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Esophageal Disorders

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Abstract: Recent trends of esophageal disorders in Japan are described. Diagnosis of esophageal cancer at early stages has come to be practiced extensively by means of endoscopic mucosal resection, which contributed greatly to improve the benefit of patients. As severity classification of gastroesophageal reflux disease has now been established, main study subjects of the disease are shifting to diagnosis of Barrett's esophagus, and diagnosis and treatment of resulting early carcinoma. In addition, esophageal achalasia is increasingly treated first by means of balloon dilatation, followed by laparoscopic surgery in case of no improvement by balloon dilatation. Progress in the endoscopic ultrasonography has now developed to the EUS-guided fine-needle aspiration (EUS-FNA), contributing to diagnosis and treatment.

Key words: Early esophageal carcinoma; EMR; GERD; Barrett's esophagus; Achalasia

This paper will report recent trends in the diagnosis, treatment, and care of disorders of the esophagus. The esophagus of approximately 27 cm in length is susceptible to various disorders. First, esophageal cancer will be discussed.

Esophageal Cancer

There is no other disease in which the resection treatment has broader variations in invasiveness than the esophageal cancer. Briefly, the extent of resection varies from endoscopic treatment such as endoscopic mucosal resection (EMR) to surgical dissection in three regions, namely thoracic, abdominal, and cervical regions. Of particular note is that patients with mucosal cancer, a superficial carcinoma of the esophagus, who are in the early stages of cancer with no lymph node metastasis, are encountered at most medical institutions every year. This fact has recently been verified by the five-yearly report of the Japanese Society for Esophageal Diseases.

In the past ten years, for instance, the inci-

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dence of mucosal cancer has increased rapidly from 21 to 43.8% while that of submucosal cancer has decreased from 79 to 56.2%. This shift is largely due to the widespread use of upper gastrointestinal endoscopy with dye-spraying. The detection rate for esophageal cancer by mass X-ray examination is 0.008%, or 1/13 the detection rate for gastric carcinoma. In contrast, the detection rate for esophageal cancer in the initial mass screening by endoscopy is 0.1%. In mass screenings by endoscopy with iodine dye in high-risk groups such as alcoholics, the detection rate is 3.6%. In addition, approximately 10% of patients with cancer in the head and neck regions also have esophageal cancer. Based on morbidity rates, this means that for every ten cases of gastric carcinoma detected by endoscopy, one case of esophageal cancer will be missed unless further testing is performed.

At the 56th meeting of the Japanese Society for Esophageal Diseases in June 2002, a general guideline on the treatment of esophageal cancer was presented. It should be noted that a clear guideline does not currently exist in Western countries. This guideline will be discussed in the following sections, beginning with the diagnosis of esophageal cancer.

1. Diagnosis

With the widespread use of EMR today, there is a demand for an accurate diagnosis of the invasion depth of cancer in the esophageal mucosa and submucosa. A detailed dynamic diagnosis using dye-spraying endoscopy is useful for distinguishing between m1 and 2 cancers and between m3 and sm1 cancers. For the diagnosis of sm2 and 3 cancers, neoplasms can be objectively visualized by high frequency ultrasound probe sonography. CT and MRI are suited to diagnose adventitial invasion. The lymph nodes can be effectively visualized by endoscopic ultrasonography (EUS), CT, or MRI, with metastasis being correctly diagnosed in 80% or more of cases.

2. Treatment

Based on the pre-operative diagnosis of the invasion depth of the cancer, EMR is selected for the treatment of mucosal cancer. Esophagectomy and surgical dissection in the cervical, thoracic, and abdominal regions are the standard treatment for patients diagnosed with cancer deeper than sm1. In regard to esophagectomy, there is a consensus that the more recent approach of thoracoscopic and laparoscopic surgery is as radical as conventional open chest surgery. In patients with very advanced cancer, radiotherapy and chemotherapy may be attempted in order to arrest the progress of the disease. However, the therapeutic effect of these treatments is controversial.

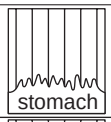
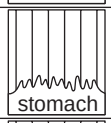
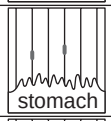
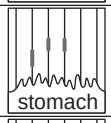
3. Course and prognosis

According to Japanese national data for 2002, the overall ten-year survival rate for patients who underwent esophagectomy for esophageal cancer was 25.5%. Of course, the prognosis varies depending on the staging, as determined by invasion depth, extent of lymph node metastasis, and organ metastasis. In terms of invasion depth, the most recent ten-year survival rates for pTis (m1), pT1 (sm), pT2 (mp), pT3 (a1-2), and pT4 (a3) were 54.4, 36.7, 26.9, 20.2, and 9.0, respectively. A study of lymph node metastasis emphasized that the number of metastases is closely reflected in the prognosis. Briefly, the most recent eight-year survival rates for patients with no metastases, one to three metastases, four to seven metastases, and eight or more metastases was 57.5, 36.6, 19.3, and 8.8%, respectively. Thus, accurate staging prior to surgery is being increasingly demanded.

Reflux Esophagitis

Reflux esophagitis, a concept which is linked to gastroesophageal reflux disease (GERD), refers to damage of the esophageal mucosa due to reflux of an acidic or alkaline substance. The severity of the damage is classified according to

Table 1 Los Angeles Classification of Reflux Esophagitis (revised by Hoshibara *et al.*)

Mucosal break: an area of white scar or erythema clearly demarcated from adjacent normal-appearing mucosa		Grade N No endoscopic change.
		Grade M Color-change type (minimal change)
		Grade A Mucosal break<5mm in length and confined to mucosal folds.
		Grade B At least 1 mucosal break≥5mm in length; mucosal breaks which are not connected to mucosal breaks in adjacent mucosal folds.
		Grade C At least 1 mucosal break which extends across 2 or more adjacent mucosal folds, but is not circumferential.
		Grade D Circumferential mucosal break.

Note: Presence of esophageal stricture, esophageal ulceration, and Barrett's esophagus.

the extent and depth of lesions.

From an epidemiological perspective, the incidence of patients endoscopically diagnosed with reflux esophagitis has increased from 5 to 17% in the past 30 years. While there may be problems with the selection of the data set and regional differences, the number of patients with reflux esophagitis is definitely increasing. Men aged in their 30s to 50s are most commonly afflicted whereas there is a marked increase in the incidence among women aged 60 or more.

Endoscopic findings of reflux esophagitis are characterized by inflammation which becomes increasingly mild with increasing distance from the gastroesophageal junction. Briefly, it is usual for patients with severe reflux esophagitis to have deep ulceration and stricture at the gastroesophageal junction and erosion and erythema toward the mouth side. The exception is stooped and/or bed-ridden patients who may unexpectedly have deep ulceration in the middle region of the esophagus. Ulceration associated with Barrett's esophagus, a disorder acquired as a result of long-standing reflux esophagitis, is treated in the same way as for gastric ulcers. Although ulcers even at a depth of U1 IV respond rapidly to proton pump inhibitors (PPI), they typically recur on discontinuation of treatment.

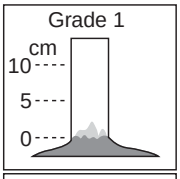
1. Classification of reflux esophagitis

The main classifications of reflux esophagitis in current use are a severity classification and a stage classification which aim to evaluate therapeutic effect. According to the classification of the Japanese Society for Esophageal Diseases, the disease was traditionally classified as "color-change type", "erosion/ulceration type", and "protruding thick type". However, since most patients fall in the category of the "erosion/ulceration type", the system was not practical

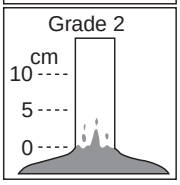
Table 2 The 1996 Classification of Reflux Esophagitis of the Japanese Society for Esophageal Diseases (Tokyo classification)

Grade 0
No evidence of esophagitis.

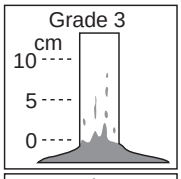
Grade 1
Red or white turbidity observed.



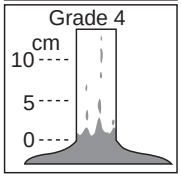
Grade 2
Erosion/ulcers<5cm from gastroesophageal junction; no adhesion.



Grade 3
Erosion/ulcers≥5cm and<10cm from gastroesophageal junction; adhesion evident but not circumferential.



Grade 4
Erosion/ulcers≥10cm from gastroesophageal junction; adhesion evident and circumferential.



Notes: 1. Barrett's esophagus: Description of the length of columnar epithelium of esophagus.
2. Stricture: Description of the approximate diameter.

Note: ①Filamentous unstained band which is first seen with iodine stain is also included in Grade 1.
②Esophagogastric junction refers to the mucosal junction (squamo-columnar junction).
③2 parallel, continuous lesions are called "adhesion". The majority of lesions without adhesions are filamentous or point-like erosions.
(Source: Kouzu, T.: *Dictionary of Gastrointestinal Terminology*, Igaku Shoin, 2002; p.206. (in Japanese))

in the actual classification of patients. Subsequently, the Los Angeles (LA) classification system which uses the concept of "mucosal break" (an area of white scar or erythema clearly demarcated from adjacent normal-appearing mucosa) was reported in Western countries. Although the LA system was used widely throughout Japan, it was difficult to distinguish between gradings A and B in the system and a modified version (Table 1) was developed in Japan which took into account the therapeutic effect. At about the same time, the Japanese Society for Esophageal Diseases proposed a new classification, called the Tokyo Classification (Table 2), based on the extent and length of lesions. Both the modified LA and Tokyo Classification systems are currently used. A third classification system shows the therapeutic effect in a single lesion and uses a similar stage classification as in the healing process of gastric ulcers (Table 3).

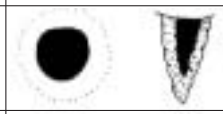
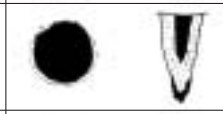
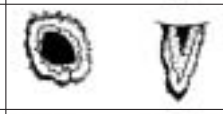
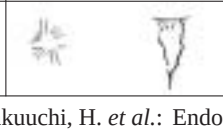
2. Differential diagnosis

In patients with severe esophageal stricture, it is important to distinguish whether the mucosa at the lower end of the stricture is columnar or squamous epithelium. In the former case, some erythema and erosion, etc. are observed at the upper end in most patients, making a diagnosis of reflux esophagitis possible. In the latter case, the presence of localized or circumferential esophageal cancer or unexplained chronic benign stricture must be considered in a differential diagnosis. Today, understanding the pathological state of an esophageal stricture at the lower end is facilitated by balloon dilatation of stenotic regions as small as a pinhole, providing a guidewire can be inserted endoscopically.

3. Treatment

The drug of first choice for esophageal ulcers and esophagitis, disorders caused by GERD, is PPIs. As maintenance therapy, PPIs should be administered at a half-dose. In patients who still complain of nocturnal reflux symptoms despite PPI treatment and in whom nocturnal acid breakthrough (NAB) is evident based on

Table 3 Stage Classification of Esophagitis

Stage			Endoscopic findings	Stain findings
Active	A_1		Thick white scar Peripheral edema Raised margin	Stains to ulcer margin with iodine. Periphery may stain randomly. Erosion surface stains reddish violet with toluidine blue.
	A_2		White scar Edema disappeared Regenerated epithelium (small amount)	Stains to ulcer margin with iodine Fluff-like densely stained appearance (small amount). Erosion surface stains reddish violet with toluidine blue.
Healing	H_1		White scar reduced Regenerated epithelium (increased) Gentle margin	White scarstains blue with toluidine blue. Regenerated epithelium does not stain. Margin has fluff-like densely stained appearance.
	H_2		White scar further reduced Ulceration virtually covered by regenerated epithelium	Margin has increased fluff-like densely stained appearance.
Scarred	S_1		Regression of ulceration Slightly raised and puckered with erythema	Slightly puckeredwith fluff-like densely stained appearance.
	S_2		Slightly puckered but no color change	Disappearence of densely stained. Almost uniformly stained. Partly non-uniformly stained.

(Source: Makuuchi, H. *et al.*: Endoscopic findings. *Reflux Esophagitis*, Bunkodo, 1988; pp.129–135. (in Japanese))

24-hour esophageal pH monitoring, administration of a H_2-blocker before bed is effective in some cases.

Esophageal stricture and Barrett's esophagus are acquired as a result of long-standing reflux esophagitis. Most patients who present with esophageal stricture are elderly and aggressive surgery is not an option favored by either the physician or patient. With early diagnosis of the disease, drug therapy and endoscopic dilatation of the stenosis are currently a satisfactory treatment.

There is a consensus that Barrett's esophagus is the end stage of reflux esophagitis. It is defined by the Japanese Society for Esophageal Diseases as "the presence of columnar epithelium continuing from the stomach to the esophagus". In light of the rapid increase in esophageal adenocarcinoma arising from Barrett's esophagus and the increasing tendency in reflux esophagitis in Japan, there is an urgent need to clarify the various canceration processes of Barrett's epithelium. Barrett's epithelium is classified as short-segment Barrett's epithelium (SSBE) or long-segment Barrett's epithelium (LSBE) based on the boundary of the esophageal columnar epithelium of 3 cm. At present, difference, if any, in the incidence of canceration between the two types, what mucosal changes are useful in the diagnosis of early cancer and how tumor suppressor genes, cancer genes, and growth factors are involved in the metaplasia-dysplasia-carcinoma-sequence, are unknown. Understanding the clinical course from inflammation to carcinogenesis will be the direction of future research.

