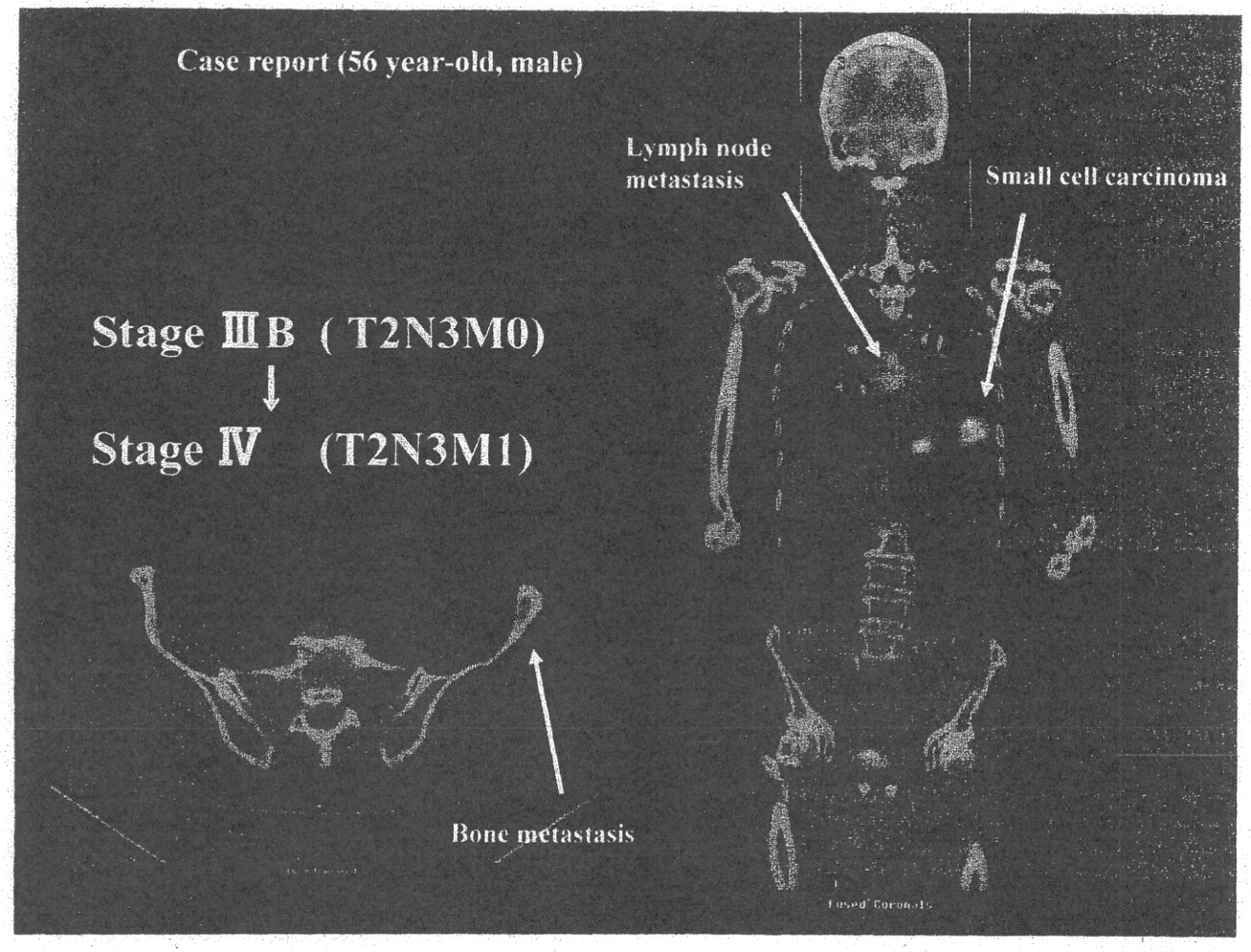

Fig. 4 Case report 2 (56-year-old male).

ing on the type of cancer cell. The mean value for each pathology was examined by obtaining both the pathology and the FDG accumulation (SUV) (Fig. 1). High SUV was observed in SCLC and squamous cell carcinoma, which have high cellular proliferation capacities. Although it has been pointed out that PET/CT might help in estimating tissue types,[9–13] at least pharmaceutically, it is useful to distinguish between SCLC and squamous cell cancer because in lung cancer, double cancers sometimes exist with different pathologies by which prognosis greatly varies. In addition, it is clinically difficult to collect lung cancer tissue. Because treatment methods differ between the SCLC or squamous cell carcinoma group and the adenocarcinoma group, it is believed that referring to Fig. 1 will facilitate the selection of a treatment method in clinical practice.[14] Unlike staging classifications for cancers of other organs, lung cancer is generally histopathologically divided into 2 groups: SCLC and non-small cell lung cancer (NSCLC). This is because the SCLC group is known to be more likely to metastasize than the NSCLC group. Also, in the results of our study obtained with combined PET/CT, a greater number of changes in stage were observed in the SCLC group (100%) than in the NSCLC group (63.3% versus 71.4%) (Fig. 2). The observation of high rates of change in the SCLC group supports conventional knowledge. Furthermore, because the SCLC group involves poor prognoses, SCLC is further classified into ED (extensive disease) and LD (limited disease; T1-2N0M0).[15] In addition, in the results of our study on combined PET/CT, LD showed an 80% correction rate, which was significantly higher than the 33% reported in the ED group. This supports the report that staging in SCLC with CI will be changed to the higher stage by staging with PET.[16,17]

Although it was initially staged as an LD with the use of CI, the lesion has actually extended over a

wider range.[18] The same can be said in cases of squamous cell carcinoma. In general, it is believed that squamous cell carcinoma mainly progresses locally and is not likely to metastasize in its early stage,[17] but according to Table 2, in the staging with combined PET/CT, the rate of change was high in squamous cell carcinoma, and metastasis was observed in many cases, indicating that it was already beyond the early stage when the patient visited the hospital for the first time, and that staging with CI is inadequate because it involves a tendency to miss the metastatic focus.

Based on the fact that staging with combined PET/CT was upgraded for each of the T, N, and M factors and that no difference was observed in the rate of change among T, N, and M factors in Table 1, it was indicated that missing the extension of the lesion had an impact not only on the size of the tumor but also on both lymph node metastasis and the distant metastasis.[19] In other words, it is indicated that the classification of ED and LD by staging with CI was inadequate not only for the detection rate of cancer but also for missing the spread of the lesion. This will have a great impact on the selection of wrong treatment methods.

Specifically with regard to the N factor (lymph node metastasis), in the same manner as it is stipulated in the general rules for cancers of other organs, the presence or absence of lymph node metastasis in lung cancer is usually diagnosed with the use of a CT scan. However, especially for the presence or absence of mediastinal lymph node metastasis, postoperative pathologic findings did not match those of CI in some cases, and there was a limitation in the diagnosis of lymph node metastasis. When a surgical method is selected in early-stage cancer, diagnosing the presence or absence of mediastinal lymph node metastasis and its range is a key issue that directly leads to the selection of video-assisted thoracic surgery (VATS) or open chest surgery. With PET/CT, regardless of the size of the lymph node, there is a limitation in the detection of tumors sized 10 mm[20] and below, but lymph node metastasis can be pointed out even if the tumor size is 10 mm.[17] However, sufficient examination has not been conducted on the pathology of lymph node metastasis, FDG accumulation into the lymph node, and tumor size; therefore, with the appearance of PET/CT, it is believed that it is time to revisit the conventional evaluation criteria of lymph node metastasis using CT scanning in the general rules for cancer.[21–23]

Conclusions

Our study presented surgeons with the following possibility: The fact that stages were changed in many cases by combined PET/CT indicates that cases of postoperative recurrence were in fact cases in which preoperatively preexisting foci were missed. This perception is resolved with the following phrase: If you suspect a cancer, do PET FIRST. In other words, in the cancer diagnosis process, the number of cases of inaccurate staging can be minimized by performing PET/CT first and then constructing a diagnostic process with various modalities. The phrase "PET FIRST" should not be forgotten, not only regarding the cancer diagnosis, but also by all physicians who are involved in cancer treatment.

