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# Application of Psychotropic Drugs in Primary Care

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**Abstract:** The incidence of mental disorder in patients seen in primary care is very high and alcohol abuse/dependence, depressive disorders, anxiety disorders, somatoform disorders, and sleep disorders, in particular, pose great problems. The primary care physician must have a basic knowledge of the screening, diagnosis and treatment for these disorders. Among these disorders, it is desirable to have somatoform disorders treated by the primary care physician, and the primary care physician can also treat depression, anxiety, and sleep disorders. The primary care physician should be aware of certain key points with regard to the use of psychotropic drugs; these include familiarity with a few drugs and simplified prescribing. In addition, the physician needs to acquire knowledge about basic usage, side effects, and monitoring of side effects of antidepressants, anxiolytics, and hypnotics. These points are described and summarized in this paper.

**Key words:** Primary care; Mental disorder; Psychotropic drug

## Introduction—Importance of Psychiatry in Primary Care

Various psychiatric problems are encountered in primary care. How to make clinical adjustments to such psychiatric problems is a very important subject.

Psychiatric problems commonly seen in primary care can be divided into the 4 categories presented in Table 1:

1. Patients with a physical disorder who present with mental symptoms as a psychologi-

cal response to the disease.

2. Organic, symptomatic and drug-induced psychiatric disorders arising from altered cerebral function influenced by a physical disorder and the therapeutic drug used in its treatment.
3. Psychosomatic disease where psychosocial factors have an influence on the development and course of a physical disorder.
4. Patients with mental disorder who visit the primary care physician. The patients in category 4 can be divided into two further categories. 4-a) Patients who have already been

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Table 1 Psychiatric Problems in Primary Care

1. Patients with a physical disorder present with psychiatric symptoms as psychological response to the disease.
2. Organic, symptomatic and drug-induced mental disorders that develop under the influence of a physical disorder and the effect of medication on the brain.
3. Psychosomatic disease where psychosocial factors have an influence on the development and the course of a physical disorder.
4. Patients with mental disorder who visit the primary care physician.
a) Patients who have already been diagnosed as having a mental disorder and who receive treatment at other clinics besides the psychiatric clinic because of their physical complication.
b) Patients with a mental disorder who visit clinics other than psychiatry to have their mental disease treated.

diagnosed as having a mental disorder and who receive treatment at other clinics besides the psychiatric clinic because of their physical complication. 4-b) Patients with a mental disorder who visit clinics other than psychiatry to have their mental disorder treated.

This report provides an outline on the proper application of psychotropic agents in primary care. Primary care physicians are likely to prescribe some type of psychotropic drug in all the cases mentioned above, but it is critical that these psychotropic agents be used properly for patients with mental disorders seen in primary care.

### **Incidence and Diagnostic Distribution of Patients with Psychiatric Disorder Seen in Primary Care**

For all patients seen in the primary care setting, the incidence of mental disorder is between 11 and 36%, according to European and American studies that employed structured interviews and operational diagnostic criteria.<sup>1)</sup> Though there have been few studies conducted in Japan, Sato *et al.*<sup>1)</sup> reported that 31% of all patients that visited the general medicine clinic at a university hospital were diagnosed as having some form of mental disorder.

According to European and American studies, the diagnostic distribution of these mental disorders shows that alcohol abuse/dependence, abuse/dependence on substances other than alcohol, depressive disorders, and anxiety disorders are common.<sup>1)</sup>

Though the incidence in Japan of abuse or dependence on substances other than alcohol is low, in common with the situation found in Europe and America, many cases of alcohol abuse/dependence (10% of patients seen), anxiety disorders (8%) and depressive disorders (5%) are seen.<sup>1)</sup>

These investigations involve methodological problems and it is surmised that the incidence of mental disorder seen in primary care could actually be much higher. In other words, most of the somatoform disorders and sleep disorders were not covered in the structured interview employed by the study mentioned above.