While the number of cases is limited, EMR has started to be used in the treatment of early cancer. Prior to a definite diagnosis of malignancy, photodynamic therapy (PDT) of precancerous foci and deciduation of Barrett's epithelium by argon plasma coagulation (APC) are performed, and PPI therapy aimed at decreasing squamous epithelium is also being investigated.

In the case of mucosal cancer patients with

squamous epithelium carcinomas, a two- to three-year study of follow-up patients would be quite feasible. However, in the case of carcinomas in Barrett's esophagus, there is little opportunity to conduct follow-up observations and future studies on the morphological changes which occur in the disease over time are warranted.

Esophageal Achalasia

Esophageal achalasia is frequently accompanied by esophageal cancer, with the incidence of both diseases occurring simultaneously being about 3.5 to 4.5%. A treatment which minimizes the period of dysphagia and remedies it early in the course of the disease is demanded. Previously, various types of abdominal and open-chest surgery have been reported and there are many reports of techniques which aim to prevent post-operative reflux esophagitis.

Given the young age of patients recently, treatment tends to be drug therapy to reduce the lower esophageal sphincter (LES) pressure and therapy using latest high-precision balloons. If there is no improvement, laparoscopic surgery is performed. There is a tendency for an increasing number of patients to recover after one or two dilatation treatments. It is not known whether this increase in the recovery rate is due to the greater precision of dilatation balloons in recent years. Surgery is reserved for patients who fail to respond to repeated dilatations. These patients tend to be very nervous because of their poor response to previous treatment. Given this background, the duration of the illness and morphological findings on X-ray both play a role.

A recent trend in the treatment of achalasia is direct injection of botulinum toxin into the LES muscle by EUS. While this procedure offers promise of reducing LES pressure by blocking cholinergic receptors, it has not yet been approved in Japan.

Submucosal Cancer

Advances in EUS have simplified the biopsy and identification of the primary lesion in submucosal cancers of the esophagus. Differentiating between benign and malignant myogenic tumors based on ultrasound images alone, however, is still difficult. The recent development of EUS-guided aspiration biopsy has enabled a tissue sample to be safely collected from within a tumor based on an ultrasound image with color Doppler function obtained via the insertion point of the aspiration needle. Endoscopic extirpation of tumors following biopsy can also be safely performed.

Other Esophageal Disorders

In the past ten years, the most common foreign object in the esophagus was a two-sided bridge prosthesis. Recently, tablets in press-through packaging continue to be common foreign objects. The incidence of fish bones and pieces of meat also tends to be high. The instruments used to remove a foreign object depend on the type of the object and the instrument needed is usually determined after an endoscopic examination.

The key to removal of a foreign object is to make every effort to prevent damage to the mucosal surface of lesions also and damage to the cardia and cervix in the esophagus. To this end, the following instruments must be at hand: ①large EMR grasping forceps, ②a polypectomy snare, ③a mesh-covered polypectomy snare, ④an endoscopic variceal ligation (EVL) overtube, ⑤an EMR overtube for esophageal mucosal resection, and ⑥a tip-mount transparent hood. Most foreign objects can now be removed without complications.

Esophageal Rupture and Perforation

The causes of esophageal perforation are classified as follows: ①inadvertent ingestion of foreign object, ②iatrogenic, ③trauma, and

④idiopathic esophageal rupture, etc. With the widespread use of endoscopic treatments, there is a tendency for iatrogenic causes to increase and an awareness of the perforation during treatment is critical.

The treatment of esophageal perforation depends on whether or not the mediastinal pleura is ruptured. Depending on the extent of the perforation and the amount of time that has elapsed, mediastinal emphysema progresses to subcutaneous emphysema of the cervical region, periesophagitis, mediastinitis, mediastinal abscess, pneumothorax, retention of pleural fluid, and empyema. Therefore, it should be borne in mind that early diagnosis of this condition is critical.

This paper has focused on recent trends in esophageal disorders.

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Diseases of the Stomach and Duodenum

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Abstract: The topics of stomach and duodenum have been described in this report. The discovery of *Helicobacter pylori* was the revolutionary event in the pathogenesis, diagnosis as well as treatment of gastrointestinal diseases. The eradication of the bacteria prevented the recurrence of peptic ulcer, namely gastric and duodenal ulcer. It is reported that this bacteria may be the main cause of gastric cancer as well as malignant lymphoma. However, direct evidence of this relevance is still lacking and further genetic studies need to be conducted.

Key words: Stomach; Duodenum; *Helicobacter pylori*; Peptic ulcer; Gastric cancer; Malignant lymphoma

Introduction

Diseases of the upper gastrointestinal tract or, in other words, esophagus, stomach, and duodenum have undergone a remarkable transformation with the discovery of *Helicobacter pylori*. In particular, the treatment of peptic ulcer or gastroduodenal ulcer has become very easy and certain because recurrence of ulcers that was once thought to be inevitable can now be prevented by eradicating the bacteria.

Insurance coverage of the treatment has finally been approved in Japan, and eradication of *H. pylori* is becoming a common practice. However, reports on the occurrence of reflux esophagitis caused by eradication of the bacteria have started to be noticed, and this has become a serious issue concerning eradication therapy. The emergence of antibiotic-resistant bacteria is also an important problem. In addition, there are many more issues that need to be solved in the future including whether or not indications for eradication therapy should be expanded to include chronic gastritis and what kind of relationships there might be between *H. pylori* and stomach cancer or MALToma.

On the other hand, there have been significant developments in Japan in the area of endoscopic treatment of early gastric cancer. The recent developments are explained below.

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Peptic Ulcer

Although peptic ulcer is a representative disease that has tormented humankind since ancient times, the problem of the disease was mostly solved as an infection at the end of last century. It is unusual for a disease to undergo such dramatic development as in this case. Peptic ulcer has been treated as a representative disease that only occurs in humans as a result of psychosomatic factors such as stress. In fact, many artists and writers such as Soseki Natsume suffered from the disease, which has also affected their works.

While the discovery of H_2-blockers and proton pump inhibitors (PPI) in the late 1970s has greatly contributed to the treatment of ulcers, the discovery of *H. pylori* in 1982 led to a Copernican development of its pathology and treatment. Specifically, by the new triple therapy that combines amoxycillin (AMPC), clarithromycin (CAM), and PPI, a 90% or greater eradication of *H. pylori* became possible. As a result, recurrence of ulcers that was once so troublesome is now prevented in nearly 100% of duodenal ulcer cases and in at least 80% of gastric ulcer cases.

Problems that now remain are how to handle *H. pylori*-negative ulcers and how to prevent and treat ulcers induced by NSAID (nonsteroidal anti-inflammatory drugs). While the former has increased in Western countries, it has not been a significant problem in Japan. However, it may become a problem as eradication therapy for *H. pylori* advances.

NSAID-induced ulcers are a disease whose incidence has risen with the increased use of analgesics in this aging society, and it will probably continue to be a problem in the future. In particular, gastrointestinal tract hemorrhage caused by this disease has turned fatal in many cases, and it has become an important disease in the field of emergency medicine. As for treatment of gastrointestinal tract hemorrhage, recent advances in endoscopic treatment has been remarkable, and hemostasis is performed by endoscopic hemostasis, notably the clipping method in most cases.

Diffuse hemorrhage is also treated endoscopically by argon plasma coagulation (APC) and rarely requires surgical procedures. There is a world of difference between the present and a decade or two ago.

H. Pylori

It has been 20 years since the discovery of *H. pylori*. During this time, the pathology, diagnosis, and treatment of upper gastrointestinal diseases have undergone revolutionary transformation. In particular, as mentioned earlier, it can be said that treatment of peptic ulcers has been established as infection treatment. It is said that chronic gastritis, particularly atrophic gastritis, is also caused by the same type of infection. Classification of gastritis has also changed radically, and the Sydney Classification is gradually starting to be used in Japan. One problem remains with respect to whether or not atrophic glands recover after bacterial eradication, and this point is still debated among pathologists.

As for diagnostic method, microscopic examination, culture technique, and rapid urease test are commonly performed as invasive methods, i.e., endoscopic methods. As noninvasive methods, serum antibody assay and urea breath test are used, and urine antibody and feces antigen measurements have also been performed more recently.

As for bacterial eradication method, the aforementioned new triple therapy has been used across the world, and the method is now covered by the national health insurance in Japan as of November 2000. However, with regard to national health insurance coverage, problems concerning the selection of diagnostic methods, secondary eradication methods, target of eradication, and many other problems exist and await urgent settlement. In addition, there are important problems following bacterial eradication that must be solved — these

include reflux esophagitis, occurrence of cardia cancer, and emergence of resistant bacteria.

Malignant Tumors of the Stomach and *H. Pylori*

It is a well-known fact that the incidence of stomach cancer in Japan largely surpasses that in other advanced countries. One of the reasons is said to be *H. pylori* infection.

Since the WHO reported the close relationship between the bacteria and stomach cancer was similar to the relationship between cigarettes and lung cancer, there has been a greater awareness of this relationship. However, the direct causal relationship between the two has not been determined.

It is strongly believed that the role of *H. pylori* is displayed at the beginning of atrophic gastritis stage and changes from intestinal metaplasia to stomach cancer, and other elements such as nitrosamine are involved in the development of the cancer thereafter. In animal experiments, a Japanese report on how stomach cancer occurred when Mongolian gerbil had been infected with the bacteria has drawn international attention. Conversely, Uemura *et al.* observed people with and without *H. pylori*-infection for eight years, and reported in *the New England Journal of Medicine* that stomach cancer did not occur in the latter and a statistically significant difference was noted between the two groups (Fig. 1).[5] This problem remains inconclusive until the results of the intervention study conducted by the cancer center in Japan are reported.

In contrast, data about the pathogenicity of *H. pylori* were recently published in *Science* by Higashi *et al.* and have drawn attention.[6] Although CagA, a cytotoxin of *H. pylori*, has attracted some interest for quite some time, Higashi *et al.* reported that CagA is injected into epithelial cells when *H. pylori* attaches to the cells, affecting cell proliferation and motility through a phosphorylation process.

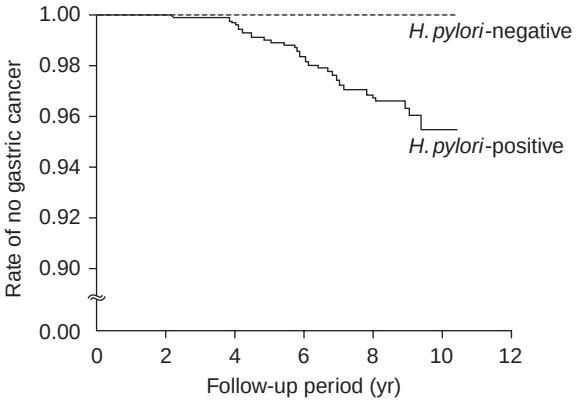

Fig. 1 Incidence of gastric cancer among people with and without *H. pylori* infection
(Excerpted from Uemura, N. *et al.*: *New Engl J Med* 2001; 345: 784–789.)

This information may be very important for elucidation of the causal relationship between stomach cancer and *H. pylori*.

Concerning the relationship between malignant tumors of the stomach and *H. pylori*, an important point is the so called low-malignancy MALToma, a type of malignant lymphoma of the stomach, which has been found to disappear when bacterial eradication is performed, thus making eradication the first-line therapy. Of course, accurate diagnosis is particularly important in this case, and it should be made carefully in cooperation with pathologists.

Recent developments in diseases of the stomach and duodenum were discussed above.

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Disease of the Small Intestine

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Abstract: Recent information on the small intestine is summarized. Concerning digestion and absorption, α-glycosidase inhibitor, which slows the absorption of carbohydrate, has become commercially available as a diabetic drug, and a number of transporters, such as peptide transporter (PepT1) that is involved in the efficient absorption of nitrogen source as well as drug absorption, have been discovered. In addition, a group of growth factors that are involved in the formation and regeneration of the small intestine have been found, and the importance of intraepithelial lymphocytes and glutamine has become known. In addition, the possibility that cells derived from the bone marrow might behave as a part of the epithelium of the digestive tract has been reported and has gained interest. Concerning intestinal motility, progress has been made in the analysis of interstitial cells of Cajal and various neurotransmitters. C-kit-positive stromal tumors were thoroughly investigated. The concept of GIST has been established and imatinib therapy for GIST has already begun. Although there is room for improvement in enteroscopy, is useful in the diagnosis of small intestinal diseases. The advancement of technology including virtual endoscopy is expected. In the area of surgery, the spread of laparoscopic surgeries as a minimally invasive approach has been marked.

Key words: Peptide transporter; Stem cells; Gastrointestinal stromal tumor (GIST); Enteroscopy; CT

Introduction

The small intestine, which plays a role in the absorption of nutrients that are essential to maintain life, is an important immune organ that serves as a barrier against foreign antigens, and its functions are while intricately interrelated with the autonomic nerves and endocrine system. However, it is also an organ where a direct approach such as endoscopy is difficult.

Recent information on the small intestine, has been summarized firstly in terms of basic research and secondly in terms of clinical research.

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Basic Research

1. Digestion and absorption

Food is degraded into glucose, amino acids, and others by digestive enzymes, and it is finally absorbed into the body through the villous epithelium in the small intestine. Carbohydrate is hydrolyzed by α-glycosidase during the membrane digestion. The α-glycosidase inhibitor, which slows the hydrolysis of carbohydrate, is presently used in the treatment of diabetes, because it prevents the blood glucose level from rapidly increasing.