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ELSEVIER

Macrophage-Dominant Sialadenitis in Human T-Cell Leukemia Virus Type I–Associated Myelopathy After Living-Donor Liver Transplantation

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ABSTRACT

A 64-year-old man who suffered from human T-cell leukemia virus type I (HTLV-I)–associated myelopathy (HAM) after living-donor liver transplantation (LDLT) for liver cirrhosis due to hepatitis C virus infection complained of xerostomia. Although exocrine function test results were positive, autoantibodies including anti-SS-A/SS-B antibodies and sialography showed negative findings. Labial salivary gland biopsy revealing infiltration of 60 counts of mononuclear cells (MNCs) in minor salivary glands led to a diagnosis of Sjögren's syndrome-like sialadenitis. Immunohistochemistry demonstrated dominant CD68 staining and major histocompatibility complex class II on the surface of infiltrating MNCs. Herein we have reported a rare condition of macrophage-dominant sialadenitis in a patient with HAM after LDLT.

BOTH hepatitis C virus (HCV) and human T-cell leukemia virus type I (HTLV-I) have been reported to be associated with the onset of Sjögren's syndrome (SS).[1,2] Because HCV infection demonstrates exocrine dysfunction along with sialadenitis, the American-European Consensus Group for SS excluded HCV infection in the diagnosis of SS.[3] We have previously reported that an epidemiological study showed a high prevalence of SS in anti–HTLV-I antibody–positive subjects.[4] In this case, a complication of HTLV-I–associated myelopathy (HAM) after living-donor liver transplantation (LDLT) has recently been reported.[5] Herein, we have additionally reported the emergence of unusual sialadenitis in this patient.

CASE REPORT

The complication of HAM in this patient was already reported by Soyama et al.[5] Briefly, LDLT was performed for a patient who had decompensated liver cirrhosis due to HCV infection in August 2002. Both the patient and his younger sister donor were seropositive for anti–HTLV-I antibody. Immediately after LDLT in October 2002, interferon (IFN) α-2b and ribavirin were administered after we confirmed recurrence of the HCV infection, but HAM appeared 18 months after LDLT. Although pegylated IFN α-2b and ribavirin were administered for 48 weeks against the HCV infection, no response was observed to the recurrent active hepatitis.

When the patient was admitted in September 2008, xerostomia was newly detected. The new clinical manifestations of HAM included spastic gait and bladder symptoms. Elevation of aspartate aminotransferase (53 IU/L), alanine aminotransferase (47 IU/L), and immunoglobulin (Ig)G (2630 mg/dL) were observed with normal total bilirubin (0.7 mg/dL). Type IV collagen and quantitative HCV ribonucleoprotein were elevated at 290 ng/mL (normal, ≤140) and 7.1 log IU/mL (normal, undetected) with reduced total branched chain amino acids (285 μmol/L; normal, 379–688). A liver biopsy, which had resulted in a hospital admission in September 2008, showed chronic hepatitis with fibrous enlargement of the portal area, inflammatory cell infiltration, and piecemeal necrosis. The relative copy number of HTLV-I against

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β-globin in the peripheral blood sample was $2.56 \times 10^2/10^4$ cells by real-time polymerase chain reaction. Along with xerostomia, both the Saxon test (1.1 g/2 minutes; <2 g, positive) and Schirmer test (3 mm/5 minutes; <5 mm, positive) were positive with negative results for anti-SS-A/SS-B antibodies and sialography. However, minor salivary gland biopsy (Fig 1A) demonstrated more than 60 counts of mononuclear cell (MNC) infiltration, which were confirmed as dominantly macrophages. Although the patient showed signs of xerostomia, positive exocrine dysfunction, and MNC infiltration into the minor salivary gland (MSG), SS was excluded according to the criteria determined by the American-European Consensus Group.[3] Immunohistochemistry using monoclonal antibodies for MSG demonstrated positive staining of CD68 on the infiltrating MNCs (Fig 1B). Compared with the prevalence of CD68, the prevalence of CD4 (Fig 1C) or CD8 (Fig 1D) was less than that of CD68, macrophage. Major histocompatibility (MHC) class II was found in human tonsil as a positive control (Fig 1E) and MNCs in the MSG of this patient (Fig 1F). Written informed consent for the use of the biopsy specimen was obtained from the patient.

DISCUSSION

HCV-related SS has been reported to be characterized by a high prevalence of cryoglobulinemia with a low frequency of anti-SS-A/SS-B antibodies.[6] In our case, sialadenitis without SS-related autoantibodies was compatible with the characteristics of HCV-related SS. However, HCV infection usually shows infiltration of CD4+ T lymphocytes into the MSG, which is incompatible with the present macrophagic infiltration. Furthermore, it has previously been reported that IFNs have the potential to cause autoimmune diseases, such as autoimmune thyroid diseases, systemic lupus erythematosus, rheumatoid arthritis, or SS.[7,8] Unoki et al reported that administration of IFN-alpha-2b for a patient with type C chronic active hepatitis induced SS with sicca symptoms and elevation of autoantibodies, suggesting that IFN per se has a potential to form autoimmune disorders in patients with viral hepatitis.[9]

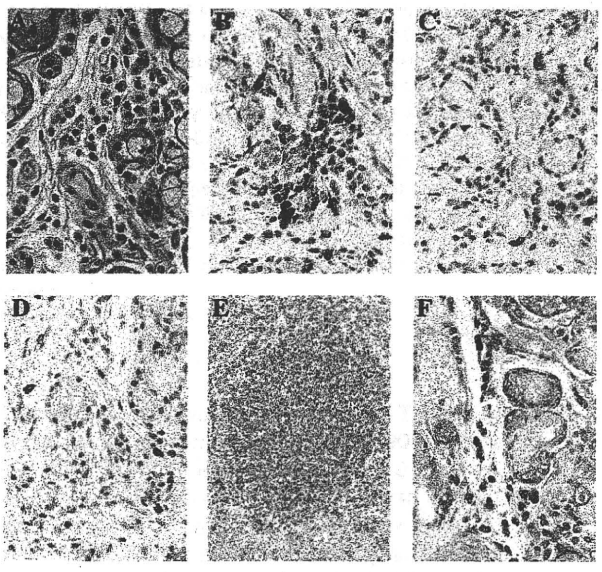

Fig 1. Phenotypic markers expressed in the minor salivary gland (MSG). Immunohistochemistry was performed for formalin-fixed, paraffin-embedded sections (3-μm thick) from the MSG using the streptavidin-biotin method. Primary antibodies were used as follows: **(A)** hematoxylin-eosin staining, **(B)** CD68, **(C)** CD4, **(D)** CD8, **(E)** MHC class II staining in human tonsil (positive control), and **(F)** MHC class II staining of the MSG of the patient. (Original magnification for A–D and F, ×200; E ×100.) Hematoxylin was used as a counterstain.

With regard to HTLV-I infection, prognosis of HTLV-I–positive renal transplant recipients has been previously reported,[10] observing that both living-related and cadaveric kidneys from HTLV-I carriers may be used for HTLV-I–seropositive recipients because of the low occurrence of adult T-cell leukemia. HTLV-I is also one of the candidates to trigger sialadenistis. We have previously reported a high prevalence of SS among patients with HAM.[2] However, the predominant phenotype of MNCs in HAM-SS patients was CD4+ T lymphocytes, which was similar to the type of MNCs in HTLV-I–seronegative SS patients.

Previously Ishiguro et al[11] established a rat model of HTLV-I infection in which massive foamy macrophages infiltrated the spinal cord and clinical manifestations of the rat resembled those of HAM patients. Meanwhile, our patient showed macrophage-dominant MNC infiltration into the MSG. Although the pathogenesis of the rat model might be different from that of human HAM, because lymphocytic infiltration is an apparent characteristic of HAM patients, an unrecognized trigger might have induced infiltration of macrophages into the MSG in our patient.

Graft-versus-host disease (GVHD) is considered to be a candidate cause of sialadenitis. Fujiwara et al[12] have previously reported sialadenitis in experimental GVHD in an animal model, in which nonirradiated mice were injected with spleen cells developing chronic GVHD. In their report, sialadenitis was observed predominantly with CD4+ T lymphocytes, although with a low frequency of macrophages, B cells, or plasma cells. However, chronic GVHD has rarely been reported after LDLT. Sun et al[13] reported a case of GVHD at 4 months after cadaveric liver transplantation. In their report, the patient showed gastrointestinal symptoms, which were determined to be T-lymphocyte infiltration based on a colonic biopsy.