In primary care, it is well known that the incidence of these two disorders is high. Results of European and American studies show that the incidence of somatoform disorders ranges from a few percent to about 20% of all patients seen in a medical institution.<sup>2)</sup> In addition, it is known that about 20% of patients seen in a general hospital are diagnosed with sleep disorders.<sup>3)</sup>

In conclusion, it may be said that the incidence of mental disorder in patients seen in primary care is very high and alcohol abuse/dependence, anxiety disorders, depressive disorders, somatoform disorders, and sleep disorders, in particular, pose the major problems.

### **Diagnostic Method for Mental Disorder in Primary Care**

It is said that mental disorder is often overlooked in primary care.<sup>4)</sup> The following reasons may account for this. One is related to medical education, where the teaching of psychiatry is frequently inadequate for clinical practice at the primary level. The second reason is that many patients with mental disorder present with only mild symptoms when seen in primary care.

However, the most important reason is that most of the patients with mental disorder seen in primary care do not complain of psychiatric symptoms but physical symptoms.<sup>2)</sup>

The clue to finding patients with mental disorder who visit the doctor complaining of physical symptoms is that no physical disorder can be found that could explain the physical symptoms, or even if a physical disorder is found, they cannot be convincingly attributed to the physical disorder.

It is known that among mental disorders diagnosed in patients who complain of physical symptoms not explained by physical disorder, depressive disorders and anxiety disorders account for a quarter respectively, and somatoform disorders account for nearly a half.<sup>2)</sup>

Conducting a screening test for depression and anxiety might be, of course, an effective way of detecting mental disorder.

However, it may be simpler and more reliable to ask the patients directly about depression and anxiety. It is said that patients with depressive disorders and/or anxiety disorders often acknowledge some change in their emotional state when asked, even when the stated purpose of the consultation is a complaint with physical symptoms.<sup>2)</sup>

When a mental disorder is suspected from such questioning, then the use of operational diagnostic criteria should be considered, including the ICD-10 (International Classification of Disease-10) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), both of which are accurate diagnostic methods. These diagnostic methods enable practitioners other than psychiatrists to diagnose simply by listing the patient's symptoms.

### **Treatment of Mental Disorders in Primary Care**

Treatments for mental disorders include drug therapy, psychotherapy and rehabilitation.

Diagnosis is the most important criterion for selection of therapeutic method. Therefore, the

diagnosis of mental disorders must also be considered when using psychotropic drugs in primary care.

#### **1. Mental disorders for which a treatment by primary care physician is desirable**

Many patients with somatoform disorders complain of only physical symptoms that cannot be adequately explained by a physical disorder and they often deny that they have any psychiatric symptoms. In many cases they do not consent to referral to a psychiatrist. Consequently, primary care physicians need to play a primary role in the medical treatment of somatoform disorders. Even if patients agree to start treatment under a psychiatrist, medical care in liaison with primary care physicians can produce good results.<sup>3)</sup>

In addition, primary care physicians should be able to undertake the initial treatment of depression, anxiety, and sleep disorders.

#### **2. Disorders for which psychotropic drug therapy is effective**

Among the mental disorders described previously, those for which psychotropic drugs are effective include depression, anxiety, and sleep disorders. In these cases, counseling, including an explanation about the diagnosis and the therapeutic effects and the adverse effects of drugs, the recommendation of rest, and providing assurance of recovery are, of course, important. An explanation on the need for sleep hygiene is necessary for patients with sleep disorders.<sup>6)</sup>

In contrast, psychotropic drugs are largely ineffective in the treatment of somatoform disorders. Symptoms gradually improve, however, in many cases where the patient is given an explanation of the symptoms, assurance regarding recovery and the absence of any malignant disease, and other supportive responses provided by the primary care physician.<sup>6)</sup>

Psychotropic drugs are also ineffective in patients with alcohol abuse/dependence and abuse/dependence on other substances. In

addition, the risk of dependence on anxiolytics and hypnotics is high.