In addition to simple diffusion, various substrate-specific transporters are also employed in the absorption process of each nutrient from the villous epithelium into the body efficiently. Thus far, a number of transporters such as sodium-glucose cotransporters (SGLT1), glucose transporters (GLUT2) that function by facilitated diffusion, transporters of various amino acids, and sodium-dependent bile acid transporters (BAT) have been reported, and their properties are being revealed at a molecular biological level. Concerning absorption of nitrogen sources, the functions and regulation of peptide transporters (PepT1), which can absorb nitrogen sources in the form of oligopeptides, have become clear. PepT1 is known to have unique characteristics, such as maintaining its functions even in various pathological conditions and being involved in the absorption of some antibiotics.

More recently, monocarboxylic acid transporter (MCT1) and non-sodium-dependent organic anion transporters (OATP) have been newly discovered, and it is expected that many more transporters will be revealed in the future. These transporters may be applied not only to absorption of nutrients but also to drug delivery.[1)]

2. Process of villus formation and regeneration of mucosa

As mentioned above, expression of nutrient transporters are mostly specific to the small intestine. It has become evident that various transcription factors such as Cdx2 are involved in the phenotypic expression specific to the small intestine. Small intestinal epithelium differentiates from stem cells that exist near the bottom of the intestinal crypt, and the entire villus is thus formed through the maturation process of these cells. However, the mechanism by which the small intestinal mucosa acquires properties specific to the small intestine, is not yet clearly understood. This is one of the major research themes today.

In addition to transcription factors, various growth factors such as epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1) are involved in this process. Among such growth factors, glucagon-like peptide-2 (GLP-2) in particular has drawn attention because its strong action for mucosa proliferation action has been proven through experiments.[2)] Moreover, stimulation by foreign antigens that has entered from the mouth and the presence of intraepithelial lymphocytes are also factors that cannot be ignored in the formation of mucosa.

In fact, the number of intraepithelial lymphocyte count in the small intestinal mucosa decreases over a short period in patients who receive parenteral nutrition, followed by a decrease in secretory IgA and finally causing villous atrophy. This induces bacterial translocation and increases the patient's susceptibility to serious infections. To prevent such villous atrophy and infections, administering glutamine and dietary fibers are effective.

With regard to differentiation and proliferation of mucosa, one recent report concerning the regeneration of the intestinal tract was particularly noteworthy. The report showed that bone-marrow-derived cells might serve as stem cells for gastrointestinal mucosa when gastrointestinal mucosa has been seriously damaged.[3)] Since intestinal disorders caused by radiotherapy and carcinostatics often make treatment difficult to continue, exploring

methods that can be used not only to prevent mucosal disorders but also to rapidly repair and regenerate mucosa is a very important project from a clinical standpoint.

3. Gastrointestinal motility and autonomic nerves

The small intestine transports food by peristaltic movement, which is appropriately regulated according to hunger, the ingestion of food, and other conditions. While it is known that sympathetic nerves (noradrengic) and parasympathetic nerves (cholinergic) serve as autonomic nerves associated with gastrointestinal motility, the mechanisms of intestinal motility are also becoming more clearly understood. In particular, a nervous system that is operated by nonadrenergic and noncholinergic transmitters has been found in the intestinal wall.

Specifically, there is a nervous system that is sensitive to various substances including vasoactive intestinal poly-peptide (VIP), nitric oxide (NO), 5-hydroxytryptamine (5-HT), and calcitonin gene-related peptide (CGRP), and each of these substances is closely involved in regulating gastrointestinal motility and secretion. The actions of 5-HT (serotonin) for secretion have drawn attention thus far, and it is thought that changes in the sensitivity to 5-HT may cause abnormal intestinal motility.

Although 5-HT_3 receptor antagonists have already been put to clinical use as antiemetics for chemotherapy, a clinical attempt has been made to use them for diarrhea-type irritable bowel syndrome based on the idea that they suppress intestinal motility. It is also becoming clear that peristaltic movement of the digestive tract is regulated by the motilin level during hunger. The cause is still unknown as for intestinal pseudo-obstruction, which makes food intake impossible due to a marked decrease in intestinal motility, but a marked decrease in interstitial cells of Cajal has been reported in some patients.

Clinical Research

1. Enteral nutrition and home parenteral nutrition

The number of patients with severe malabsorption due to short-bowel syndrome and Crohn's disease is increasing each year. In Japan, nutritional management using enteral nutrition is the first choice followed by home parenteral nutrition (HPN).

According to a survey done by an HPN Research Group, 149 out of 355 patients were given HPN each year due to a benign disease. It is striking that the majority of these patients, (132 cases) are able to return to work or to live at home because of HPN, which confirms the benefits derived from HPN.[4)]

In contrast, due to the patients who require nutritional management by enteral nutrition and HPN over one year, new problems concerning vitamins and trace elements have surfaced. For example, well-known trace element deficiencies such as copper deficiency and selenium deficiency cause anemia and heart dysfunction, respectively. Conversely, the excess manganese has become a problem, as studies have shown that manganese is deposited in the brain. Effective management methods of trace elements that do not cause deficiency or excess must be established through prescriptions and over-the-counter supplements of trace elements.

2. Tumors of the small intestine

Neoplastic diseases in the small intestine are not very common. In general, non-epithelial tumors are more common than epithelial tumors. Recently, new information on stromal-cell-derived tumors has become available.

Conventionally, it has been thought that stroma-derived tumors were mostly leiomyoma or leiomyosarcoma, and tumors originating from the nervous system were distinguished by immunostaining. Recently, however, the tumor originating from interstitial cells of Cajal has drawn attention. This tumor has been narrowly defined as a gastrointestinal stromal

Table 1 Immunohistological Diagnosis of Gastrointestinal Stromal Tumors

GIST	c-kit (+)
Leiomyoma	c-kit (−), SMA (+), desmin (+)
Neurogenic tumor	c-kit (−), S-100 (+)

(SMA: smooth muscle actin)
(Excerpt from Fletcher, C.D. *et al.*: *Hum Pathol* 2002; 33: 459–465)

tumor (GIST).

Interstitial cells of Cajal, which are distributed in the muscularis propria throughout the digestive tract, serve as pacemaker cells for intestinal motility. Since interstitial cells of Cajal are c-kit- and CD34-positive cells, c-kit and CD34 are used as markers for diagnosis (Table 1). Re-evaluation of stromal tumors by this diagnostic method has revealed that many of the tumors that had been considered to be leiomyoma were tumors that had originated from the interstitial cells of Cajal (GIST).[5] While GIST itself is said to be most commonly found in the stomach, it is a representative neoplastic disease of the small intestine where non-epithelial tumors are common. There is also a malignant GIST, and metastatic cases with this type of tumor have a very poor prognosis.

Recently, it has been reported that tyrosine kinase inhibitor (imatinib), which has been developed to treat chronic myelocytic leukemia, also inhibits the tyrosine kinase of GIST and exhibits a contractionary effect against tumors.[6] Although the use of this drug has already become available in Japan, there remain unresolved problems concerning indications and adverse drug effects. One should note that the term GIST is occasionally used broadly to refer to stromal-cell-derived tumors.

3. Recent developments in diagnostic imaging

Since popularization of helical CT has dramatically reduced the amount of time required for exposure and improved resolution, CT has become an imaging method that is very easy to use. Although there was a tendency to shun overdependence on CT, the situation seems to have somewhat changed with the appearance of helical CT, and CT is now viewed essential in acute abdomen examinations.

Contrast-enhanced CT is the first-line test for ileus, which is a disease that is encountered on a daily basis, and location of obstruction, degree of obstruction, and condition of intestinal ischemia can be grasped by CT. Makita, *et al.*, have established six types of findings and reported that diagnosis of cases with intestinal necrosis was possible at a sensitivity of 94% and a specificity of 89%.[7] This method has also made it possible for physicians to quickly determine surgical need. It is also particularly useful for confirming diseases that are difficult to find, such as obturator hernia.

Another new and noteworthy form of applied technology is virtual CT. With the popularization of hardware and software, the daily clinical application of virtual CT will become a common procedure in the near future.

4. Enteroscopy

In the field of endoscopy, a relatively thin push type video enteroscope has become popular and it is utilized for diagnosis or treatment of the upper jejunum. While the use is somewhat limited, as the small intestinal wall is weak, treatment such as polypectomy is possible by using this method. Attempts at deeper insertion of the enteroscope by using of a sliding tube and a balloon have been reported. Although widespread use of enteroscopy is hoped for, a remote-controlled capsule endoscopy, which is swallowed by the patient, has been developed recently. This method awaits clinical application in the very near future.

While diagnosis and treatment of hemorrhage from the small intestine often seem difficult, perioperative endoscopy has been known to be useful in identifying the source of small intestinal hemorrhage. In addition, when lapa-

rotomy is performed in patients with Peutz-Jeghers syndrome, it is recommended that small intestinal polyps be thoroughly searched and treated by perioperative endoscopy so that intussusception may be prevented.

5. Inflammatory bowel disease

A representative inflammatory bowel disease of the small intestine is Crohn's disease, and the number of patients with the disease has been increasing yearly in Japan. While the true cause of the disease is still unknown, an abnormality was discovered in 2001 in a gene called *NOD2*, which is one of the innate immune mechanisms. This abnormality was seen in approximately 10% of patients in Western countries.[8] However, this gene abnormality has not been found in Japan.

A topic of interest in the area of treatment is that monoclonal antibody therapy against tumor necrosis factor α (TNFα), a representative inflammatory cytokine, is now covered by Japan's national insurance system as of May 2002. Insurance coverage is applicable for cases with external fistulae or cases in which inflammation could not be relieved by other methods. However, as concerns for adverse drug reactions have been emphasized since the beginning and it has been pointed out that the treatment is not easy to use in cases with a strong stenosis, the type of cases in which the treatment would be appropriate needs to be determined in the future.

In the field of surgery, it seems that laparoscopic surgery is being used more widely. Laparoscopic surgery reduces invasiveness and makes it possible for patients to return to work earlier, and the procedure is not inferior in its effectiveness compared to open surgery. In addition, prevention of short-bowel syndrome caused by resection, a surgical method called strictureplasty rather than resection, is recommended to relieve the stenosis in cases of Crohn's disease.

Intestinal adhesion has been a major problem for quite some time not only in cases with inflammatory bowel disease but also following laparotomy, and adhesion-induced ileus should be avoided when it can be helped. In recent years, a carboxyl methylcellulose membrane has become popular in preventing adhesion, serving as an effective adhesion prevention method. In fact, when patients with ulcerative colitis and familial adenomatous polyposis were randomly allocated to a group that used the membrane and a group that did not use the membrane in first-stage surgery, an examination of the degree of adhesion during the second-stage surgery revealed that adhesion had been prevented significantly in the group that used the membrane.[9]

Conclusion

Since peptides common to both the central nervous system and the small intestine have been discovered, the small intestine is called the second brain. It works while intricately interrelating with the endocrine, the nervous, and the immune systems. The study of this organ is a major field with many topics remaining to be explored.

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Diseases of the Large Intestine —Neoplastic diseases—

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Abstract: Neoplastic lesions of the large intestine are increasing in Japan in conjunction with the changes in the dietary life of the population. Exact diagnosis of the diseases of the large intestine are still being debated. However, recent advances in diagnostic imaging provide improved diagnosis of neoplastic lesions of the large intestine without undue stress on the patient. In this paper, recent diagnosis, treatment and surveillance of neoplastic lesions such as early cancer, advanced cancer, mucosa-associated lymphoid tisssue tumor (MALToma) and gastrointestinal submucosal tumor (GIST) are discussed.

Key words: Large intestine; Neoplastic lesion; Colorectal cancer; EMR; MALToma; GIST; Virtual

Introduction

Recently, there has been increased interest in diseases of the large intestine due to the growing number of patients with colorectal cancer. In particular, rapid progress has been made in the diagnosis and treatment of neoplastic diseases of the large intestine including colorectal polyps.

The large intestine consists of the cecum, colon, and rectum. The characteristics of diseases of the large intestine differ according to the part of the large intestine. With a focus on early cancer, this paper reports on recent trends in the diagnosis and treatment of colorectal cancer. It also discusses carcinoid, mucosa-associated lymphoid tissue (MALT) lymphomas and gastrointestinal stromal tumors (GIST) which have been the focus of recent interest, despite the limited number of cases.

New Diagnostic Methods for Neoplastic Lesions of the Large Intestine

The main diagnostic tool for neoplastic lesions of the large intestine is colonoscopy. However, this examination places a significant onus on the patient and requires trained skills.

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Table 1 Merits and Demerits of Virtual Endoscopy by Helical CT Scanning

Merits
1. Minimal onus on patient with little discomfort
2. Examination requires short time (minutes)
3. Provides information on lesion depth, involvement of lymph nodes, and relationship with peripheral organs
4. Possible to diagnose proximal lesions, even with obstruction and stenosis
5. Possible to obtain complete image of lesion from any direction
6. Reproducibility
Demerits
1. Difficult to diagnose submerged lesions because contrast with air is required
2. Poor resolution of images
3. Not possible to determine color and hardness
4. Not possible to perform histological examinations
5. Image processing requires a long time
6. Equipment is expensive

Three-dimensional diagnostic imaging, or virtual endoscopy, offers a solution to these problems. Virtual endoscopy uses computer processing of image datasets obtained by helical CT scanning to reconstruct 3D images. In fact, virtual endoscopy requires the same preparation as for colonoscopy, and the CT scan is performed after introducing air via the anus. The merits and demerits of this procedure are outlined in Table 1.

It has been reported that virtual endoscopy can detect protruded lesions of 5 mm or more and flat and/or depressed lesions of 10 mm or more. Since the problems associated with the method are mainly computer-related issues, which are expected to be resolved with rapid advances in this area, it is anticipated that virtual endoscopy will be used in the clinical setting as a screening test in the near future.