In summary, the mechanism by which sialadenitis is induced remains to be clarified. However, both active hepatitis and HAM have the potential for viral-induced recruitment of mononuclear infiltration. Furthermore, double viral infection may provoke a strong elimination reaction compared with a single viral infection. Although an antiviral reaction is considered to be increased by innate immunity through Toll-like receptors,[14] intense antigen-presentation capacity might be yielded by induction of macrophages.

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SURGERY TODAY

Presidential Address

The Happy Marriage of Surgery and Science/Technology Would Lead to Prosperous Surgical Development Towards the Year 2050

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My choice of title for this Presidential Address is based on my prediction and hope that advancement of future surgery will be offered with the advent of new science and technology.

Many have contributed to the development of modern surgery. In the late nineteenth century, anatomy was the foundation of its structure; then, as the nature and causation of disease became clearer in the first half of the twentieth century, physiology and pathology were added to provide the essential background. For example, Theodor Billroth performed the first successful gastric resection in 1881, and Carl Schlatter performed the first total excision of the stomach in 1890. Lester R. Dragstedt left a very durable impression by reporting the role of vagotomy in surgery for peptic ulcers,[1] based on the physiology of gastric function, although this procedure was soon replaced by H_2-blocker drugs. Thus, an increase in life expectancy has been brought about by these brilliant advances in our understanding of the basic mechanisms of disease.

In the second half of the twentieth century, the art of surgery, in its upward climb, was always based on a substrate of science. Table 1 shows Thompson's[2] nominations for great contributions to surgery in the last half of the twentieth century, and Table 2 shows his collected surgical research contributions of great promise during the same period.

Surgeons as Nobel Prize Winners

In the past 100 years, six surgeons have won the Nobel Prize for Medicine (Table 3).[2,3] They were as follows: in 1909, Emil Theodore Kocher (Switzerland), who worked on the physiology, pathology, and surgery of the thyroid gland; in 1912, Alexis Carrel (France), a pioneer of vascular suture and the transplantation of blood vessels and organs; in 1923, Sir Frederick Grant Banting (Canada), who discovered insulin; in 1956, Werner Theodor Otto Forssmann (Germany), who opened the door to heart catheterization and the pathologic changes in the circulation system; in 1966, Charles Brenton Huggins (USA), for his hormonal treatment of prostate cancer; and in 1990, Joseph Edward Murray (USA), who was co-winner with E. Donnall Thomas for their work

Table 1. Surgical research contributions in the last half of the twentieth century (compiled by Thompson[2])

Contribution
Cardiopulmonary bypass
Transplantation
Vascular surgery
Total parenteral nutrition
Metabolic response to sepsis and trauma: burn care
Controlled clinical trials for cancer (breast)
Effect of hormones on cancer
Minimally invasive surgery
Joint replacement
Stereotactic neurosurgery
Urinary lithotripsy

Table 2. Surgical research contributions with great promise (compiled by Thompson[2])

Contribution
Tumor immunobiology
Telepresence surgery
Combined therapy for tumors (e.g., Wilms')
Fetal surgery
Angiogenesis research
Endocrine surgery
Extracorporeal gas exchange
Immune therapy for cancer
Correction sensory (vision and hearing) defects

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Table 3. Nobel Prize-winning surgeons

Surgeons	Award year	Workplace	Prize-winning work
Theodore Kocher	1909	Switzerland	Physiology, pathology, and surgery of the thyroid gland
Alexis Carrell	1912	France	Vascular suture and organ transplantation
Sir Frederick Banting	1923	Canada	Discovery of insulin
Werner Forssmann	1956	Germany	Heart catheterization
Charles Huggins	1966	USA	Hormonal treatment of prostate cancer
Joseph Murray	1990	USA	Organ transplantation

in lifesaving organ- and tissue-transplant techniques. These six distinguished surgeons elevated the discipline of surgery to the summit of the scientific world in the twentieth century.

Among these six Nobel Prize-winning surgeons, Huggins was a urologist and Murray was a plastic surgeon. Although these disciplines are included in the Society of the American College of Surgeons, they are specialties outside the Japan Surgical Society. Thus, based on the organization of the Japan Surgical Society, there have been four Nobel Prize-winning surgeons.

New Concepts in Surgical Treatment

When we focus on the development of gastric surgery in the nearly 130 years since Billroth's success in 1881, surgery for gastric diseases has become much safer and is now relatively established. In recent years, the laparoscopic approach has gained popularity in Japan for selected patients.[4] This minimally invasive procedure is much better for the patient in many regards; however, when we consider the basic principles of gastric surgery, the laparoscopic approach is simply a modification of conventional open surgery. From this point of view, to surpass Billroth's procedure, new concepts for treating gastric diseases should be anticipated. In 2003, Maemura et al.[5] reported that a tissue-engineered stomach could replace a native stomach in a rat model. Therefore, such tissue engineering is expected to promote a twenty-first-century solution to surgical reconstruction.[6]

How Surgical Articles Have Contributed to the Advancement of Surgery

Scientific research is important for the advancement of surgery. We recommend that young surgeons write scientific articles, and many articles by Japanese surgeons have been published. However, the question arises as to whether these scientific articles have contributed to the development of surgery. The quality of scientific articles is generally evaluated by the impact factor as well as by the science citation index. For the present Presidential Address, therefore, I evaluated the quality of surgical articles in a new way: by investigating those articles

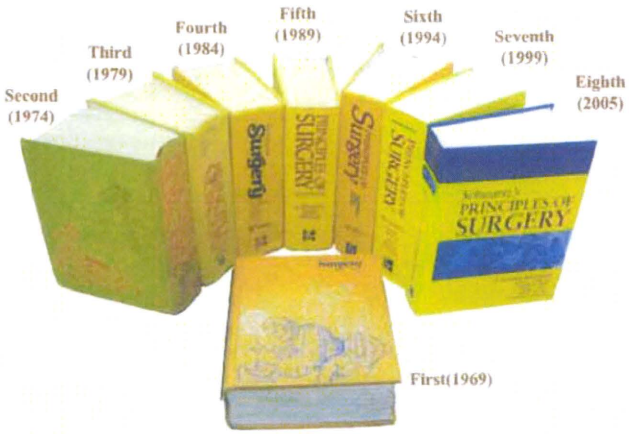

Fig. 1. *Schwartz's Principles of Surgery*

referred to in the textbook *Schwartz's Principles of Surgery* (McGraw-Hill Medical Publishing Division). Schwartz's surgical textbook has been used worldwide since its first publication in 1969. A revised edition has appeared every 5–6 years, and the most recent issue (8th edition) was published in 2005 (Fig. 1). The number of referenced articles written by Japanese surgeons and the objective work done in Japan was counted in each edition.

Of the 24 835 articles referred to in this textbook, from the first to the 8th edition, 334 (1.4%) were written by Japanese surgeons. In the first edition, only 4 (0.2%) articles were written by Japanese surgeons, but this number has been increasing, until the latest edition refers to 95 (3.3%) articles written by Japanese surgeons (Table 4). When comparisons were made among the various surgical fields, the most notable increase is in the field of liver surgery, with 23 (13.1%) articles by Japanese surgeons referred to in the 8th edition. In fact, the number and rate of articles written by Japanese surgeons have increased in all the surgical fields (Table 5).

Government Support of Science and Technology

To promote science and technology, government support is imperative. A comparison among other countries in terms of budget for research and development reveals

Table 4. Number of papers written by Japanese surgeons among the cited references in each edition of *Schwartz's Principles of Surgery*

Edition	Issue year	Total No. of cited references	No. of cited papers written by Japanese
1	1969	2350	4 (0.2%)
2	1974	2913	12 (0.4%)
3	1979	3018	14 (0.5%)
4	1984	3424	31 (0.9%)
5	1989	3276	45 (1.4%)
6	1994	3663	73 (2.0%)
7	1999	3286	62 (1.9%)
8	2005	2905	95 (3.3%)
Total		24835	336 (1.4%)

Table 5. Papers written by Japanese surgeons, based on their specialty, among cited references in each edition of *Schwartz's Principles of Surgery*