### 3. Referral to a psychiatrist

It is advisable to refer patients with more severe symptoms of depression or anxiety to a psychiatrist immediately. In particular, if the patients show evidence of suicidal ideation or suicidal attempts or have severe anxiety or irritation in a depressive state, they should be referred to a psychiatrist as early as possible.

In addition, patients in whom specific sleep disorders such as sleep apnea syndrome or narcolepsy are suspected, patients with alcohol abuse/dependence and patients in whom schizophrenia is suspected (in spite of a low frequency of visits to a primary care provider) should be referred to a psychiatrist as soon as possible.

In addition, patients suffering from depression or anxiety where common therapeutic methods have not had a sufficiently positive effect should also be referred to a psychiatrist.

## Psychotropic Drug Therapy in Primary Care

### 1. Classification of psychotropic drug

Major psychotropic drug groups include anti-psychotics, antidepressants, mood stabilizers, anxiolytics, and hypnotics. Among these drugs, antidepressants, anxiolytics, and hypnotics are frequently prescribed in primary care.

### 2. Principles of use of psychotropic drug in primary care

- (1) Become familiar with the characteristics of a few selected drugs.

At present many psychotropic drugs are sold in Japan. However, drugs belonging to the same group have similar effects and it does not make great difference which particular drug is chosen. The most practical approach is to become familiar with the usage of one or two drugs within each group.

In addition, it is desirable to be able to pre-

scribe the following drugs: one drug each from the various antidepressant groups such as tricyclic, tetracyclic or atypical antidepressants, SSRIs (selective serotonin reuptake inhibitor) and SNRIs (serotonin-noradrenaline reuptake inhibitor); one drug with a mild effect and another with a relatively potent effect from the anxiolytic group; and one drug with a short and another with a moderate duration of action from the hypnotic group.

#### (2) Prescribing in practice

Prescriptions should be kept as simple as possible and it is recommended that a single drug appropriate to the diagnosis be prescribed. However, combining an antidepressant with a hypnotic is possible in depression attended by severe insomnia. Begin with a small dose and increase gradually. When symptoms improve and withdrawal of medication is being considered, the dose should be tapered off to discontinue the medication.

#### (3) Side effects and monitoring

Psychotropic drugs, in spite of side effects, can be used relatively safely when adequate care is taken.

Major side effects that physicians should be particularly aware of include symptoms that may be attributable to central and peripheral anticholinergic effects, hypotension, suppression of conducting system, hepatic dysfunction, suppression of hematopoiesis, and drug-induced [skin] eruption. However, the incidence of these events is fortunately low and these side effects are rarely observed in anxiolytics and hypnotics, in particular.

These side effects may occur 1–2 weeks after starting treatment or after a long period of continuous use. Accordingly, it is recommended that blood and urine should be checked and an ECG taken before initiating the medication and about 2 weeks later, and after that at least once every few months.

### 3. Drug groups

Only basic matters are described here.

#### (1) Antidepressants

Antidepressants are initially given in small doses, which is gradually increased to a moderate level at the interval from twice a week to once every 2 weeks. They are given continuously for 4–8 weeks to observe the effect. Any antidepressant takes at least one week to have an effect after the standard dosage is attained. When no effect appears, a psychiatrist may increase dosage to the maximum usual dosage. However, in primary care, it is better to refer the patient to a psychiatrist.

The development and course of a depressive disorder are related to many factors. The effect of antidepressants is insufficient when depressive symptoms are caused by organic, symptomatic or drug-induced psychiatric disorders or when personality problems play a dominant role. A detailed study by a psychiatrist is required to clarify these factors and there are many cases where referral for professional psychotherapy is indicated as well. It is not recommended that patients with depressive disorders that show no sign of improvement be treated at the primary care level.

We would like to mention the characteristics of each antidepressant briefly. Tricyclic antidepressants have both a potent therapeutic effect and potent side effect. Tetracyclic and atypical antidepressants have relatively mild therapeutic effects and only minor side effects. SSRIs are effective and have only mild side effects although the potential for drug interactions requires caution. The only SNRI sold in Japan at present is milnacipran, which does not undergo liver metabolism and is excreted via the kidney, meaning that it is not the best first option for patients with deteriorated renal function.