Laterally Spreading Tumors

The wide use of colonoscopy has resulted in the detection of neoplastic lesions of various shapes. It has been recognized that polyps as well as flat and/or depressed tumors occur commonly in the large intestine and that they have significant importance as the beginning of colorectal cancer. These lesions, which spread on the surface, are called laterally spreading tumors (LST). LSTs are classified into two subtypes — granular type LSTs, which have a nodular and granular form, and non-granular type LSTs, which do not have these morphological features.

Gene analysis has shown that granular type LSTs have a high incidence of mutations of the oncogene K-*ras* and they are presumed to adopt the carcinogenesis of the adenoma-carcinoma sequence. Non-granular type LSTs have few K-*ras* mutations, but mutations of the cancer suppressor gene *p53* are observed over a wide area, suggesting that the non-granular type may undergo a *de novo* carcinogenesis. In both cases, the incidence of cancer increases as the lesion increases in size and special attention should be paid to non-granular type LSTs because of the greater risk of their infiltrating into the submucosa.

It should be noted that these lesions are not defined in the "Japanese Classification of Colorectal Carcinoma" (ed. Japanese Society for Cancer of the Colon and Rectum, Kanehara & Co., Ltd.) which may result in some confusion. However, the clinical features of these lesions are easily identified in certain circumstances and further studies of their subtypes and significance are needed.

Recent Trends in the Treatment of Colorectal Cancer

1. Early cancer

In the case of early cancer, it is quite feasible to obtain a complete cure of intramucosal carcinoma by endoscopic polypectomy or endoscopic mucosal resection (EMR). The choice of treatment becomes a problem when the resected margin is positive, namely, in the case of an incomplete resection, or when the resection is complete but the lesion has infiltrated into the submucosa (sm). If the only resected

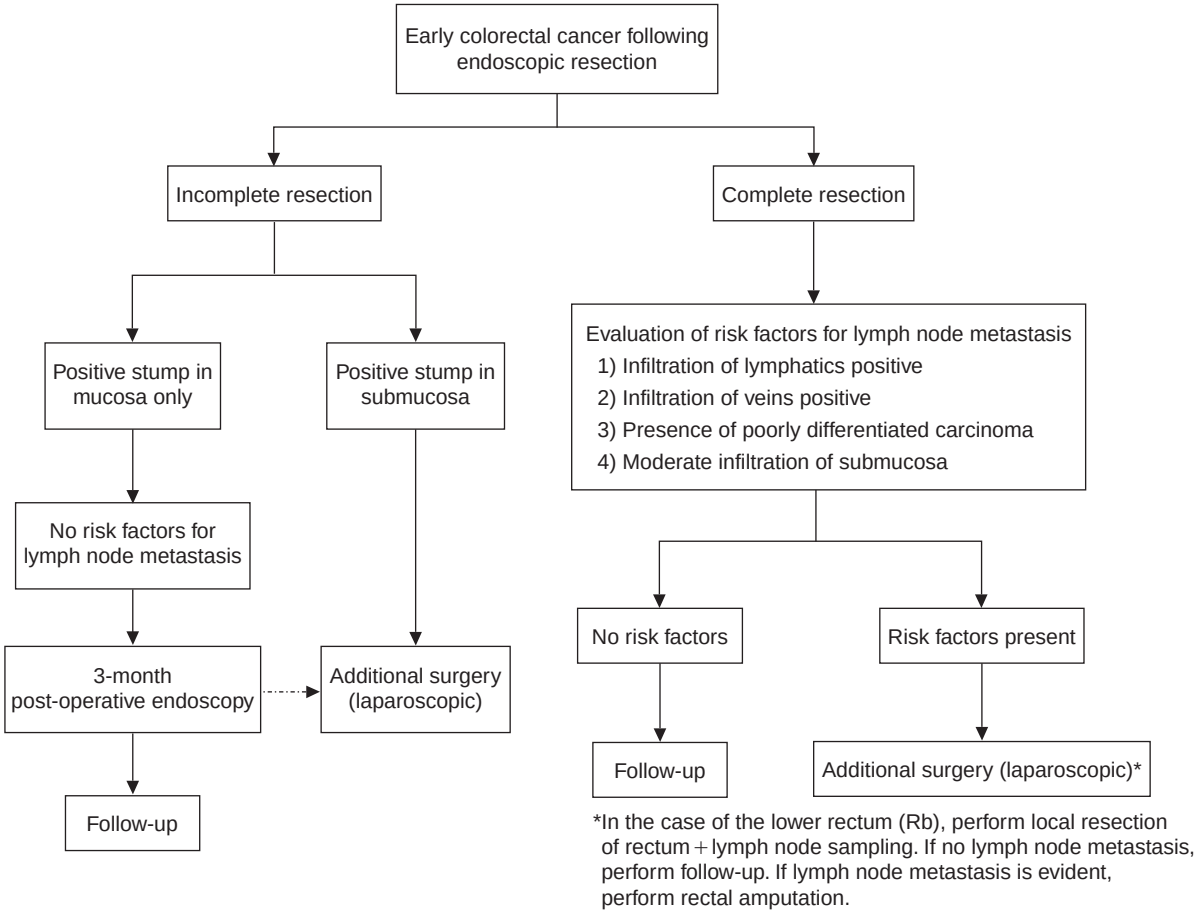

Fig. 1 Flow-chart of treatment for early colorectal cancer following endoscopic resection

stump of the mucosal surface is positive based on a thorough pathological examination of the resected specimen, the endoscopic examination may be repeated three months later if there are no risk factors for lymph node metastasis. In the absence of problems, the patient should be followed periodically. Surgery is indicated if the resected stump in the submucosa is positive.

In contrast, if the resection was complete but submucosal carcinoma is evident and there are no risk factors for lymph node metastasis (e.g., positive vascular infiltration of lymphatics and veins, poor differentiation of cancerous tissue, the depth of cancer infiltration is moderate or more), the patient should be followed carefully by endoscopy. If even one of these risk factors is evident, colectomy with lymphadenectomy is required. Dissection of the second lymph node group (N2) is sufficient and laparoscopically-assisted colectomy, a minimally invasive procedure, is indicated.

It should be noted that in the case of the rectum, QOL is decreased following rectal amputation or low anterior resection due to an artificial anus, micturition disorders, and/or sexual dysfunction. Therefore, the recommended treatment is initially a local excision of the rectum with lymphadenectomy in the neighbouring mesorectum; and the necessity of additional surgery should be discussed depending on the absence or presence of lymph node metastasis (Fig. 1).

2. Advanced cancer

With the aim of maintaining and improving

post-operative QOL, laparoscope-assisted colectomy is becoming widespread as the best surgical option for the patient. While early colorectal carcinoma is a good indication for this procedure, the case for advanced cancer is controversial. In terms of recurrence and metastasis, there is a lack of consensus. Some maintain that this procedure is indicated if the cancer has not invaded the serosa surface while others believe that it is needed in all cases of advanced cancer. A randomized controlled trial (RCT) is required but there are several difficulties with the implementation of such a trial. Although this problem is being investigated overseas, the extent of lymph node excision and the techniques used are different from those in Japan, preventing a direct application of the results obtained overseas.

Surveillance Following Resection of Neoplasms of the Large Intestine

Surveillance following endoscopic resection or surgical resection of neoplasms of the large intestine is an important issue. This surveillance serves a double purpose. The first is early detection of the recurrence of cancer and the second is the early detection of colorectal carcinoma of multifocal origin. For patients with colorectal carcinoma, 5 to 10 percent will experience synchronous or metachronous multifocal lesions. The question is how often surveillance should be carried out in what kind of patient.

In the case of adenomatous lesions of the large intestine, endoscopic resection should be performed for multifocal lesions until all lesions have disappeared, followed by three-yearly endoscopic examinations. In the case of localized lesions, it is sufficient to revert to the usual test for colorectal carcinoma of fecal occult blood following resection.

It is a little different in the case of cancer. In the case of multifocal colorectal carcinoma, recent gene analysis has reported a high incidence of abnormalities in DNA repair genes or microsatellite instability (MSI), the cause of hereditary non-polyposis colorectal cancer (HNPCC). The incidence of colorectal carcinoma and malignant neoplasms of other organs in family members is known to be also high. Therefore, patients with this genetic abnormality or with a family history of colorectal carcinoma must be followed post-operatively by annual endoscopic examinations. In other cases, it is sufficient to test patients with colorectal carcinoma annually for five years after surgery and, providing there is no evidence of carcinoma, at three-yearly intervals thereafter.

Submucosal Neoplasms

The final section will discuss submucosal neoplasms of the large intestine which are important in terms of diagnosis and treatment, despite the relatively low incidence of cases.

1. Carcinoid tumors of the large intestine

In Japan, the most common site of carcinoid tumors in the digestive tract is the rectum, followed by the duodenum, stomach, and appendix. In America, in contrast, the most common site is the appendix, followed by the rectum and ileum, with few cases reported in the stomach and duodenum. It is presumed that endocrine cells deep in the mucosa give rise to gastrointestinal carcinoid tumors and, because of the ease with which they progress to submucosal levels, they are often handled clinically as submucosal neoplasms.

Morphologically, carcinoid tumors of the large intestine are hemispherical (Yamada classification: type II or III) with a slight depression on the surface, and are often slightly yellowish in color. In terms of site, they almost invariably develop within six centimeters from the anal verge. These tumors occur in a younger age cohort (mean age: about 50 years) than cancer patients.

While small carcinoid tumors of the large intestine may be treated by endoscopic resec-

tion, some tumors of about one centimeter in size metastasize to the lymph nodes or liver. Therefore, the patient must be treated for cancer.

2. Mucosa-associated lymphoid tissue lymphoma

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a well-known lymphoma of low-grade malignancy which develops due to inflammation of the gastric mucosa associated with a *Helicobacter pylori* infection. It has been reported that gastric MALT lymphoma often disappears in many people with gastric MALT lymphoma following eradication therapy.

Recently it has been reported that MALT lymphoma has also been detected in the large intestine and, as in the case of the stomach, the MALT lymphoma of the large intestine disappears following eradication therapy of the *Helicobacter pylori* infection. However, the mechanism by which *H. pylori*, which are primarily active in and inhabit the stomach only, are involved in the development of MALT lymphoma in the large intestine is unclear.

Based on gene analysis, translocation involving the No. 11 and No. 18 genes is frequently observed in cases of MALT lymphoma in the large intestine. When translocation occurs, it has been reported that *H. pylori* eradication is ineffective even against gastric MALT lymphoma. Therefore, further studies of the development and treatment of MALT lymphoma in the large intestine are warranted.

3. Gastrointestinal stromal tumor (GIST)

Submucosal neoplasms of the gastrointestinal tract which is assumed to arise from spindle-shaped cells have previously been classified as smooth muscle type neoplasms and neural type neoplasms. Recent studies using markers for both types, however, have shown that the majority of GISTs do not stain for either marker (Tables 2, 3). It has also been shown that these tumors are characterized by genetic abnormalities known as *c-kit* and that they grow and metastasize by tyrosine autophosphorylation.

Table 2 Classification of GIST

1. smooth muscle type
2. neural type
3. combined muscle-neural type
4. uncommited type (GIST in narrow sense)

(Classification of Rosai *et al.* Source: *Ackerman's Surgical Pathology,* 8th ed., Mosby, St. Lois, 1996; pp. 645–646)

Table 3 Main Immunohistological Diagnosis of GIST

Myogenic	smooth muscle actin, desmin
Neurogenic	S-100, neuronspecific enolase
Mesenchymal	vimentin
Cajal cells	CD34, c-kit protein (CD117)

These tumors are thought to originate in interstitial cells of Cajal which are known as pacemaker cells in the gastrointestinal tract. For further information, several books have recently been published on various aspects of GISTs, including their definition, classification, and gene analysis.

GISTs of the gastrointestinal tract are most common in the stomach, followed by the small intestine. GISTs in the large intestine are uncommon. The usual method of diagnosis is diagnostic imaging but, in most cases, endoscopic biopsy does not lead to a confirmed diagnosis. Recently, endoscopic ultrasonography-guided fine needle aspiration biopsy has been employed in the differential diagnosis between benign and malignant GISTs. It has been reported that the degree of malignancy increases in tumors five centimeters or more in size and with increasing mitosis of tumor cells. Most malignant GISTs metastasize to the liver or recur in the peritoneum, with lymph node metastasis being extremely rare.

As treatment, local resection of the gastrointestinal tract including the primary lesion is sufficient, with a laparoscope-assisted operation indicated. In the case of metastatic lesions, it

has been reported that the tyrosine kinase inhibitor STI 571 (Glivec®), which has been approved as a therapeutic drug for chronic leukemia, is effective because, as mentioned previously, activation of tyrosine kinase is closely involved in the metastasis of tumors. We have also obtained a complete response (CR) of tumors by administering this drug to a malignant gastric GIST patient with liver metastasis. This treatment method promises to be a significant addition to the armamentarium for malignant GISTs.

This paper has focused on recent issues in the diagnosis and treatment of neoplastic lesions of the large intestine aimed at improving patient care. It is hoped that the information will be of help in daily clinical practice.