Edition	Esophagus	Stomach	Small intestine	Colon	Liver	Biliary	Pancreas	Spleen	Thoracic	Cardiovascular	Pediatric	Thyroid	Breast
1	2 (1.2)	(–)	(–)	(–)	(–)	1 (0.7)	(–)	(–)	(–)	(–)	(–)	1 (0.3)	(–)
2	5 (2.5)	(–)	(–)	(–)	(–)	1 (0.6)	(–)	(–)	(–)	2 (0.3)	3 (1.5)	1 (0.2)	(–)
3	6 (2.2)	(–)	(–)	(–)	(–)	2 (1.2)	(–)	(–)	(–)	2 (0.2)	3 (1.9)	1 (0.3)	(–)
4	7 (2.1)	7 (2.4)	(–)	(–)	1 (0.7)	4 (2.8)	1 (0.9)	(–)	1 (0.5)	2 (0.2)	5 (2.1)	3 (0.7)	(–)
5	3 (1.6)	6 (2.2)	(–)	3 (1.0)	7 (5.2)	1 (0.8)	1 (0.9)	(–)	8 (2.8)	4 (0.4)	10 (4.1)	2 (0.9)	(–)
6	6 (2.0)	7 (2.1)	(–)	2 (0.5)	9 (6.3)	6 (4.7)	4 (3.1)	1 (1.6)	14 (4.9)	5 (0.6)	15 (5.2)	2 (0.7)	2 (0.7)
7	9 (2.2)	8 (7.0)	3 (1.2)	1 (0.3)	7 (5.7)	5 (5.3)	2 (1.8)	1 (2.3)	9 (2.9)	7 (0.8)	9 (5.5)	1 (0.9)	(–)
8	9 (2.0)	8 (3.4)	1 (1.4)	(–)	23 (13.1)	4 (5.1)	13 (4.3)	7 (5.4)	2 (1.5)	23 (2.9)	4 (4.4)	1 (1.0)	(–)

Values in parentheses are percentages

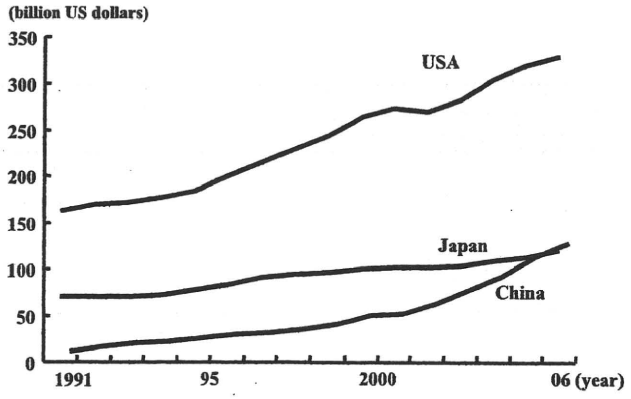

Fig. 2. Government financial support toward surgical advancement in the United States, China, and Japan[7]

that the United States budget has been extremely high, whereas the Japanese budget has recently fallen lower than that of China (Fig. 2).[7]

Japan also faces a decline in the number of researchers and technicians. An annual report on the Promotion of Science and Technology in 2003[7] predicted that the number of researchers and technicians will decrease from 2730 in 2000 to 1683 in 2050. One of the reasons for this decline is our aging society. By 2050, 40% of the population of developed countries such as Japan, Germany, and Italy will be over 65 years of age, while in the United States 70% will be senior citizens by as soon as 2030. By 2050, 22% of the global population will be over 60 years old, versus only 10% now, and by the end of the century this figure will have risen to 34% as the industrial world ages.[8]

The advancement of medicine, including surgery, is closely linked to the development of science and technology. Science and technology are costly, and when we look at their circumstances we must feel anxiety about whether Japan will be able to offer the chance of promotion in this field with a lack of budget and a shortage of researchers.

The Future: What Will Happen in 2050?

If we consider the advances of the last 100 years, think of what will be revealed by 2050! Dyson[9] stated that speciation in nature occurs with a time scale on the order of a million years. Human speciation pushed by genetic engineering may have a time scale of a thousand years or less. Compared with the slow pace of natural evolution, our technological evolution is like an explosion. We are tearing apart the static world of our ancestors and replacing it with a new world that spins a thousand times faster.

Greenfield cited futurologist Pearson's prediction that machines will probably surpass overall human intellectual capability by 2020 and will have an emotional feel just like people.[9,10] Although it may take years, it is undeniable that different genres of robots will dominate medicine and surgery in the future. The robots of the future will be far more interactive and prepared to learn. At the University of California, San Diego, for example, artificial intelligence investigators are developing an all-terrain wheeled rescue robot, with the basic aim of cutting 5 min off response times and saving an estimated 49 more lives a year. The idea is that a scanning system detects an accident and immediately deploys a robot, equipped with cameras and a wireless link, to investigate.[10] Another type of robot designed to save lives is the "Virtual Human": an artificial but integrated system of vital organs, which can be used for pharmaceutical or safety testing. Far from a mere concept on a screen, the technology is already being developed for an artificial "real" system that actually breathes, with cells that replicate and die, and blood that flows.[10]

If and when these automated procedures prove to be completely fail-safe, Greenfield[10] predicts that robots might gradually replace human surgeons. Within this century we will see a radical change in the traditional medical professions.[11] For those with a premium on a large amount of quickly accessed information combined with utterly reproducible manual precision, robots will be strong candidates.

Interestingly, robot football has been under way since 1997. On 4 August 2001, the Fifth World Robot Soccer competition, the "Robo Cup", was held in Seattle (Fig. 3). Over a hundred entrants competed in four different leagues according to size and ability. The ultimate goal is to develop a team of humanoid robots by 2050, to take on the human victors of the most recent World Cup and play according to FIFA rules.[10] Thus, robots will be an important tool in the support of future medicine.

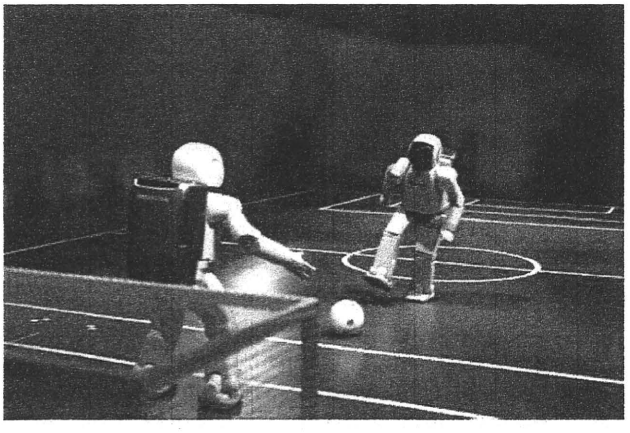

Fig. 3. World Robot Soccer competition (used with permission)

Innovative Surgical Procedures and Medical Ethics

Extreme technology such as robotic surgery continues to push the frontiers of medicine into domains that summon forth troublesome ethical questions. At this point, we draw on the criteria advanced by Dr Francis D. Moore[12] in the late 1980s for introducing innovative surgical procedures. These criteria require that the scientific preparation for proceeding to carry out an innovative surgical procedure must have been carefully and fully developed. He emphasized that the skill and experience of the team undertaking the innovative procedure is crucial. He also expressed concern about the ethical climate of the institution in which the innovation would be performed. When the epiphenomena of medical care, such as capital gain, investor profit, institutional representation, surgeon ego, municipal pride, and chauvinism, become the ultimate objective of the procedure, then the ethical climate of the institution is no longer acceptable for therapeutic innovation. It is crucial that innovative surgical procedures be openly displayed before the broad community of professionals in the field as well as the general public. Feedback from public and professional discussion might prompt us to rethink and revise various components of new procedures.

Conclusion

The great wave of surgical progress brought to the fore a large number of creative practitioners and scientists. In the first half of the twentieth century there was a most intimate interdependence of anatomy, physiology, pathology, and surgery, and in the second half of that century the development of surgery was boosted by the advent of new science and technology. In the twenty-first century, an innovative approach will change the scenery of surgery; however, surgeons should not leave the development of science and technology to researchers in other fields. What I want to stress here is that surgeons should take responsibility for the advancement of surgical science, and to do this, they must nurture an academic mind. Surgeons are also requested to give full play to the leadership of scientists and technologists. Thus, the happy marriage of, or good correlation between, surgery and science/technology will lead to a prosperous future for surgery. Along what lines will surgical progress be made? It probably will not result from improvements in technique, but from the application of discoveries made by teams of investigators interested in diverse aspects of a complex problem. Thus, the recent era has been characterized by an exponential growth in the science of surgery. Finally, we must pay great attention to fulfilling innovative procedures within

the boundaries of the established ethical climate and with public agreement.

Acknowledgments. I thank all the members of Department of Surgery, Graduate School of Biomedical Sciences, Nagasaki University, for their support and help in preparing this Presidential Address.