## (2) Anxiolytics and hypnotics

It is important not to prescribe higher than normal dosage when using anxiolytics and hypnotics. In addition, as a general rule, administration of more than one drug from within either the anxiolytic or hypnotic categories should be avoided. Multiple agents from the same category are unlikely to produce an additional beneficial effect, which may in turn, if

accumulated, result in exceeding usual dosage. The development of dependency is a particular problem related to these two groups of agents. Abrupt discontinuation may trigger withdrawal symptoms when a usual dosage has been sequentially administered. Risk of dependence increases remarkably when doses in excess of the usual dosage are taken. It is, however, inappropriate not to treat anxiety and insomnia out of an excessive fear of dependence. In fact, the majority of patients can discontinue these drugs without any particular problem if symptoms abate.

Recently, particularly when long-term treatment is indicated SSRIs are substituted for anxiolytics, and tetracyclic or atypical antidepressants are substituted for hypnotics, in view of the risk of dependence. These substituted regimens have few side effects as well as being effective in inducing deep sleep in many individuals. Since anxiolytics and hypnotics are very frequently used in Japan (in comparison to the rest of the world) these measures may be important in the future.

In addition, these two classes of drugs have weak anticholinergic effects, may suppress respiratory function to a minor degree, and also act as muscle relaxants. Though these effects rarely pose problems in the usual patient, more caution is needed when treating elderly patients and patients with severe physical disorder as they may cause serious complications.

## Conclusion

It is predicted that medical treatment of patients with mental disorders at the primary care level will become more important in the future. Psychotropic drug therapy is one of the main treatment options so physicians must have sufficient knowledge and experience in these therapies.

In addition, liaising with psychiatrists is also important. Making the acquaintance of a reliable psychiatrist is of enormous value when conducting medical care. In addition, we think

it may be valuable for primary care physicians to deepen their experience by participating with psychiatrists in conferences where case studies are examined.

#### REFERENCES

- 1) Sato, T. and Takeichi, M.: Lifetime prevalence of specific psychiatric disorders in a general medicine clinic. *Gen Hosp Psychiatry* 1993; 15: 224–233. (in Japanese)
- 2) Horikawa, N.: Somatoform autonomic dysfunction. *Somatoform Disorders and Psychosomatic Disease, Encyclopedia of Clinical Psychiatry vol.6* (ed. Yoshimatsu, K. and Kamijima, K.), Nakayama-Shoten, Tokyo, 1999; pp.145–158. (in Japanese)
- 3) Shirakawa, S., Ishigouoka, J., Ishizuka, Y. *et al.*: Investigation of actual state on sleep disorders and sleep habit at outpatient clinic in general hospitals. *Ministry of Health and Welfare Reports for 1995 on Psychiatric and Neurological disease: Study on diagnosis, treatment and epidemiology of sleep disorders* 1996; pp.7–23. (in Japanese)
- 4) Ormel, J. and Tiemens, B.: Recognition and treatment of mental illness in primary care; Towards a better understanding of a multifaceted problem. *Gen Hosp Psychiatry* 1995; 17: 160–164.
- 5) Hosaka, T., Sato, T. and Yamamoto, K.: Therapeutic models for somatoform disorders in liaison psychiatry. *Int J Psychiatr Clin Pract* 1998; 2: 189–193.
- 6) Horikawa, N.: Somatoform disorders and their treatment in primary care. *Treatment* 2000; 82: 1716–1720. (in Japanese)

# Safe and Effective Use of Psychotropic Drugs

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**Abstract:** This paper outlines the safe and effective use of psychotropic drugs commonly employed in primary care practice. If a patient undergoing primary care develops psychiatric symptoms that necessitate the administration of psychotropic drugs, one needs to be aware of the possibility that the underlying physical disease may have altered the patient's pharmacokinetics and pharmacodynamics. Changes in pharmacokinetics may cause delays in absorption, distribution, metabolism, and excretion of the drug, leading to high blood concentrations that can result in unexpected adverse reactions. It is also important to consider possible interactions with therapeutic drugs prescribed for the patient's physical condition. In Japan, recently developed psychotropic drugs, particularly selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) among the antidepressants and serotonin-dopamine antagonists (SDAs) among the antipsychotic drugs, are associated with greater safety and fewer adverse reactions than conventional psychotropic drugs. Thus, they appear to be appropriate for patients who have both physical and psychiatric disorders and who have visited a primary care clinic.