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Disease of the Pancreas

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Abstract: Recent advancement in pancreatic diseases, particularly in the clinical field, is herein stated. Genetic mutations of trypsin, pancreatic secretory trypsin inhibitor, and CFTR have been drawing attention in relation to the onset of pancreatitis. Although hereditary pancreatitis has been attributed to abnormality in trypsin, the causal relationships have not been determined yet in other types of pancreatitis. In acute pancreatitis, assessment of severity as well as prediction and prevention of aggravation is important, as prognosis of severe acute pancreatitis is poor. Among different types of chronic pancreatitis, autoimmune pancreatitis that is characterized by stenosis of the pancreatic duct, swelling of the pancreas, hypergammaglobulinemia, infiltration of lymphocytes in the pancreas, and fibrosis has gained a growing interest. In particular, it is easily misdiagnosed as pancreatic cancer because images and symptoms are very similar. The condition of this disease, however, improves with oral administration of steroid. Unnecessary surgical procedures can be avoided if one is familiar with its pathology. According to a national survey on registration of pancreatic cancer, 5-year survival rate was 18.9% for 7,326 cases that underwent pancreatectomy. Since prognosis does not improve even with extended resection, surgeries and chemotherapy that prioritize QOL are hoped for.

Key words: Pancreatitis; Genetic mutation; Pancreatic cancer; Autoimmune pancreatitis

Introduction

Topics regarding recent development in pancreatic diseases that have been taken up in reports and presentations at relevant academic societies, particularly in the clinical field, are herein presented.

Thanks to the advancement in molecular biology and diagnostic imaging in recent years, pathophysiological breakthroughs in the area of pancreatic diseases and development of diagnostic technologies have been remarkable. In comparison, treatment has not benefited as much from science and technology, and may

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not for a while longer.

Genetic Mutation and Pancreatitis

Genetic mutation seems to be related not only to the onset of pancreatitis but also to the clinical course following the onset as well as the severity of the disease.

1. Onset of pancreatitis and genetic mutation[1–3)]

1) Trypsin[1–2)]

Hereditary pancreatitis is a disease that is autosomal dominantly inherited at an 80% penetrance, and the cause was identified in 1996 as a point mutation of trypsin (cationic trypsinogen, PRSS1) at R122H. Trypsin that has been activated by this point mutation is not easily autodigested, and since trypsin becomes difficult to inactivate, the mechanism that keeps trypsin activity from increasing within the pancreas breaks down, supposedly leading to the onset of pancreatitis. It has been newly discovered that point mutation of trypsinogen also occurs at N29T and R122C in addition to N29I, A16V, D22G, and K23R. These genetic mutations are all related to the onset of pancreatitis, and the incidence is close to 80%. Such mutated trypsins are 1) easily activated, 2) not easily inactivated, or possess both properties 1) and 2). It is therefore speculated that trypsin activity within the pancreas easily increases, leading to the onset of pancreatitis.

2) Pancreatic secretory trypsin inhibitor (*SPINK1*)[1,2)]

This inhibitor, also referred to as PSTI, is a serine protease inhibitor that is synthesized in the pancreas and secreted into pancreatic fluid, and it is involved in the defensive mechanism that inhibits the activity of protease as it is secreted from the pancreas to the duodenum. Point mutation of *SPINK1* includes mutation at N34S. Although pancreatitis is not induced by mutation of *SPINK1* alone, it is thought that combination of causative components for pancreatitis such as alcohol and genetic mutation of trypsin and other elements may lead to the onset of the disease. Some have reported that the incidence of point mutation of *SPINK1* at N34S is high among cases of pancreatitis in the tropical region and alcoholic pancreatitis.

3) *CFTR* (cystic fibrosis transmembrane conductance regulator)[1–3)]

Since *CFTR* regulates the function of the chloride channel in exocrine gland cells such as those in pancreas, lungs, and sweat glands, abnormality of *CFTR* causes problems in reabsorption of chloride. Depending on the degree of mutation of the *CFTR* gene, consequences of the mutation can vary from typical cystic fibrosis (CF) to no abnormality at all. Recurrent acute or chronic pancreatitis occurs when severe genetic mutation of *CFTR* and mild mutation of *CFTR* are combined. In 1998, it was reported for the first time that many cases of idiopathic pancreatitis display a point mutation of *CFTR*. Also, it has become known that mutation of *CFTR* is frequently detected in alcoholic pancreatitis in addition to idiopathic pancreatitis.

In addition, it has also become evident that the risk of pancreatitis increases with the aforementioned combination of mutation of *SPINK1* and mutation of *CFTR*. Namely, the risk of pancreatitis increases by 40 times when there are 2 *CFTR* mutations, 20 times when the mutation is limited to *SPINK1*, and 900 times when there are mutations of both *CFTR* and *SPINK1*.

4) Current situation in Japan[2,3)]

Concerning genetic mutations of trypsin and *SPINK1*, findings similar to those in the Western countries have been discovered among cases of pancreatitis in Japan. As for *CFTR*, representative mutations that have been reported in the Western countries are very rare, and the relationship with pancreatitis has not been determined. As for chronic pancreatitis, however, mutation of *CFTR* different from that found in the Western countries seems to be related to the onset of pancreatitis, as approximately half of the cases show elevated chloride

concentration in sweat.

2. Severity of pancreatitis and genetic abnormality[1)]

Various cytokines are reportedly involved in the severity of acute pancreatitis. Some have reported that genetic mutations of cytokines such as IL-8, IL-10, and tumor necrosis factor (TNF) α and their receptors are related to the aggravation of acute pancreatitis. However, as there are also reports that negate this relationship, consensus has not been reached yet.

3. Relationship to treatment of pancreatitis[4,5)]

The idea that proteases such as trypsin and their inhibitors play a key role in the onset and prevention of pancreatitis seems clear from the relationship between hereditary pancreatitis and mutation of trypsin and mutation of *SPINK1*. Reports on a synthetic low-molecular protease inhibitor that has been used for treatment of acute pancreatitis in the Western countries have mostly been discouraging. However, recently, there has been a report on how post-ERCP pancreatitis can be prevented by continuous infusion of protease inhibitor for approximately 10 hours starting immediately prior to endoscopic retrograde cholangiopancreatography (ERCP).

Methods of how to administer protease inhibitors need to be devised based on the fact that blood half-life of synthetic protease inhibitors ranges from several minutes to 1 hour, and the fact that the involvement of protease is limited to several days within the onset of pancreatitis and infection control is what will alter prognosis beyond that point. As for antibiotics, the use of imipenem, which displays an effective level of pancreatic tissue concentration and has a wide antibacterial spectrum, is recommended.

As for cytokines, clinical studies on receptor antagonists of platelet-activating factor (PAF) and TNF have been performed but did not produce expected results.

4. Pancreatic cancer and genetic abnormality

From an epidemiological perspective, age and smoking habits are factors strongly related to the onset of pancreatitis. Cancer gene, however, has not been identified.

Acute Pancreatitis[1,2,4,5)]

Acute pancreatitis starts with intense upper abdominal pain. Approximately 70% of cases are mild cases whose general condition is good and whose symptoms clear up in a week after 2–3 days of fasting. However, 10% of cases are severe cases that accompany failure of important organs such as circulatory failure, and manifests serious symptoms such as shock, dyspnea, and oliguria. Despite very intensive treatment, prognosis is poor, and fatality is as high as 30–50%. Although prediction and prevention of aggravation of the disease are important for improvement of prognosis, they are not necessarily easy.

According to the first national survey (cases during 1982–1986), mortality was 30% in severe cases and 2% in moderate cases. The second national survey (cases during 1995–1998) showed that mortality was 23% for severe cases and 1.7% for moderate cases. In other words, a 7% improvement was seen in severe cases in approximately 15 years. This may be largely attributed to advancement and popularization of intensive care.

Examination of cause and time of death showed that 40% of deaths occur within 5 days of onset due to shock or respiratory failure. Deaths on Day 6 and thereafter are mostly due to multiple organ failure and sepsis. Fatality and cause of death both vary during 5 days to 1 week following onset. Evaluation of severity and an early start of intensive care are important.

1. Evaluation of severity

It is safe to say that fatal cases are limited to severe cases. Also, since approximately 40% of deaths occur within 5 days, aggravation must be

predicted and treatment started as soon as possible following onset if prognosis is to be improved.

1) **Prediction of severity based on a single marker in blood**

Trypsinogen-activated peptide (TAP), markers that reflect the activation of pancreatic enzymes such as trypsinogen, cytokines such as TNF and IL-6, and related substances have been reported as severity marker for acute pancreatitis. However, ideal markers with high sensitivity and specificity that also appear shortly after onset and which can be measured quickly and easily have not been discovered as yet.

2) **Evaluation by severity score**

In Japan, a scoring system proposed by the Intractable Pancreas Disease Research Group (Ministry of Health, Labour, and Welfare) has been used more widely. Comparison of the diagnostic capability by an ROC curve has revealed that the capability of this scoring system to diagnose severity is comparable to the internationally used APACHE-II and Ranson score. Currently, we are making an effort to have this system be recognized across the world.

2. Treatment

The primary objectives of treatment of acute pancreatitis include 1) maintenance/improvement of the systemic condition, 2) attenuation of pancreatitis, and 3) prevention and treatment of complications.

Staring a sufficient level of fluid replacement during the early stage is still important today for maintenance/improvement of the systemic condition. In addition to this, pancreatic exocrine stimulation must be blocked to let the pancreas rest, and activated pancreatic enzymes and harmful physiologically active substances that have been synthesized as a result of such activation must be inactivated. Somatostatin, cholecystokinin (CCK) receptor antagonists, protease inhibitors, various cytokines and their antagonists, and antibiotics have been developed and tried out for prevention of complications such as infections.

Clinical trials on somatostatin, its derivatives, and CCK receptor antagonists intended for inhibition of pancreatic exocrine function and cytokine antagonists such as TNF, IL-1, and PAF and IL-10 intended for prevention of multiple organ failure and maintenance/improvement of systemic condition have not proven to be effective, contrary to our expectations.

As for prevention of post-ERCP pancreatitis, protease inhibitor gabexate mesylate and somatostatin have proven to be effective in meta-anlysis.

Risk of infection increases and prognosis worsens when necrosis spreads to at least 50% of the pancreas. Therefore, when a wide-spread necrosis is observed, the use of antibiotics such as imipenem and new quinolone, which can reach the effective concentrations in pancreatic tissue, are effective for improvement of prognosis. However, when infectious pancreatic necrosis occurs in cases of necrotic pancreatitis to which antibiotics has been preventatively administered, bacteria resistant to the antibiotics are detected in 1/4 of the cases. Unless the use of antibiotics is limited to high-risk cases of necrotic pancreatitis, resistant bacteria will only increase in the future.

3. Clinical guidelines for acute pancreatitis (draft)

This draft was proposed by a guideline preparation committee of the Japanese Society for Abdominal Emergency Medicine in 2001, and a revision was submitted in 2002. Although the guideline is supposed to be based on EBM, it is still more confusing than helpful for daily medical practice. For example, "for diagnosis of acute pancreatitis, serum lipase is superior to serum amylase (recommendation level A)." This is unrealistic for the following reasons: 1) as amylase, lipase is not completely specific to pancreas; 2) compared with measurement method for amylase, measurement method for lipase is less complete; 3) emergency

measurement of lipase is possible in few institutions; 4) there is no marked difference in positive ratios of the two in acute pancreatitis, and false-negative or false-positive results for lipase are as common as they are for amylase. Therefore, at this point, it would be safer to use the diagnostic criteria and severity assessment for acute pancreatitis proposed by the Intractable Pancreas Disease Research Group.

Chronic Pancreatitis[6–8)]

1. Autoimmune pancreatitis[7)]

Diagnostic criteria for this disease have been proposed by the Japan Pancreas Society.

1. In pancreatic duct images obtained by pancreas imaging tests, characteristic narrowing of the main pancreatic duct is observed in at least 1/3 of the entire pancreas, and swelling of the pancreas is also observed.
2. Blood chemistry reveals hypergammaglobulinemia, hyper-IgG, or autoantibody.
3. Histopathological examination reveals marked infiltration of cells such as lymphocytes and plasma cells as well as fibrosis in the pancreas.

Autoimmune pancreatitis is diagnosed when a case meets at least two of the items above, including 1.

Reasons why the disease has drawn attention are as follows: 1) it has become easier to discover morphological abnormality in the pancreas due to advancement/popularization of diagnostic imaging of the pancreas; 2) it is not easily differentiated from carcinoma of head of pancreas, since the disease accompany swelling of the pancreas, stenosis of pancreatic duct, stenosis of the distal end of the common bile duct, and obstructive jaundice; 3) if correctly diagnosed, the disease can be treated effectively by steroid, and unnecessary surgical procedures can be avoided.

2. Interventional treatment of complications of pancreatitis[8)]

Percutaneous or endoscopic drainage, stent insertion, laser or shock wave lithotripsy, etc. have been added to the treatment options for pancreatic cysts, stenosis of pancreatic/bile ducts, and pancreatic stones. Treatment options for the pre-operative stage have increased. While short-term response to treatment has certainly improved, long-term efficacy has not been verified yet.

Pancreatic Cancer[9,10)]

According to a national survey (summary of cases in 1999) on registration of pancreatic cancer, 5-year cumulative survival rate was 18.9% for 7,326 cases that underwent pancreatectomy during a 19-year period ranging from 1981 to 1999. Five-year survival rate for palliative surgery, simple celiotomy, and non-surgical cases ranged from 0.9–1.1%. Resection rate for the entire population (18,495 cases) was 39.6%, and of these cases, 18.9% or 7.5% of the entire population survived for at least 5 years. Five-year survival rates for stages I and II were 61% and 36%, and these cases corresponded to 8% of all resection cases. These early-stage cases are not necessarily symptomatic. Also, as the high-risk group for pancreatic cancer has not been identified yet, early discovery in which better prognosis can be expected relies solely on incidental discovery.

