However, the issue of whether the levels of glycosyltransferase genes were changed remains unclear. We reported the

direct implication of the transcriptional factor, Ets-1 in the underlying mechanism of the activation of activated GnT-V in cancer.[11] These phenomena were observed in various cancer cell lines and human cancer tissues and when Ets-1 is highly expressed in cancer cells in which GnT-V is highly expressed and a dominant negative of Ets-1 actually suppressed GnT-V expression. This was not observed in the case of Ets-2 gene transfection indicating that this phenomena constitutes an Ets-1 specific event and that the regulation of the GnT-V gene is regulated by Ets-1.[12] These results may provide with a new route for cancer metastasis via Ets-1 even though its underlying mechanism of cancer and GnT-V gene expression is unknown.

The β1-6 branching sugar chain, an enzymatic product of GnT-V affects the elongation of other sugar chains.

A different types of underlying mechanism for cancer metastasis may exist but the acquisition of β1-6 branching sugar chains of a specified glycoprotein(s) may undergo functional changes and may cause change in metastatic potential. Very recently we succeeded in the development of a highly GnT-V-expressed cell line and identified a matriptase, a serine proteinase, as a target glycoprotein for GnT-V which may undergo aberrant glycosylation by GnT-V and this may in turn, cause the activation of this proteinase and enhance cancer metastasis.

Mechanism Underlying Suppression of Cancer Metastasis

Even though the association between cancer metastasis with GnT-V and its mechanism are not presently clear, we hypothesized that the suppression of β1-6 branching by the inhibition of GnT-V biosynthesis would be possible, from substrate specificity studies. Namely, it is clear that GnT-III and GnT-V compete with the same substrate but once GnT-III acts on the substrate first, to produce a bisecting GlcNAc structure, GnT-V may not be able to act further and we assume that this may lead to a suppression in metastatic potential *in vivo*. *In vitro* substrate specificity studies using purified enzymes as well as tertiary structure analysis of bisecting GlcNAc residues also support these data. Even though GnT-III and GnT-V use the same substrate, once GnT-III acts to form a bisecting GlcNAc, the sugar structure was found to undergo conformational changes and GnT-V will no longer act, as evidenced by computer analyses. Based upon these analyses, we transfected the GnT-III gene into the melanoma B16F1 cells with a high metastatic potential, and attempted to remodel the sugar chains. When the GnT-III gene transfected cells were injected into the syngeneic mice via tail vein, in the case of control mice, many lung metastatic foci were observed whereas in the case of GnT-III transfected cells, lung metastasis was barely observed[13] (Fig. 3). Sugar analyses due to lectin blotting of the cells indicated that the β1-6 GlcNAc branching originally found in the parental cells had nearly disappeared in the GnT-III transfectants. Moreover, most of the glycoproteins including the adhesion molecules and receptors were functionally modi-

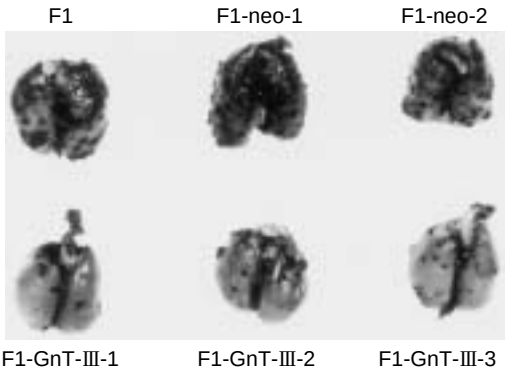

Fig. 3 Suppression of experimental lung metastasis of melanoma in mice by GnT-III gene transfection. When mouse melanoma cells, B16F1 were injected via the tail vein of syngeneic mice, after 3 weeks, metastatic foci were observed in the lung. In the case of melanoma cells in which GnT-III genes had been transfected, a marked suppression in lung metastasis was observed.

fied and cell biological parameters such as cell adhesion capacity and cell invasion capacity were decreased in the GnT-III transfectants.