**Key words:** Antipsychotics; Pharmacokinetics; Pharmacodynamics; SDA; SSRI; SNRI

## Introduction

The safe and effective use of psychotropic drugs in primary care practice will be discussed on the basis of recent findings in Japan. Along with the aging of society as well as changes in the social and economic climate that are apt to

increase stress, basic and marginal symptoms of dementia, depressive state, panic disorder (anxiety neurosis), and hypochondria appear to be increasing among patients who visit primary care clinics. In other words, patients with mental disorders such as psychosomatic disease and depression may be included among

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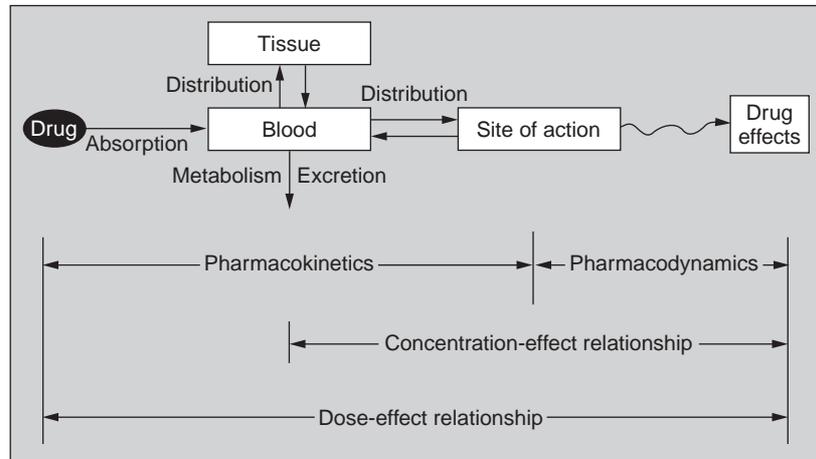


Fig. 1 Pharmacokinetics and pharmacodynamics  
(From Ikeda, Y. *et al.* (ed.): *Beneficial and adverse effects of drugs: How Best to Use Drugs in Patient Care*. Ishiyaku Publishers, Inc., Tokyo, 1992. (in Japanese))

those who visit a primary care clinic because of physical symptoms. These patients may be diagnosed as having pseudodementia, masked depression, or hypochondriacal neurosis.

Therefore, the use of psychotropic drugs in primary care clinics is considerable. For example, drugs for insomnia and anxiolytics of the benzodiazepine group are prescribed for patients complaining of sleeplessness, anxiety, or hypochondriasis. Because patients in a depressive state are estimated to account for at least 15% of those who visit primary care clinics, antidepressants are prescribed frequently in such clinics. In addition, antipsychotic drugs are used for the treatment of dementia and concomitant delirium.

### Pharmacokinetic Considerations in Drug Treatment

Some patients attending primary care clinics may have a physical disease complicated by an overlying condition that necessitates psychotropic drug treatment. Therefore, pharmacokinetic and pharmacodynamic changes resulting from the physical disease may render these patients at risk for enhanced drug effects or adverse reactions even when the usual dose is

given. Multiple drug use for the treatment of multiple diseases may cause serious toxic effects from interactions among the drugs.

To avoid these issues of drug treatment, it is necessary to choose appropriate drugs and dosage regimens, on the basis of a clear understanding of the mechanisms of change occurring in the patient as a result of aging and drug combinations.