Since even extended resection does not necessarily improve prognosis, pancreatectomy should be limited to curable and resectable cases based on post-operative QOL. Addition of post-operative chemotherapy and radiotherapy has not contributed to improvement of prognosis. In incurable or unresectable cases, minimally invasive treatments that also improve QOL, such as bypass surgery and stent insertion, should be performed to treat symptoms. A new chemotherapy drug gemcitabine is expected to improve QOL by alleviating pain and extending the period of home care, even though it is not very effective in reducing tumor size.

Surgeries and chemotherapy that prioritize

QOL are increasingly hoped for in cases with pancreatic cancer.

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Estrogen Receptor Function and Molecular Mechanisms

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Abstract: Estrogen receptors (ERs), ERα and ERβ, are ligand-dependent transcriptional factors that mediate various estrogen actions. The ERs belong to the superfamily of nuclear receptors and are composed of six modular domains, A to F. Estrogen binds to ERs via their E-F domains (ligand-binding domain, LBD) and ERs bind to DNA as dimers through their C domain (DNA-binding domain, DBD) at specific estrogen responsive elements (EREs) on the genome, leading to activate transcription of their target genes. Using genomic binding-site cloning technique, our group newly identified several primary estrogen-responsive genes including *NR2D* and *Efp*. NR2D is a subunit of *N*-methyl-D-aspartate receptor complex expressed in the brain and may function in sexual behavior. Efp has been revealed as a RING finger-type ubiquitin ligase that targets the proteolysis of a cell-cycle checkpoint 14-3-3σ. Efp promotes proliferation of breast cancer through breakdown 14-3-3σ. Analysis of each estrogen-responsive gene may elucidate the diverse physiological roles of estrogen functions.

Key words: Estrogen; Nuclear receptors; Breast cancer; Efp; Ubiquitin Ligase

Introduction

Estrogen is a sex steroid hormone that is essential for the manifestation of female secondary sexual characteristics and reproductive functions. It has diverse physiological effects on the central nervous system, immune system, and cardiovascular system as well as lipid and bone metabolism. The hormone plays a crucial role in the growth and development of women, while the postmenopausal decline of estrogen secretion is closely associated with the onset as well as treatment of various menopausal symptoms including hot flushes, osteoporosis, and dementia. Recent studies have shown that estrogen is important for men as well, since

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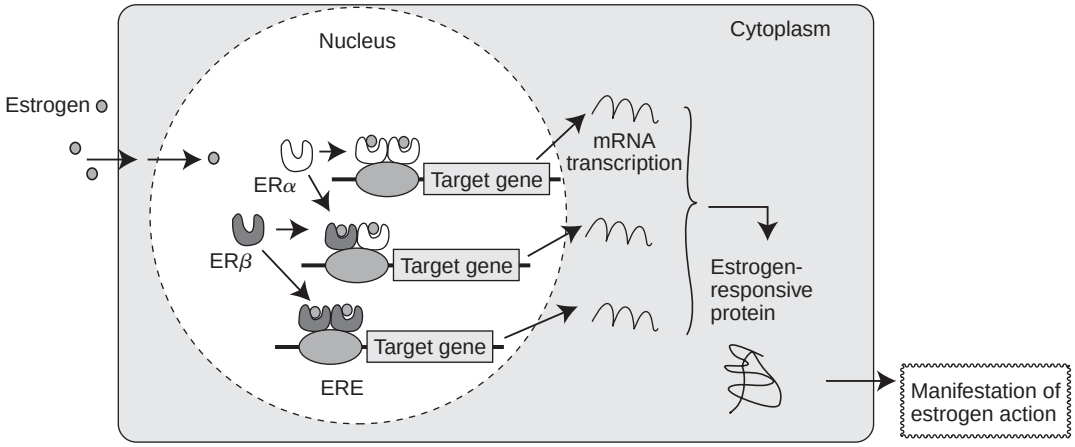

Fig. 1A Mechanism of estrogen action
Estrogen-bound ERα and ERβ bind to estrogen-responsive elements (EREs) in forms of homodimers or heterodimers, leading to activate the transcription of target genes.

there are reports that estrogen action is involved in spermatogenesis and estrogen receptors (ERs) are expressed in the testis and prostate. It has been also revealed that estrogen is a requisite in male bone homeostasis based on the clinical data of the first male patient with ERα deficiency. Furthermore, estrogen is profoundly related to the etiology, diagnosis, treatment, and prognosis of hormone-dependent cancers such as breast cancer, endometrial cancer, and prostate cancer.

The various functions of estrogen are mediated through its cognate nuclear receptors, ERs. The estrogen-bound ERs form dimers by themselves and bind to specific estrogen response elements (EREs) on genomic DNA, leading to activate transcription of various target genes. Thus, ERs act as ligand-dependent transcription factors. The first ER was cloned in late 1980s and its structure and functions have been extensively studied. Recently, another subtype of ER (ERβ) has been identified in the prostate, and there have been efforts to reevaluate estrogen signaling.

This article focuses on the mechanism of estrogen action mediated through ERs, the comparisons between ERα and ERβ, and the physiological functions of estrogen-targeted genes.

Structure and Function of the ER

The ERs are members of the nuclear receptor superfamily including receptors for steroids, retinoic acid, thyroid hormone, and vitamin D, functioning as ligand-dependent transcription factors.[1–3] In the nucleus, estrogen binds to ERs via their C-terminal ligand-binding domain (LBD). The estrogen-bound ERs in turn bind to genomic EREs in dimerized forms via a central DNA-binding domain (DBD), and thus control the transcription of target genes to exert specific physiological actions (Fig. 1A).

Since 1996, a novel subtype of ER designated as ERβs has been identified in rodents and humans. Consequently, the classical ER has been renamed ERα to distinguish it from ERβ. A comparison between the amino acid sequence of the full-length human ERβ isolated by our group[4] and ERα showed that the A/B domain of ERβ is shorter than that of ERα. The amino acid sequence of ERβ is closely related to that of ERα, as the C domain (DBD) of ERβ is 96% identical to that of ERα, while the E domain (LBD) of ERβ shows 53% similarity to that of ERα (Fig. 1B). ERβ has a similar affinity and specificity to 17β-estradiol compared with ERα and its transactivation through EREs is also enhanced in the presence

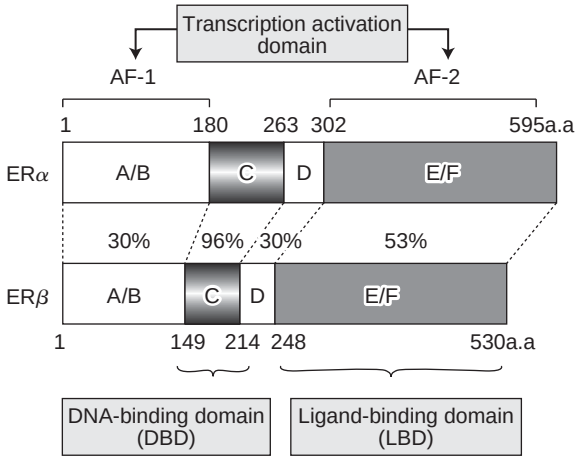

Fig. 1B Comparison of the structure of estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ)
The DNA-binding domain (DBD) is highly conserved between the two receptors. a.a: amino acid residue.

of 17β-estradiol and reduced by tamoxifen. On the other hand, the ligand specificities of ERα and ERβ are not identical regarding various estrogen-like compounds. It has been shown, for example, phytoestrogen exerts functions on ERβ at a lower concentration compared with ERα.

Regarding tissue distribution of ERβ, it has been shown that the receptor is abundantly expressed in prostates and ovaries in rats. The ERβ expression has been also observed in bladder, lungs, uterus, testes, brain, and arteries. It is notable that ERβ expression is not so strong in organs that highly express ERα, such as uterus, hypothalamus, and pituitary gland, while ERβ is abundantly expressed in the prostate.

There is an overall similarity of physiological functions between ERβ and ERα, yet there might be functional differences between two ERs based on their structural variances. Multiple functional domains are usually involved in the transcription activation of nuclear receptors. The A/B and E domains are particularly important in the process and they are also known as two transcription activation domains AF-1 (activation function-1) and AF-2, respectively. In regard to these transcription activation domains, ERβ has a shorter AF-1 compared to ERα, and the amino acid identities of AF-1 and AF-2 are not so high between the two ERs. Thus, the functional analysis of AF-1 and AF-2 may be useful for understanding the differences of transactivation machinery and specific actions between ERα and ERβ.

Estrogen Receptor Downstream Genes and Their Physiological Functions

The estrogen-dependent transcription factor ER elicits diverse estrogen functions by modulating the transcription of various downstream genes that locate in the vicinity of EREs.[1)] The known estrogen-inducible genes can be classified into three groups. One is a group of primary estrogen-responsive genes that can be directly activated by ERs, the other two are groups of secondary and tertiary estrogen-responsive genes that are downstream of primary estrogen-responsive genes (Fig. 2).

Vitellogenin is well studied as a prototypic primary estrogen-responsive gene. There is a functional ERE that locates in the vicinity of vitellogenin gene, and it has been revealed that transcription of vitellogenin gene can be induced promptly by estrogen stimulation. It has been also shown that the estrogen-induced transcriptional activation of vitellognin is not affected by protein synthesis inhibitors such as cyclohexamide. Prolactin, *pS2*, and *c-fos* are thought to be other examples of primary estrogen-responsive genes, yet apparent EREs have not been identified in the vicinity of those genes. In such cases, the estrogen-induced transactivations are mediated through alternative pathways such as activating protein-1 (AP-1). *BRCA1* has been reported as a secondary or tertiary estrogen-responsive gene. Much attention has been given to this gene in association with estrogen and estrogen-dependent proliferation of its target tissues including mammary epithelial cells, breast cancers, and the endometrium.

We are searching for novel primary estrogen-

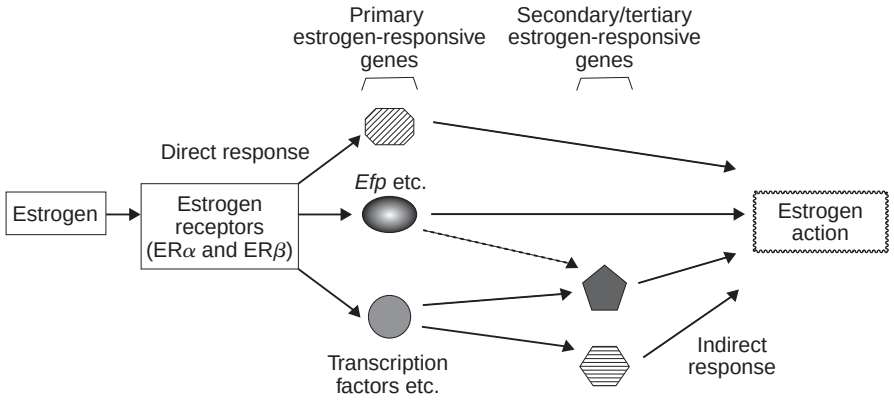

Fig. 2 Cascade of ER downstream gene expression
ER downstream genes are subdivided by three groups: a group of primary estrogen-responsive genes that are directly regulated by ERs, and downstream groups of secondary and tertiary estrogen-responsive genes that are regulated by the primary genes.

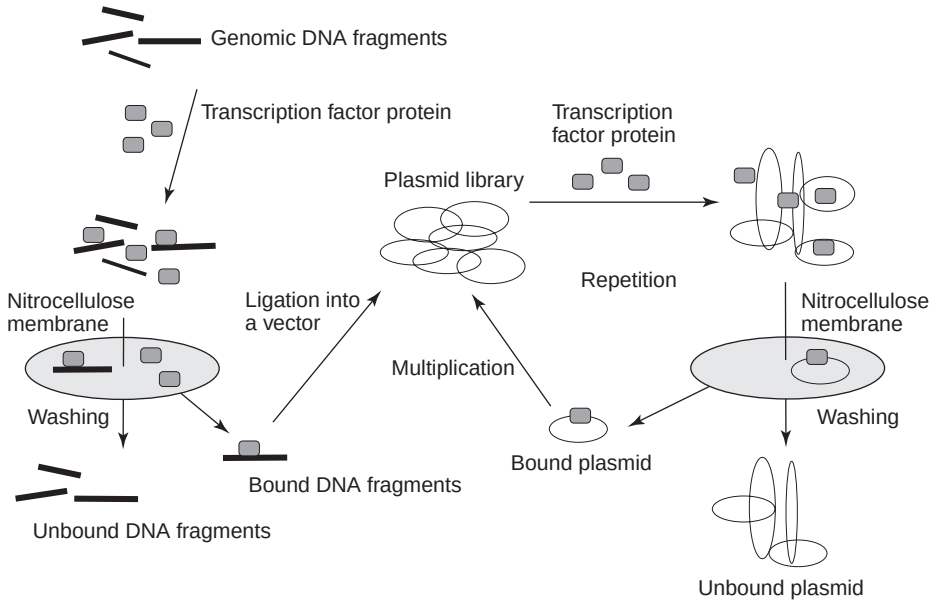

Fig. 3 Searching for novel estrogen-responsive genes by genomic binding-site (GBS) cloning
Purified DNA-binding domain of ERα prepared from bacterial culture was used as a transcription factor protein in this assay. The transcription factor protein-genomic DNA complexes bound to a nitrocellulose membrane were isolated and the obtained DNAs were cloned into a plasmid vector. The generated plasmid library was again associated with the transcription factor and the DNA isolation and condensation process was repeated several times, leading to isolate estrogen-responsive genes.