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肝移植後早期合併症

生体肝移植後に非閉塞性腸管虚血症(Non-Occlusive Mesenteric Ischemia; NOMI)をきたした1例

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はじめに

非閉塞性腸管虚血症(Non-Occlusive Mesenteric Ischemia；NOMI)は，腸間膜の主幹血管や腸管壊死領域を支配する腸間膜動脈に閉塞がみられず，腸管の虚血・壊死が，非連続・分節状に存在し，病理学的に腸管の出血および壊死を伴う病態である[1]。

Ⅰ．症　　例

患　者：50歳，女性
主　訴：全身倦怠感

現病歴：1996年，肝機能異常，耐糖能異常を指摘され，脂肪肝との診断で近医外来にて内服治療されていた。2008年8月23日より37℃台の発熱・下痢が出現。8月30日頃より黄疸を指摘され前医受診。精査にてT-Bil：20.7mg/dl，PT：35.6%，Plt：$9.2\times10^4/\mu$Lなど，肝不全の状態であった。また，MRCPでは総胆管と肝内胆管に口径不同を認め，原発性硬化性胆管炎が強く疑われ，肝移植の適応の有無も含め，当科紹介となった。

肝障害度に関しては，Child-Pugh分類が12点でgrade C，MELDスコアは34点であった。

入院後経過：入院4日目に凝血塊を混じた暗赤色の下血を認めた為，上部消化管内視鏡検査を施行。Red Color Sign陽性の食道静脈瘤を認めたが，その他明らかな出血の所見は認めなかった。全身状態不良であった為，この時点で下部消化管内視鏡は施行できなかったが，1週間前に行った前医での下部消化管内視鏡所見では，S状結腸までの観察ではあったが，粘膜の若干の発赤を認める以外，明らかな異常所見は見られなかった。

入院5日目，配偶者をドナーとし(血液型：O(+))，生体部分肝移植を施行した。グラフト肝重量(拡大左葉＋尾状葉)は360g，標準肝容積比は31.3%，手術時間15時間31分，出血量6,830gであった。胆道再建は胆管空腸吻合にて行った。

術後経過(図1)：術後より，免疫抑制剤としてステロイド，mycophenolate mofetil(MMF)の投与を開始。術後5日目までプロスタグランディン(0.01γ)の静脈内持続投与を行った。術後7日目より食事開始となったが，術後8日目より腹満感が出現した為，腹部造影CTを施行。著明な結腸の拡張を認めたが，穿孔を疑わせる所見は見られず，上腸間膜動脈根部の閉塞等も認められなかった。術後9日目より39℃台の発熱および腹痛，腹膜刺激症状が出現。収縮期血圧60mmHg台とショック状態を呈した。腹膜炎による敗血症性ショックの疑いで，同日，緊急手術を施行。回腸に飛び石状に色調変化が散在しており，さらに，回盲部からS状結腸にかけて壁の菲薄化を伴った腸管の著明な拡張を認めた。中毒性巨大結腸症に伴う敗血症性ショックを疑い，大腸亜全摘，回腸

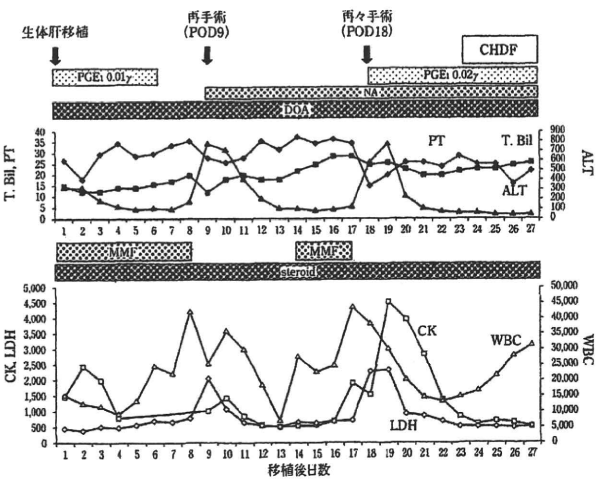

図1　入院後経過

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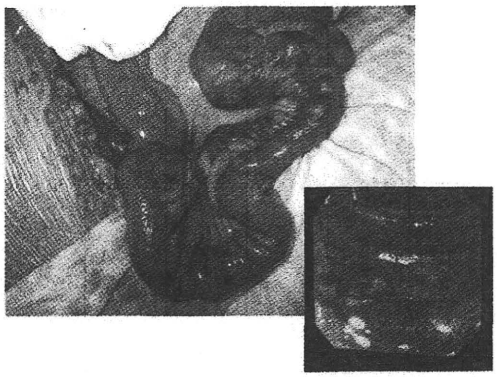

図 2　再々手術時開腹所見および術中内視鏡所見。回腸の漿膜面は，散在性に暗赤色に変色。粘膜面にも同様に色調変化を認めた。

ストーマ造設，S状結腸粘液瘻造設術を施行した。

その後，一旦，炎症所見は落ち着いたものの，再び肝機能の悪化とともに，白血球，LDH，CKの上昇，代謝性アシドーシスが出現。ストーマから出血量の増加，さらに血圧低下を認めた為，移植手術後18日目に再々開腹を施行した。回腸ストーマ部より，30cmおよび50cm口側の腸管の漿膜面は暗赤色に変色。また，術中内視鏡検査では粘膜の発赤および暗赤色の色調異常が散在していた(図2)。ストーマより75cm口側の粘膜は正常であったので，同部で小腸を切除して，ストーマ再造設を行った。摘出標本の病理検査では，粘膜下の静脈の鬱血や動静脈内に血栓を認めた。この時点で，臨床所見も考慮し，NOMIと診断した。

その後，血管攣縮の改善目的にPGE_1の持続投与を行ったが，再々手術後7日目頃より再び白血球数の増加，血圧低下，ストーマからの出血，ストーマの色調変化が出現した。全身状態不良であり，耐術不能と判断し，血漿交換等を行ったが全身状態の改善なく，移植手術後27日目に多臓器不全にて死亡した。

Ⅱ．考　　察

NOMIは，腸間膜動脈の閉塞なしに腸間膜の虚血を呈する病態である[1]。心拍出量低下及び血圧低下に伴う腸間膜血管の攣縮が原因であると考えられているが[2]，特徴的な所見に乏しく，早期発見が困難な場合も少なくない為，死亡率は70～90％とその治療成績は，いまだ満足のいくものではない[3]。

Mitsuyoshiら[1]は，13例の経験をもとにNOMI発症の危険因子およびNOMIを疑う所見として，以下のような項目を挙げている。①腹部不快感に続き，緩徐に進行する腸閉塞症状，②カテコラミン投与を必要とするショック状態であること，③低血圧のエピソードがあること，④徐々に進行する肝酵素レベルの上昇[1]である。本症例は，50歳と比較的若年ではあったものの，非代償性肝硬変に対する生体肝移植術後であり，Matsuyoshiらの①～④の項目を満たしていた。

腸管粘膜の壊死を来たしていない初期の段階に診断可能であった場合には，papaverineやPGE_1などの血管拡張薬の静脈或いは腸管膜動脈持続投与にて死亡率が40％まで向上したとの報告も見られるが，本症例のように腸管壊死を示唆する所見が見られた場合には，壊死腸管の切除に加え，腸管の減圧および残存腸管の血流確認の目的に口側および肛門側断端への人工肛門造設が推奨される[7]。

臓器移植とNOMIとの関連は，我々が調べ得た限りでは，膵腎同時移植後にNOMIを来たした症例[8]とABO血液型不適合生体腎移植後の症例[9]の2例のみであった。2例の共通点としては，腎移植患者であったことと免疫抑制剤として移植直後よりMMFを投与されていたことであった。NOMI発症後，2例ともMMFの投与は中止されており，MMFによる消化管障害がNOMIの発症に何らかの影響を与えている可能性は否定できない。本症例でも肝移植直後よりMMFの投与を開始しており，NOMI発症の誘因となった可能性は否定できないが，更なる検討が必要であると考える。

結　　語

NOMIは一旦発症すると，腸管壊死から多臓器不全まで急激に進行するいまだ救命率の低い疾患である。早期発見，早期治療開始が重要であり，臓器移植後患者においても進行する腹痛を認めた場合には念頭におき，診断・治療をすすめるべきである。