### Changes in Metabolic Fate and Pharmacodynamics of Drugs

The pharmacologic action of a drug is determined by two characteristics: (1) its pharmacokinetics, the process by which it reaches the site of action, and (2) its pharmacodynamics, the reaction between the drug and the living body (Fig. 1).<sup>1)</sup>

Any change in these processes causes variation in the pharmacologic action of the drug. Such changes may be either pharmacokinetic or pharmacodynamic, or both.

#### 1. Pharmacokinetic changes in ill or elderly patients

Changes occurring in elderly patients or those with physical complications may be related to

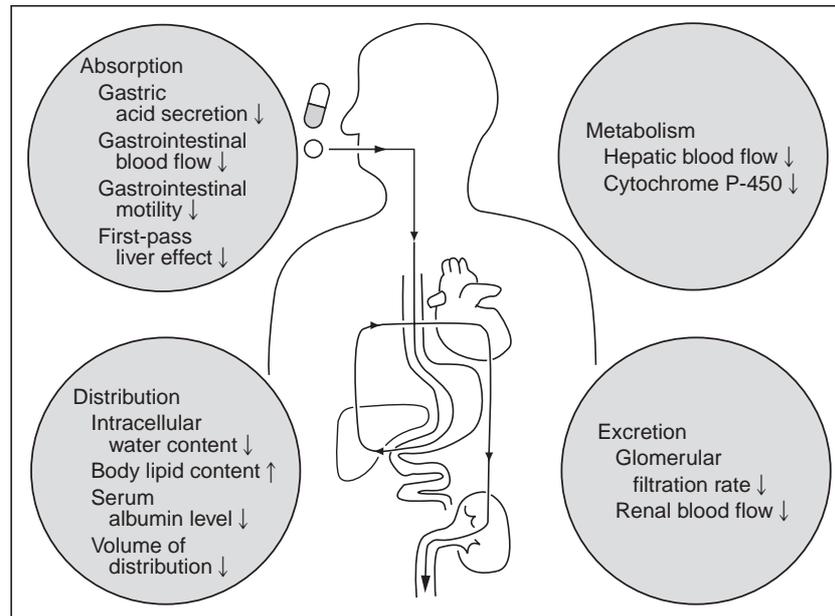


Fig. 2 Aging-related changes in various indices of absorption, distribution, metabolism and excretion of drugs

(From Ebihara, A.: Changes in the metabolic fate of drugs in the elderly. *Geriatr Med* 1993; 31: 185–190. (in Japanese))

several factors, shown in Fig. 2.<sup>2)</sup> For example, drug absorption is decreased with declining gastric secretion, gastrointestinal blood flow, or motility of the gastrointestinal tract resulting from aging or physical illness. Decreased hepatic blood flow and a decline in the drug-metabolizing enzyme cytochrome P-450 cause delays in drug metabolism. In addition, when the intracellular water content or serum albumin is decreased, and body lipid content is increased, the volume of distribution of water-soluble drugs lessens, resulting in elevated drug concentrations in blood. In contrast, under these conditions, most psychotropic drugs, which are lipophilic to facilitate their passage through the blood-brain barrier, have an increased volume of distribution. As a result, their elimination half-lives are prolonged, while blood concentrations are decreased.

For example, it has been reported that the volume of distribution of diazepam increases with aging, reaching a four- to fivefold difference between the elderly and younger indi-

viduals. When the serum albumin level is decreased by aging or the presence of physical disease, the protein binding rates of drugs that have a high albumin-binding capacity decline, and free drug concentrations rise, occasionally leading to a strong pharmacologic effect. Therefore, measurement of blood drug concentrations has no meaning unless free drug concentrations are determined.

Most drugs are metabolized mainly in the liver. Aging and hepatic disease lower the number of parenchymal cells, resulting in reduced liver weight. In addition, hepatic blood flow, by which the drug is delivered to the liver; activity of the drug-metabolizing enzyme cytochrome P-450; and the bile flow required for excretion of the drug also decline, inducing hepatic dysfunction. Therefore, complications and aging may cause high blood concentrations of drugs that are ordinarily metabolized in the liver, leading to a strong pharmacologic effect and strong adverse reactions.