responsive genes using a method designated as "genomic binding-site (GBS) cloning", which has been developed by us to identify EREs on the genome (Fig. 3).[5] Among the estrogen-responsive genes that we have recently identified, *NR2D* is a subunit involved in the *N*-methyl-D-aspartate (NMDA) receptor complex, a receptor for excitatory neurotransmitter glutamate.[6] Because the presence of ERα or ERβ has been shown in the nuclei of specific neurons, it is likely that the estrogen action on sexual behavior, memory, and emotion are mediated through

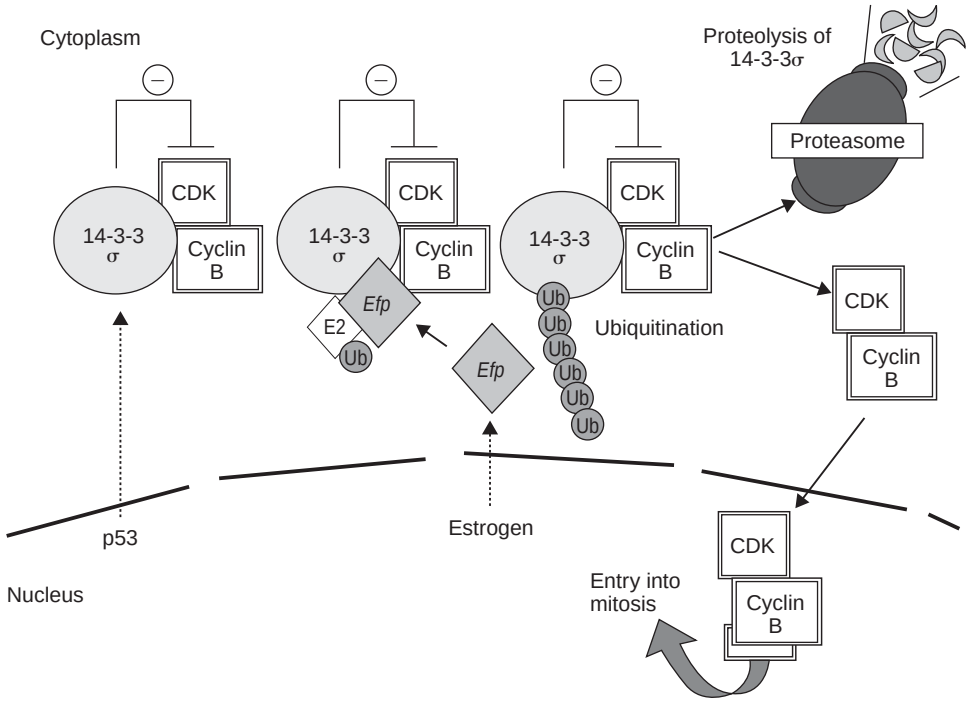

Fig. 4

Efp mediates proteolysis of 14-3-3σ and stimulates proliferation of breast cancer cells. 14-3-3σ is a p53-inducible protein that sequesters mitotic cyclin-dependent kinases (CDKs) in the cytoplasm to inhibit entry into mitosis. Estrogen stimulates production of Efp, which binds to 14-3-3σ and acts as a ubiquitin ligase by forming a complex with ubiquitin-binding enzyme (E2). Ubiquitinated 14-3-3σ is destroyed by the proteasome, releasing complexes of CDKs and cyclins. Those CDK-cyclin complexes are now free to escape into the nucleus and promote mitotic entry.
Ub: ubiquitin
(Cited with modification from Nalepa, G. and Harper, J.W.: *Efp*: A ring of independence? *Nat Med* 2002; 8: 661–662)

the ERs expressed in the central nervous system and subsequently through the ER downstream factors such as the NMDA receptor.

In regard to the estrogen-inducible RING finger protein Efp[7] that has been also identified by GBS cloning, the tissue distribution of the gene in reproductive tissues including endometrial cells, mammary epithelial cells, and ovarian granulose cells[8] was overlapped with that of ERα. Our experimental data showed that the levels of *Efp* mRNA in the uterus were rapidly elevated and reached a peak 2 hours after injection of 17β-estradiol into mice,[9] suggesting that the gene mediates a specific estrogen action as a primary estrogen-responsive gene. In addition, homozygous mice lacking *Efp* could grow normally, but female mice showed underdevelopment of the uterus and reduced estrogen responsiveness.[9] These findings suggest that Efp positively regulates the proliferation of endometrium in an estrogen-dependent manner. Moreover, we have recently shown that Efp is a RING finger-type ubiquitin ligase that targets the ubiquitination and the proteolysis of 14-3-3σ, a cell cycle check point that arrests cell cycle at G_2 phase[10,11] (Fig. 4). The Efp-mediated breakdown of 14-3-3σ provides a new mechanism for the proliferation of breast cancer.

Conclusion

Here we have briefly reviewed recent progress in the research addressing the structure, the functions, and the target genes of ERs. The discovery of a novel ER subtype ERβ, cofactors recruited by ERs, and ER downstream genes have provided an insight into the

molecular mechanisms and pathophysiological implications of estrogen actions. Although not much described in this article, it has been revealed that estrogen exerts its effects on diverse physiological functions including the homeostasis in postmenopausal women, spermatogenesis and sexual behaviors in men, cardiovascular system, and bone metabolism as well as female reproduction and sexuality, based on new knowledge provided by the generation and analysis of ER-deficient mice along with the discovery and the clinical manifestation of a male patient with ERα null mutation.

Among the multiple aspects of estrogen action, the effect on the cardiovascular system has lately become the focus of attention. The recent randomized clinical trials performed by the Women's Health Initiative (WHI) in the United States[12] indicate that the hormone replacement therapy using estrogen plus progestin in postmenopausal women increases the risk of thrombosis and heart attack. Further studies are required in terms of the risks and the benefits of estrogen use on the vasculature. Moreover, progress in the study addressing the oncogenic role of estrogen in hormone-dependent cancers has been also achieved.

Future advances in various areas of estrogen research may elucidate the precise molecular mechanisms and the diverse physiological roles of estrogen functions, leading to the clinical application of novel diagnostic procedures and therapeutic strategies.

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Pneumoconiosis and Lung Cancer

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Key words: Pneumoconiosis; Lung cancer; Spiral CT; Occupational disease; Silicosis

Introduction — Potential carcinogenicity of crystalline silica

The age-old controversy about the carcinogenicity of silica remains unresolved. In 1987, the International Agency for Research on Cancer (IARC) concluded that silica was a Group 2A carcinogen (probably carcinogenic to humans). It was then classified as an IARC Group 1 carcinogen (carcinogenic to humans) in 1998, and as a human carcinogen by the Japan Society for Occupational Health in 2002. The current classification is based on the following findings: 1) the risk of lung cancer is increased by 1.5 to 8 times among workers exposed to silica in some special occupations such as quarrying and firebrick manufacturing, 2) carcinogenicity cannot be excluded although bias owing to smoking cannot be completely removed, 3) the incidence of lung cancer is partly associated with the duration of exposure although the dose-response relation has not been fully verified, and 4) carcinogenicity has been demonstrated experimentally (although only in rats).

The Japanese Ministry of Health, Labour and Welfare has not recognized lung cancer as an occupational disease in workers exposed to workplace dust because of the lack of sufficient proof of carcinogenicity, as described above, and the low risk of lung cancer (only an increase of 1.2 to 1.5 times). The Ministry regards lung cancer as occupational in workers with Management Class 3 and 4 pneumoconiosis, which is mainly characterized by a Type 2 roentgenographic pattern, because such severe pneumoconiosis can interfere with the diagnosis and treatment of lung cancer.

1. Conclusions of the Japanese Ministry of Health, Labour and Welfare "Study Group on the Health Management of Pneumoconiosis That May be Complicated by Lung Cancer"

The study group held meetings in 2001 and 2002, and reached the following conclusions.

(1) A meta-analysis of the epidemiological studies conducted outside Japan showed that the risk of lung cancer was slightly increased among workers exposed to silica dust (Table 1).

(2) Among exposed workers with no signs of pneumoconiosis, the risk of lung cancer is approximately the same as in the general population (Table 1 and Fig. 1).

(3) Among workers exposed to silica dust who show and signs of pneumoconiosis, the risk of lung cancer is high. The risk is particu-

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Table 1 Risk Assessment by Meta-analysis

Epidemiological study included in the statistical analysis	Weighting by paper evaluation	Fixed effect model*	Random effect model**
Investigation of exposure to silica and lung cancer	−	1.31 (1.24–1.38)	1.34 (1.22–1.47)
	+	1.32 (1.24–1.39)	1.34 (1.22–1.47)
Investigation of lung cancer in workers with pneumoconiosis	−	3.52 (3.30–3.76)	2.89 (2.32–3.60)
	+	3.71 (3.45–3.99)	3.14 (2.40–4.10)
Separate investigations in workers with or without pneumoconiosis			
With pneumoconiosis		2.13 (1.75–2.59)	2.13 (1.75–2.59)
Without pneumoconiosis†		0.97 (0.84–1.14)	0.96 (0.81–1.15)
Investigation in workers with pneumoconiosis by smoking status			
Non-smokers		1.89 (1.37–2.61)	2.31 (1.68–3.19)
Smokers		4.93 (4.49–5.41)	4.73 (3.71–6.31)

* Petitti, D.B.: *Meta-analysis Decision Analysis, and Cost-Effective Analysis* 1994; Oxford University Press, Oxford.
** DerSimonian, R. *et al.*: *Control Clin Trials* 1986; 7: 177–188.
† In groups other than that marked with a dagger (†), the risk was significantly increased.

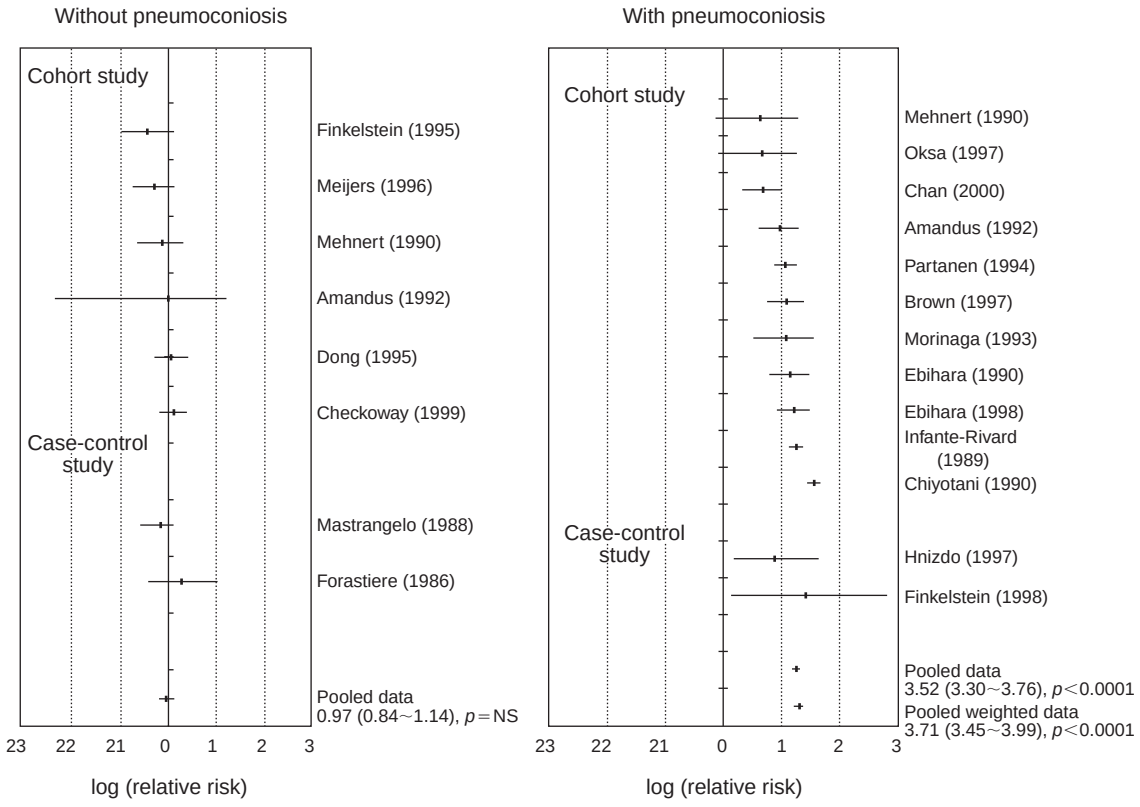

Fig. 1 Meta-analysis of the studies on lung cancer risk in workers exposed to silica (Cited from the 2002 Report of the Ministry of Health, Labour and Welfare)

larly high in the smoking subgroup, but it is also high for non-smokers.

(4) The risk of lung cancer is not associated with the severity of pneumoconiosis. The risk for workers with Management Class 2 pneumoconiosis is as high as those with Management Class 3 or 4 disease.

(5) In animal experiments, lung cancer developed only in rats, which have lungs that are vulnerable to fibrosis. In humans, the risk of lung cancer is also increased among patients with idiopathic pulmonary fibrosis.

(6) Crystalline silica is not mutagenic.

Amendments to the relevant law are being prepared according to the following proposals based on the findings described above.