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肝移植後早期合併症

生体肝右葉移植後の胆管吻合部難治性胆汁瘻の治療にT-tubeが奏功した1例

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はじめに

生体肝移植後の胆道合併症は肝移植後の中長期成績に関わり，また胆管炎の合併，黄疸の出現等によりQOLの低下や，全身状態の悪化を来しうる。合併症の程度やタイプによるが，保存的治療，局所ドレナージ，再手術のいずれを選択するかは施設間に差が認められる[1)2)]。

今回，胆管空腸吻合（H-J）後の縫合不全に対し，経皮的ドレナージや内視鏡的加療が奏功せず，最終的に開腹下のT-tubeによるドレナージにて改善した症例について報告する。

Ⅰ．症　　例

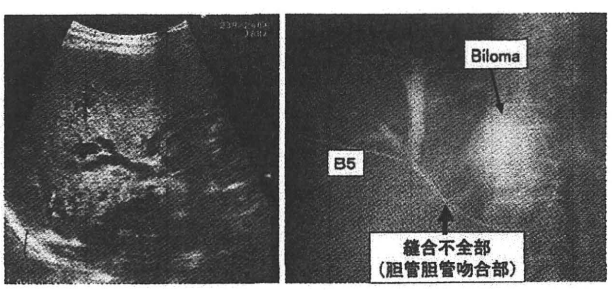
患者は54歳女性。肝細胞癌を伴うC型肝硬変に対し生体肝移植を施行した。長男から肝右葉の提供を受け，グラフト重量/レシピエント標準肝容積比は65.1%であった。グラフトの胆管は前区域枝が3穴・後区域枝は1穴であったため，吻合に際し前区域枝の3穴を1穴に形成した後に，前・後区域枝を別々に吻合した。

術後経過は良好であった。外来フォローアップ中の術後2ヵ月の腹部造影CTにて肝門部に5cm大のfluid collectionを認めたが，臨床症状や炎症反応も認めず，腹水貯留と判断し経過観察とした。

術後3ヵ月，AST/ALTの上昇を認め，その後黄疸が出現した。USにて肝内胆管の拡張を認め，黄疸の原因として肝門部fluid collectionによる胆管の閉塞が考えられた。前区域枝からの経皮経肝ドレナージ(Percutaneous transhepatic cholangio drainage，以下PTCD）を施行した際，ガイドワイヤーの肝門部fluid collectionへの迷入を認め，同病変は胆管吻合部の縫合不全によるbilomaと診断した。前区域枝に挿入したPTCDチューブにて胆管，biloma両者のドレナージが可能であった（図1）。ドレナージにて黄疸は速やかに軽快し，その後，チューブを総胆管内へ進め，内瘻化を図った（図2）。多孔式チューブによるドレナージにて瘻孔閉鎖を期待していたが，チューブ閉塞による胆管炎を発症し，チューブ交換や抗生剤投与による保存的治療を行った。

炎症が改善した後にランデブー法にてEndoscopic retrograde biliary drinage（ERBD）チューブを留置した。別のFluid collectionに経皮経肝的にドレーンを留置した際に施行した造影にてfluid collectionと総胆管との間の交通は認めず，縫合不全部の閉鎖が得られたと思われた。

しかし，その後，徐々に後区域枝の胆管拡張が目立つ様になり，B6からPTCDを施行するも，胆管炎から敗血症を合併し，全身状態の悪化を来たし，内科的・保存的治療のみでは改善困難と判



a）腹部超音波検査にて肝内胆管の著明な拡張を認める。
b）経皮経肝的胆道ドレナージ施行時に，縫合不全部を経由してbilomaを同時にドレナージした。

図　1

長崎大学移植・消化器外科

図 2　ドレナージチューブを総胆管内へ進め，内瘻化を図った。

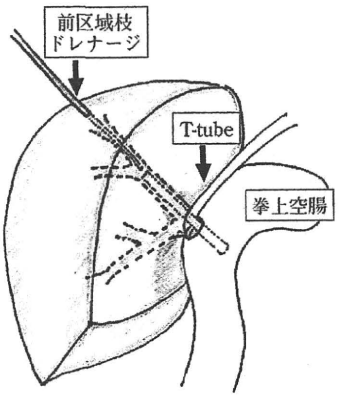


図 3　肝管空腸吻合部縫合不全部に6Fr T-チューブを側孔をあけることなく，そのまま肝内胆管・腸管内に留置した。

断し，再手術を施行した。肝門部の剥離を進めると，グラフト前区域胆管とレシピエント胆管の吻合部半周以上の離解が縫合不全の責任病変であった。胆道再建をH-Jに変更し，前区・後区それぞれ1穴，合計2穴による再吻合を施行した。胆管吻合部にはY脚断端より2㎜のRTBDチューブを1本ずつ留置し，外瘻とした。術後早期から吻合部後面に留置したドレーンから胆汁流出を認め，また減圧目的に術中に留置したRTBDチューブが逸脱しており，持続吸引にてドレナージを行ったものの，限局性胆汁性腹膜炎を合併したため，再々手術を施行した。前区域枝吻合部頭側よりleakageを認めたが，後区域枝吻合部はintactであった。前区肝内胆管末梢に2㎜RTBDチューブを留置し，肝外に誘導した。さらに縫合不全部に6Fr T-チューブを側孔をあけることなく，チューブの形状を保った状態で，肝内胆管・腸管内に留置した（図3）。T-チューブ後面の胆管組織はもろく，縫合できないため，肝実質と腸管壁を縫合，さらに大網を充填した。術後は胆汁漏を認めるものの，ドレナージ良好であり，発熱の消退，また血液生化学検査でも炎症反応・肝機能の改善を認めた。吻合部後面からのleakageは徐々に減少した。瘻孔造影でも前区域の造影で挙上空腸が描出されるのみで，明らかなleakageはないことを確認し，吻合部後面に留置していたドレーンを抜去した。

その後炎症所見を認める事無く，全身状態徐々に改善，15ヵ月後，T-tubeを抜去し，その際，肝内胆管に留置していたRTBDチューブを腸管内に進めた。同チューブは位置変更後8ヵ月の時点で抜去した。現在，肝機能，全身状態に問題なく，外来通院中である。

Ⅱ．考　　察

肝移植に伴う胆道合併症の頻度は20～40%と報告されている[3]。我々はD-D後の合併症対策として，縫合不全に対してはドレナージ後ERBDを，また狭窄の場合もERBDで対応している。H-J例では，縫合不全に対しドレナージを行い，必要があれば再吻合術を，狭窄に対してはドレナージ後バルーン拡張を試みるという方針で胆管合併症に対応しており，上記対応にて，再手術を施行する事無く症状軽快している症例が多い。本症例では，ERBDやPTCDを併用してのランデブー法にて改善が認められず，むしろ吻合部を介したドレナージにて感染を助長した可能性があり，治療方針の選択を反省させられる症例であった。LDLT後の胆道合併症は，多くの場合，内視鏡や経皮経肝アプローチを用いて対処可能であるが，中には対処困難な状況も存在し，そのような症例に対する再手術のタイミングを適切に判断する事が重要である。生体肝移植D-D症例における術後胆道狭窄に対して，開腹下に総胆管を切開してのT-tube長期留置の有用性が報告されている[4]。H-J症例においても長期にわたる炎症の為，再吻合に際し健常な胆管組織が確保出来ない場合は，本症例で我々が行ったようにT-tubeをスプリント兼ドレナージとして用い，瘻孔形成の後に抜去するという方法が有用であると考える。

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Topics

英国の医療事情の一側面と専門医制度の仕組み

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日本専門医制評価・認定機構（以下機構：池田康夫理事長）では、厚生労働省専門医制度推進支援事業の一環として専門医制度推進支援事業委員会（八木總明委員長）が設置され、国内の各科領域専門医制度の調査とともに、諸外国の専門医制度事情を視察し、わが国の専門医制度を推進するための情報収集を行うことになりました。対象国は米国、ドイツ、英国、そして韓国の4カ国で、各々に調査のためのワーキンググループ（WG）が置かれました。私は英国担当のご下命を受けました。早速、八木委員長にご相談の上、WGメンバーとして矢永勝彦先生（日本外科学会：東京慈恵会医科大学）、益田宗孝先生（日本外科学会：横浜市立大学）、坂本照夫先生（救急医学会：久留米大学）、藤澤正人先生（泌尿器科学会：神戸大学）の4人に加わってもらいました。さらに英国での臨床経験のある矢野秀朗先生（国立国際医療センター）と現在英国で癌化学療法の勉強中の森下真理子先生（長崎大学）にはアドバイサリーとして協力してもらうこととしました。