Among those molecules, if one focuses on a representative adhesion molecule, E-cadherin which is highly associated with suppression of metastasis, in the GnT-III gene transfectants, the degradation of E-cadherin on cell surface was found to be inhibited by sugar remodeling. As a result of these changes, the cancer cells became resistant to detachment from the cells. Recently we found that phosphorylation of β-catenin which forms a complex with E-cadherin was also reduced.[15] It is conceivable that the suppression of phosphorylation of β-catenin left a β-catenin/E-cadherin complex remaining on the cell surface and this may enhance homophilic interactions of E-cadherin and contribute to the suppression of cancer metastasis.

On the other hand, the transfection of the α1-6 fucosyltransferase gene into the hepatoma cells resulted in a suppression of intrahepatic cancer metastasis. The underlying mechanism appears to be the decrease in adhesion capacity due to the remodeling of the sugar chains on the integrin molecule. It is now clear that the transfection of one glycosyltransferase gene into the cells, resulted in a dramatic change of the biological activity in the cells and this provides evidence for the presence of biological diversity of sugar chains. At the same time, the fact that we could suppress cancer metastasis *in vivo* suggests the possibility of gene therapy in the future.

Studies on the Regulation of Growth Factor and Growth Factor Receptors by Sugar Chains

The above findings cannot be explained simply by alterations in sugar chain structures. It is clear, however, that transfection of the GnT-III gene resulted in the alteration of various adhesion molecules of the function of growth factor receptors. The authors' group, in collaboration with Dr. Moskal group, found that GnT-III offers the functions of epidermal growth factor receptors.[16] Moreover, the EGF receptor, which was modified by GnT-III gene, enhances MAP kinase (intracellular signaling regulation kinase, ERK) activity.[17] This may lead to the completely different biological changes in processes such as cell growth and apoptosis.

On the other hand, regarding growth factors, it is known that nerve growth factor facilitates the differentiation of PC12 cells into neurite cells. An overexpression of the GnT-III gene in PC12 cells, resulted in the addition of a bisecting GlcNAc to TrkA, Nerve growth factor (NGF) receptor and even if NGF was added to the cells the dimerization of the receptor was inhibited and therefore the signal for differentiation was suppressed.[18] Moreover, a deletion mutant of Asn-420 of the EGF receptor resulted in spontaneous oligomerization and signaling was transmitted independently of the presence or absence of the EGF ligand.[19]

We also found in collaboration with Dr. Hashimoto, that HB-EGF, one of the growth factors, is highly associated with wound healing[20] and relationships between mutations of transforming growth factor β and its role in patients with Camurati-Engelmann disease in collaboration with Dr. Niikawa.[21,22]

α-Gal Epitope and Application of the Xenotransplantation from the Pig to Human/Monkeys

The shortage of the donor organs is a major problem. One of the strategies to solve this problem is to use xenotransplantation strategy. Pigs are considered to be a likely target animal for xenotransplantation. However, pigs contain α-galactosyl epitope (α-Gal epitope) which is composed of α1-3 Gal structure whereas human and old world monkeys lack this glycosyltransferase and the gene has become a pseudogene and has no function. Therefore, these structures are lacking in human and old world monkeys but in stead, natural antibodies against α-

Gal epitope are present in blood, as a result, after transplantation of an organ from pigs to human a superacute rejection reaction occurs. In order to avoid this reaction, the deletion of α-Gal epitope from pigs is essential. However, to obtain knock out pigs are difficult at present because ES cells are not available and other strategies need to be developed.

Our group in collaboration with Drs. Shirakura and Miyagawa, developed GnT-III transgenic pigs and examined the decrease in the α-Gal epitope. The α-Gal epitope on glycoproteins found in those pigs are markedly reduced.[23] Preliminary studies on the transplantation of a pig heart to a monkey resulted in a marked reduction of superacute rejection.

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