(1) All patients with Management Class 2 and 3 pneumoconiosis should undergo spiral CT and sputum tests once a year.
(2) Lung cancer is to be considered as one of the complications of pneumoconiosis, and hence is an occupational disease. Consequently, work-related disability compensation should be available for this condition.
(3) Workers with pneumoconiosis of both Management Class 2 and Class 3 should be qualified to receive a Health Management Note, which should be issued when they quit their jobs.
(4) The necessity of medical treatment should be stipulated for workers who have lung cancer complicating pneumoconiosis (Article 23 of the Pneumoconiosis Law).
(5) Measures to prevent or control exposure to workplace dust should be fully implemented. In addition, the current permissible concentration limit for airborne dust that is specified in order to control exposure should be reduced.
(6) All possible action to control tobacco smoking should be carried out.

2. Usefulness of spiral CT

According to an investigation conducted by Cornell University in the United States, spiral CT was superior to conventional radiographic examination for the detection of lung cancer and the detection rate with spiral CT was 4 times higher than with conventional methods. Tumors measuring of 20 mm or less in size accounted for 85% and 57% of the lung cancers detected by spiral CT and conventional methods, respectively. The rate of detection of stage IA (or early) tumors by spiral CT and conventional methods was 81% and 57%, respectively.

The results of an investigation conducted in Japan were similar to the above findings obtained in the United States. In addition, spiral CT employs a low radiation dose and thus can reduce exposure to radiation.

It is important that lung cancer in workers with pneumoconiosis has now been officially recognized as an occupational disease, and that screening examinations and preventive measures for pneumoconiosis have been improved.

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Diagnosis and Treatment of Chronic Prostatitis

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Abstract: New topics in the diagnosis of prostatitis include the revised classification of prostatitis and the development of a symptom scoring system proposed by the U.S. National Institute of Health (NIH). The new classification features the inclusion of chronic prostatitis/chronic pelvic pain syndrome. The development of the symptom scoring system facilitated the comparison of treatment effects and clinical study results. Epidemiological research on chronic prostatitis-like symptoms has been conducted using this scoring system. The role of bacterial infection as a cause of chronic prostatitis/chronic pelvic pain syndrome has not been clarified. With respect to treatment of prostatitis, the administration of antibacterial agents is an established treatment for acute or chronic bacterial prostatitis, but there is no established treatment for chronic prostatitis/chronic pelvic pain syndrome. The paucity of large-scale randomized trials and the diversity of causes are preventing the establishment of treatment for this disease.

Key words: Prostatitis; Epidemiology; Questionnaire; Treatment

Introduction

Except for a limited number of cases caused by bacterial infection, prostatitis is not easy to diagnose and treat. The reasons for this difficulty include the diversity of causes and the lack of reliable test methods for confirming the presence of inflammation. This article reviews new topics related to the diagnosis and treatment of prostatitis.

Classification of Prostatitis

Recently, the National Institute of Health (NIH) in the U.S. proposed to classify prostatitis into 4 categories (Table 1).[1] While the new system does not differ much from conventional classification of prostatitis, a new feature is the inclusion of abacterial prostatitis and prostatodynia in 1 category (Category III). The asymptomatic inflammatory prostatitis in Category

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Table 1 Classification of Prostatitis (NIH)

Category I	Acute bacterial prostatitis
Category II	Chronic bacterial prostatitis
Category III	Chronic prostatitis/ chronic pelvic pain syndrome
Category IIIA	Inflammatory
Category IIIB	Noninflammatory
Category IV	Asymptomatic inflammatory prostatitis

IV is defined based on histological diagnosis.

Without exception, acute bacterial prostatitis is caused by infection of Gram-negative bacilli, typically *Escherichia coli.* Chronic bacterial prostatitis in Category II is caused by Gram-negative bacilli and by some Gram-positive cocci. Category III is chronic prostatitis/chronic pelvic pain syndrome, which is subdivided into inflammatory and noninflammatory. The "inflammatory" Category IIIA refers to so-called chronic abacterial prostatitis, while the "noninflammatory" Category IIIB refers to chronic pelvic pain syndrome. Category III represents 80% of all prostatitis cases. Because the most important problems of diagnosis and treatment are associated with prostatitis cases in categories II and III, the following sections focus on the discussion of problems concerning these 2 categories.

Chronic Prostatitis-like Symptom Scores

Questionnaires have been used for the evaluation of symptoms of chronic prostatitis, but unfortunately, there were no established forms for this purpose. Recently, a questionnaire form for scoring chronic prostatitis-like symptoms was developed by a group supported by NIH.[2] A draft version that was translated into Japanese is also available.[3]

This questionnaire consists of 9 questions in total: 4 regarding pain or discomfort, 2 regarding urination, and 3 regarding the quality of life (QOL). In contrast to patients with benign prostatic hyperplasia (BPH) and healthy adults, the main complaints in those with chronic prostatitis are pain and discomfort. The questionnaire features questions concerning pain and discomfort during urination and after ejaculation, in addition to those in the perineum, testicles, penis, and lower abdomen.

A major difference from similar forms used previously in Japan is the inclusion of questions related to QOL. This enabled relatively easy comparison regarding how symptoms of chronic prostatitis affect the patient's QOL. We translated the NIH questionnaire into Japanese and examined its validity and reproducibility.[3]

The results show that the score regarding pain or discomfort and that regarding QOL are clearly higher in patients with chronic prostatitis as compared with those with BPH and healthy adults. This result suggests that this type of questionnaire is useful for evaluating not only symptoms but also QOL of patients with chronic prostatitis. Our evaluation of reproducibility also provides satisfactory results. Thus, we conclude that this questionnaire can be applied for Japanese patients with chronic prostatitis. The Japanese Urological Association is currently evaluating the final Japanese version of the questionnaire.

It must be emphasized that this questionnaire is not intended for diagnosis of chronic prostatitis but for objective evaluation of symptoms and evaluation of treatment effects. This precaution is the same as that concerning the International Prostate Symptom Score (IPSS) for BPH. The IPSS is not used for the diagnosis of BPH.

Epidemiology of Chronic Prostatitis-Like Symptoms

The prevalence and number of patients with chronic prostatitis-like symptoms in Japan have not been ascertained exactly. A study in Canada using the aforementioned questionnaire reported a prevalence of 9.7% among men in the age range of 20 to 79, although the definition as to what score indicates the

presence of chronic prostatitis-like symptoms has not been concretely established.[4)]

When we analyzed our data using the same definition, the prevalence in the above age range was 5%.[3)] If we assume that all patients with these symptoms have chronic prostatitis, the number of patients in Japan is estimated to be between 1 to 1.5 million.

Diagnosis of Prostatitis

Diagnosis of acute prostatitis can be made easily based on clinical findings. Most patients show evident systemic symptoms, including fever of 38°C or higher, pain on urination, and difficulty of urination. Urinary sediment tests show leukocytes and bacteria without exceptions. The causative bacteria are Gram-negative bacilli, in particular *Escherichia coli*. The prostate is swollen with marked tenderness. Prostatic massage is contraindicated, because it increases the risk of sepsis.

As mentioned above, chronic prostatitis is classified into Category II (chronic bacterial prostatitis) and Category III (chronic prostatitis/chronic pelvic pain syndrome). A four-glass test using first voided urine, midstream urine, expressed prostatic secretion (EPS) obtained by massage, and post-massage voided urine has conventionally been recommended for the purpose of diagnosing prostatitis in these categories. However, this test has rarely been used in daily clinical practice.

A simplified test called the two-glass test has been used recently. This test uses pre-massage (midstream) urine and post-massage voided urine. When either method is used, the presence or absence of inflammatory signs and bacteria in the EPS or post-massage voided urine is diagnostically important. Generally, the presence of inflammation is presumed when EPS or the sediment of post-massage voided urine contains at least 10 to 20 leukocytes in a $\times 400$ field of view. If the number of leukocytes is smaller, the probability of inflammation is considered low, although there are some objections in this respect.

On the other hand, bacterial infection is inferred when at least 10^3/m*l* Gram-negative bacilli or 10^4/m*l* Gram-positive cocci are isolated. In the case of the two-glass test, the diagnosis as having chronic bacterial prostatitis requires a lack of inflammation and bacteria in pre-massage urine and the presence of both in post-massage voided urine. In the U.S., if the number of bacteria isolated from EPS or post-massage voided urine exceeds 10 times that of the first voided and midstream urine, the isolated bacteria are usually considered the causative bacteria. When the test did not show involvement of bacteria, patients are diagnosed as having category III disease. In addition, chronic abacterial prostatitis in Category IIIA is suspected if EPS or post-massage voided urine had inflammation, and chronic pelvic pain syndrome in Category IIIB is suspected otherwise.

The question remains that whether Category III prostatitis really lacks the involvement of bacterial infection or the inability to prove bacteria merely reflects the insufficient sensitivity of the test. In particular, involvement of bacterial infection cannot be ruled out when there is an inflammatory finding. Indeed, there is an argument that prostatic massage cannot yield bacteria from the prostatic ducts, as well as a study reporting that bacterial genes could be demonstrated in a fairly large percentage of cases without clinical isolation of bacteria.[6)] More basic study is needed before we are able to rule out bacterial infection as the cause of inflammation observed in a case lacking clinical demonstration of bacteria.

With respect to the causes of chronic pelvic pain syndrome showing no isolatable bacteria and no signs of inflammation, our understanding is poor. While bacterial infection cannot be ruled out completely, the involvement of inflammation unrelated to bacterial infection, prostatic calculus, urinary disturbance, congestion of pelvic veins, and mental or psychological factors is also suspected.

Recently, interstitial cystitis is also suspected as a possible cause in some patients. It may also be possible that the development of symptoms may be mediated by the same mechanism.

Treatment of Prostatitis

In the final section, we discuss the treatment of prostatitis. As mentioned above, the causative bacteria of acute prostatitis are mostly Gram-negative bacilli. Accordingly, parental antibacterial agents that have antibacterial activity against these bacteria (e.g., second and third generation cephems, carbapenem, and monobactam) are used for treatment. Since fever is alleviated usually within 3 to 5 days, antibacterial chemotherapy using oral antibacterial agents (fluoroquinolones and new oral cephems) is followed for 2 to 3 weeks. In the case of acute aggravation of chronic bacterial prostatitis, prolonged antibacterial chemotherapy may be needed even after the disappearance of acute symptoms.

Chronic bacterial prostatitis is basically caused by bacterial infection. Whether the causative bacteria are Gram-negative or Gram-positive, treatment should be based on antibacterial chemotherapy.

A large number of antibacterial agents are currently covered by the national health insurance for use in prostatitis. Those frequently used for chronic bacterial prostatitis include tetracycline antibiotics (doxycycline and minocycline) and various new quinolones. These antibacterial agents show relatively good drug penetration to prostatic tissue. New quinolones are used most frequently, because of their advantage in drug penetration to prostatic tissue and antibacterial activity against possible causative bacteria. While antibacterial chemotherapy is usually used for 4 weeks, many patients require a treatment period of 12 weeks. Prostate massage in parallel with antibacterial chemotherapy may be effective.

Chronic bacterial prostatitis is often complicated with obstruction of prostatic ducts, reflecting its nature as a so-called biofilm disease.[7] Treatment can sometimes be difficult, and the presence of urination disturbance, prostatic calculus, etc. must be considered in such cases. While sympathetic alpha-receptor blockers (alpha-blockers) and TURP are sometimes needed in these cases, the effectiveness of these treatments has not been established.

As compared with chronic bacterial prostatitis in Category II, the treatment of chronic prostatitis/chronic pelvic pain syndrome in Category III is more likely to be difficult. Various regimens have been attempted for the treatment of this disease, and this fact may be ironically viewed as a reflection of the lack of definite therapies. A major problem is the fact that few large-scale controlled trials have been conducted on this disease.

The effectiveness of several treatment methods has been confirmed in a small number of cases, but data have not been accumulated to establish evidence. Since a questionnaire for the objective evaluation of chronic prostatitis-like symptoms has been developed, we now can take a more scientific approach to the treatment of this disease. If not, we will have to repeat the process of trial and error that continued for decades in the past.

As discussed above, inflammatory category (IIIA) of chronic prostatitis/chronic pelvic pain syndrome (Category III) does not show isolatable bacteria. However, antibacterial agents are usually used as the initial therapy at least temporarily.

The antibacterial agents used in this disease are new quinolones, and the therapy is continued usually for 2 to 4 weeks. Combinations with plant extracts or antiinflammatory agents such as NSAIDs may be effective, but these combinations have not been confirmed to enhance the action of antibacterial agents. Among plant extracts, *in vitro* effects of Cernilton® have been reported.[8] This preparation is attractive for inhibition of proinflammatory cytokines, but it has not been examined whether this activity is generated in clinical

setting. In addition, prostate massage, hot sitz bath, and other treatments can be effective in some patients, as well as life guidance such as avoidance of drinking, long sitting, and fatigue.

When treatment extends over a long period, it is desirable to discontinue antibacterial therapy and continue other methods of treatment. If symptoms do not respond to these treatments, alpha-blockers, Chinese herbal medicines, antidepressants, etc. may be used. However, it should be noted that none of these treatments has been established. In particular, the effectiveness of alpha-blockers has not been established, although some reports have indicated the clinical efficacy of these agents and there is a possibility that some patients with disturbance of urination mechanisms were included in the disease of this category.

The treatment for chronic pelvic pain syndrome in Category IIIB is even more empirical than that for Category IIIA. In addition to the treatments for Category IIIA, psychosomatic approaches, skeletal muscle relaxants, and other methods are attempted. Recently, prostate thermotherapy has been reported to be effective in Category III prostatitis. Future study in this direction is expected.

As discussed above, the methods for treatment of chronic prostatitis other than acute and chronic bacterial prostatitis have not been established. Because of a large number of patients with the disease, more clinical studies are crucial.

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