まず、割り当てられた国内調査を行った後、それから英国の専門医制度事情についての勉強会を持ちました。英国の制度に詳しい矢野先生にプレゼンテーションをお願いしながら、日本との違いなどについて情報の交換をいたしました。

2009年12月初旬に焦点をあて、英国に調査訪問をすることになりましたが、WGメンバーは多忙な方々であるだけに、約1週間の渡英日程を組むことはなかなか難しく、最終的には矢永、益田両先生と私の3名が出張することになりました。

お互いの日程を一致させることも難しく、結局は別々の航空便とルートをとり、ロンドンで集合することとしました。私は12月3日（木）夕刻にロンドンのホテルに入り、翌4日（金）午前中に矢永先生が到着、そして、益田先生は4日夜にロンドンに到着、といった具合でした。

訪問先はあらかじめ機構と打ち合わせ、各組織に予約をもらっていました。12月4日（金）にBritish Medical Association（BMA）、週明けの7日（月）にRoyal College of Surgeons（RCS）、8日（火）にPostgraduate Medical Education and Training Board（PMETB）といった3つの組織を訪問しました。なお、RCS訪問にはアドバイサリー役で英国留学中の森下真理子先生に、また、PMETBにはKing's College Hospitalへ留学中の永田茂行先生（九州大学）にロンドンで合流し、同行願いました。

その調査を通じて明らかになった英国の医療システムと専門医制度の現況は次の通りです。

1．National Health Service（NHS）

英国の医療はDepartment of Health（DoH：日本の厚労省に相当）の下部組織としてNHSがあり、DoHとNHSが医療施設数や専門診療科、医療の質を管理しています。ただし、NHSによる保健制度以外に、Private practice（PP）というものがあり、NHSの病院の中でPPができるシステムです。ただ、英国内でPPをするにはNHSの仕事を一定以上していることが必要です。したがって、専門医資格をとり、Consultantという地位につかないとPPは許されないといった制約もあります。

2．British Medical Association（BMA）

日本における医師会的な役割を果たしている組織です。

3．General Medical Council（GMC）

GMCは医師の生涯にわたっての医療行為に対する適正を評価・認定する役割を担っています。英国には日本式の医師免許制度はありません。英国で診療をするためには、医師資格を国に登録（Registration）する必要があります。それを管理するのがGMCです。登録のためには卒後研修コースに所属しているか、それを修了したかの証明が必要ですが、これがないとNHSのもとでは医師として働くことができない仕組みとなっています。これまでGMC登録は名目上の手続きによる1年ごとの更新でしたが、近々、公式の評価を受ける免許制になり、5年ごとの審査制度（Revalidation）が導入されるのが、最近の話題だそうです。

4．PMETB（Postgraduate Medical Education and Training Board）

英国はEngland、Scotland、Wales、North Irelandの4つの地域に分かれており、その各々の地域で別々のプログラムで卒後教育が行われていましたが、国の指示の下、統一して教育を管轄するための機関として、05年に新たにPMETBが設立されました。この時点までは各学会などの機構に任されていた卒後専門医教育プログラムの決定と承認、遂行と評価および認証をPMETBが行うようになったのです。この制度改革に対し各学会の抵抗は当然のごとく大きかったようですが、PMETBのみでこれらの業務を行うことは不可能であり、各専門学会の協力の下で実行されているのが実情だそうです。教育の実施については各地域の機関（全英で20機関：England 16、Scotland 2、WalesとNorth Irelandで各1）であるLocal deaneryに任されており、その実行についてはPMETBが定期的に査察（書類審査）を行っています。専門医教育が終了するとCertificate for completion of training（CCT）が授与されます。PMETBの財源は教育を受ける医師からの登録料と国からの補助金によってまかなわれています。なお、設立から数年を経た現在、専門医教育のみを担当するPMETBに関する問題が提起されており、近い将来、PMETBは初期研修やConsultantを管轄するGMCを補完する機構に移行する予定とのことでした。

図1　Royal College of Surgeons事務局のある建物風景

5．Royal College of Surgeons（RCS）

今回、訪問者の3名は外科医でしたので、RCSを訪問しました。英国にはいろんな分野でRoyal College……といった組織がありますが、王制の英国でのそれはとても権威あるものと位置づけられています。外科系のRCSの事務局がある建物も威厳に満ちたものでした（図1）。英国ではEngland、Scotland、Wales、North IrelandにそれぞれRCSがありますが、そこでは標準治療法の確立、教育プログラムの作成、Fellow試験合格者数の調整などの役割を担っています。以前は4つのCollegeが別々の試験を行って、その合格者にFellow of RCS（FRCS）の称号を付与していましたが、それを統一した資格Membership of RCS（MRCS）に変革したのも最近のトピックスの1つだそうです。専門医資格を取得すると、ほとんどの専門医はRoyal Collegeの学位取得を目指します。RCSでは毎年、50人のFellowに研究費支援を行っています。RCSは職員数280名、それとは別に各外科系のSubspecialtiesの職員が80～100名勤務している大所帯の組織です。RCSの財源はFellowの年会費（410ポンド）、MRCS受験料（200

万ポンドの収入）と寄付でまかなわれ、国からの援助は受けていません。今後もこの方針を維持することを説明者は強調していたのが印象的でした。

6．EU内での動き

EU内ではCCT資格をとり、勤務しようと希望する国の語学試験に合格すると、そのCCT資格はEU内のどこでも通用する専門医制度にはなっています。ただし、国や地域差もあり、共通の専門医資格とみなされるには現実には難しい面もあるようです。

以上のような制度の中、専門医の養成は図2のように行われています。医学部を卒業すると2年間の基本的領域のトレーニングを受けます。そして、General Practionar（GP）か、もしくは専門医のコースのどちらかを専攻します。一度、方向性を決めたら、途中での変更は認められません。GPはその道のSpecialty Trainingを3年間受けて、資格試験に合格するとCCTが授与され、その後に空席があればGP開業ができます。一方、専門医コースを専攻すると2年のCore Medical Trainingの後に、4～6年のHigher Specialty Trainingが待っています。そこを修了して資格試験に合格すると、CCTの資格が取得できます。それから平均4、5年Specialist Registrarとして勤務し、評価が高ければLocum Consultantとして一定期間試験的に雇用され、その後にポストの空きがあり、また、成績優秀と認められた者はConsultantに就任できる可能性があるといった道のりです。

英国全体ではGPが35,000人ほどいます。GP 1人当たり1,500～2,000人の登録患者を受け持っています。

医師の診察を受けたい場合は、まず、自分担当のGPに診てもらわねばなりません。必要あれば診察したGPが専門医を紹介するシステムとなっていますが、実際に専門医に紹介されるケースは2～5％に過ぎないそうです。

英国には日本と同様に「医師の偏在」があるのでしょうか。結論から言えば、偏在は若干あるものの、問題として取り上げられるほどではないようです。それはGPも病院専門医も、空きポストがないとそこで開業や就職ができません。しかし、全国各地に何人の専門医、GPが配置されるかは国の基準で決められているため、ポストは満遍なく全国に作られているから、医師の偏在は少ないのです。

診療科の偏在については、麻酔科、小児科、産婦人科といった地域の中核病院の運営に欠かせない医師群についてはNHSが全国の医師の人事権を持っていて、全国各地のポストへ医師を異動させ、ローテーションを行うシステムになっているそうです。

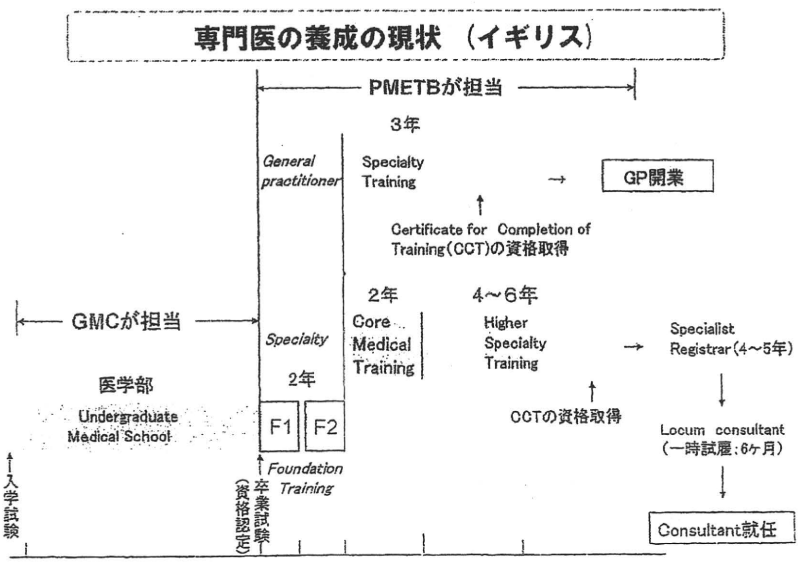

図2　英国の専門医制度

今回、英国の医療事情と専門医制度の成り立ちを知る機会を得ました。英国もその仕組み作りには歴史的に振り返っても苦労を重ねてきたことがわかりました。その国に適したシステムを生み出すには気の遠くなるような時間と先人の努力の結晶があることがうかがわれました。

このような機会を与えてくれた機構にこの場を借りて感謝申し上げます。

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Impact of the National Access to Antiretroviral Program on the incidence of opportunistic infections in Thailand

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ABSTRACT

The National Access to Antiretroviral Program caused a decline in HIV mortality in Thailand, but its impact on opportunistic infections (OI) remains unknown. The aim of this study was to compare the incidence of different OIs before and after the initiation of highly active antiretroviral therapy (HAART). Data from a prospective cohort at a hospital in northern Thailand were analysed. In total, 704 patients enrolled from July 2000 to October 2002 and not on HAART were followed up until October 2004. In addition, 409 patients who started HAART between April 2002 and January 2004 were followed up for 24 months. The impact of HAART on OIs was analysed using Cox proportional hazard models. HAART was associated with a strong reduction in OIs. The reduction appeared to vary by type: tuberculosis (TB), adjusted hazard ratio (AHR) = 0.2 (95% CI 0.1–0.5); pneumocystis pneumonia (PCP), AHR = 0.03 (95% CI 0.007–0.1); cryptococcal meningitis, AHR = 0.2 (95% CI 0.1–0.5); and penicilliosis, AHR = 0.1 (95% CI 0.06–0.3). In conclusion, HAART was very effective in reducing OIs, especially PCP. TB and cryptococcal meningitis remained frequent in the early phase of antiretroviral drug therapy. More attention to prophylaxis as well as earlier diagnosis and starting treatment for these OIs is recommended.

1. Introduction

Highly active antiretroviral therapy (HAART) has greatly decreased AIDS and AIDS-related mortality in developed countries.[1–3] However, only recently has HAART become more widely available in resource-limited countries. The WHO estimates that more than 4 million people were receiving HAART in middle- and low-income countries at the end of 2008, representing an increase of 36% in 1 year and a 10-fold increase over 5 years.[4] The HIV mortality rate has declined in middle- and low-income countries but is still higher compared with high-income countries, especially in the first few months after starting HAART.[5,6] Thailand has been one of the first Asian countries severely affected by the HIV epidemic since the early 1990 s. The Thai government expanded the antiretroviral drug programme to the national scale in 2004, as the National Access to Antiretroviral Program for People living with HIV/AIDS (NAPHA).[7] This programme rapidly

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increased patient access to HAART by supplying a fixed-dose combination of generic drugs ('GPO-Vir'). As a result, a substantial decline in mortality has been observed (unpublished data).

Since opportunistic infections (OI) are the major cause of death in HIV-infected individuals, the decline in AIDS-related mortality in the HAART era is mainly attributed to the decline in OIs.[8] There are several reports from high-income countries in North America and Europe showing that the introduction of HAART has greatly lowered the incidence of AIDS-defining illnesses.[2,9] It is known that there is a considerable difference in the distribution pattern of OIs in different geographical areas.[10] There are few data on the impact of HAART on OIs from low- and middle-income countries in Asia and Africa. Several studies in Africa investigated the effect of OI prophylaxis on the incidence of OIs.[11,12] However, only two papers evaluated the impact of HAART on OIs. Badri et al.[13] showed that HAART reduced the incidence of HIV-associated tuberculosis (TB) by >80% in a cohort study in South Africa. One study from India reported changes in TB incidence before and after HAART, but they did not quantitatively determine the impact of HAART. Neither of the studies evaluated the incidence of OIs other than TB.[14]

To determine the impact of HAART on AIDS in Thailand, changes in the incidence of different OIs at a government hospital in northern Thailand before and after initiation of the National Access to Antiretroviral Program were examined.

2. Materials and methods

2.1. Study site and study populations

A prospective cohort study was conducted at the HIV Clinic, Day Care Center (DCC) of Lampang Hospital, a government referral hospital with approximately 800 beds situated in the centre of Lampang province in upper northern Thailand. The DCC was established in October 1995 as an outpatient clinic providing treatment, care and support for HIV-infected patients.[15] Recruitment of this cohort started on 6 July 2000 by contacting all HIV patients attending the HIV clinic.[16] Over 95% of patients agreed to participate in the study. All patients were requested to visit the clinic at least every 3 months regardless of the presence of clinical symptoms. If patients developed a clinical event of interest, follow-up was censored at the date of occurrence for this diagnosis, but patients were followed-up for further OIs as long as they survived. In April 2002, the Thai government introduced GPO-Vir (stavudine, lamivudine and nevirapine) into the clinic on a pilot basis and the number of patients receiving GPO-Vir gradually increased. In 2004, the number of patients on HAART rapidly increased as the government integrated the GPO-Vir regimen into the national health insurance service. GPO-Vir became freely available for any HIV patient fulfilling one of the following criteria: low CD4 count of <200 cells/μl; or diagnosis of AIDS. The incidence of OIs in these patients during the follow-up period was used in the current analysis, with the data from the first part of the cohort (before HAART) serving as a control.

2.2. Data collection

For each participant in the study, sociodemographic data and medical history [HIV-related symptoms, history of antiretroviral therapy (ART), mode of transmission and history of OIs] were obtained at the initial visit by trained research staff through face-to-face interviews using structured questionnaires. In addition, a full blood count, CD4 cell count and viral load were measured. The CD4 cell count was determined using a FACScan flow cytometer (BD Biosciences, San Jose, CA, USA) and HIV viral load was measured using a Cobas Amplicor HIV-1 Monitor Test (Roche Diagnostics, Basel, Switzerland). Diagnosis of OIs was made following the guidelines of Lampang Hospital, which are based on the Thai national guidelines.[17] All clinical information was collected by three physicians specialised in HIV care.

2.3. Clinical management of opportunistic infections

Standard clinical algorithms were used to guide the initiation of prophylactic and therapeutic interventions based on the treatment guidelines of Lampang Hospital (modified from reference[17]). Briefly, as for primary prophylaxis, patients with a CD4 count <200 cells/mm^3 were given two double-strength tablets of trimethoprim/sulfamethoxazole (TMP/SMX; 80 mg TMP and 400 mg SMX) orally once daily or three times per week for prophylaxis against pneumocystis pneumonia (PCP). The same regimen was administered to prevent toxoplasmosis when the CD4 count was <100 cells/μl. Fluconazole 200 mg orally once daily or 400 mg once a week was given for prophylaxis against cryptococcosis when the CD4 cell count was <100 cells/μl. No primary prophylaxis for TB or *Mycobacterium avium* complex (MAC) infection was given in this study. These treatment guidelines did not change throughout the study.

2.4. Analysis

To analyse the impact of HAART on the incidence of OIs, HIV patients were grouped into before and after receiving HAART. For the 756 patients who were recruited for the cohort between 6 July 2000 and 15 October 2002, information on OIs was collected up to 15 October 2004. For the 409 patients who started GPO-Vir at the clinic between 10 April 2002 and 31 January 2004, information of OIs was collected for 24 months. Incidence rates were calculated by dividing the number of patients developing an event by the number of person-years at risk. To evaluate the impact of HAART on the incidence of OIs, Cox's proportional hazard models with the time since enrolment as time axis was used. Patients who entered the cohort before receiving HAART and who then went on to receive HAART during the follow-up period were included as two separate observations. Therefore, hazard ratios were adjusted using robust standard errors to account for within-person correlation of disease susceptibility. Kaplan–Meier survival plots were used to show the incidence of different OIs in relation to CD4 cell counts at enrolment separately for the before and after HAART groups.

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