Hypofunction of the kidney, the organ respon-

sible for the excretion of drugs, delays their urinary excretion. Aging alone is associated with a linear decrease in creatinine clearance, an index of drug excretion. Therefore, the blood concentrations of drugs normally excreted through the kidneys may be increased in the presence of renal hypofunction, creating a strong pharmacologic effect, adverse reactions, or toxicities. Although renal function is assessed in terms of creatinine clearance, it should be kept in mind that the serum creatinine level may not be elevated even under decreased renal function if muscle mass is decreased because of chronic disease or aging.

In summary, when prescribing psychotropic drugs in primary care clinics, it is necessary for the physician to be aware in advance of the drug's metabolism, excretion, and protein binding and to take into account interactions with other drugs prescribed for the treatment of concomitant physical disease.

## 2. Influence of psychotropic drugs on biofunction

Unlike drugs used for the treatment of physical diseases, psychotropic drugs are fat-soluble and usually act to depress the central nervous system. Therefore, when the effect of the drug is too strong, fatal reactions such as inhibited respiratory function and decreased blood pressure may be elicited.

The use of psychotropic drugs, particularly the antipsychotics, may cause adverse reactions like supraduction of eyeballs, akathisia, and dystonia in the acute stage, owing to dopamine (D2) receptor blocking in the central nervous system. In the chronic stage, extrapyramidal symptoms such as tardive dyskinesia, parkinsonism, amenorrhea, lactation due to hyperprolactinemia, thirst, constipation, ileus, urinary disturbance, and delirium caused by the anticholinergic action also may occur. Anticholinergic side effects are another problem related to the use of antidepressants.

The mental status of the patient may decline as a result of oversedation in cases of psycho-

tropic drug overdose.

## Development of Safe Psychotropic Drugs

It would not be much of an exaggeration to say that the entire history of psychotropic drug development has been a struggle to reduce side effects. Problems that need to be solved include reduction of the muscle relaxant effect and dyskinesia associated with hypnotics, reduction of anticholinergic side effects associated with antidepressants, and inhibition of the occurrence of extrapyramidal symptoms associated with antipsychotics. Various new psychotropic drugs have been developed recently and applied to clinical practice.

### 1. Benzodiazepines (BZ)

A new drug for insomnia, zolpidem (Myslee<sup>®</sup>), which has higher selectivity for BZ $\omega_1$  receptors, has recently been developed. This drug has a shorter half-life, the same as triazolam (Halcion<sup>®</sup>). In comparison with conventional drugs used to induce sleep, there is hardly any antianxiety effect, muscle relaxation, movement disturbance, or enhancement by alcohol, whereas it has sedative, amnestic, and anti-convulsant actions. Therefore, it is expected to reduce the incidence of fractures resulting from "wooziness" caused by the overdosing of sleep-inducing drugs.

Although lormetazepam (Loramet<sup>®</sup>, Evamyl<sup>®</sup>) is a sleep-inducing drug of the BZ group, it can be used for patients with liver injury because it is metabolized in the liver by simple glucuronic acid conjugation, unlike other drugs used to induce sleep.

Japan has been criticized by other countries for its overuse of BZ drugs. Prudence is necessary in prescribing these drugs because there is a risk of amnesia with prolonged use, dependence at the usual dose, and rebound insomnia/anxiety after abrupt withdrawal. In this connection, the use of selective serotonin reuptake inhibitors (SSRIs) has been tried.

## 2. Antidepressants

Tricyclic and tetracyclic antidepressants have a long history of clinical use, and therefore their clinical efficacy has been relatively well established. However, as mentioned previously, these drugs are often associated with low compliance owing to anticholinergic side effects and resultant recrudescence.

In this regard, new drugs with higher sensitivity to serotonin (5-HT<sub>2</sub>) or noradrenaline receptors have been developed in conjunction with the pathological hypothesis of depression. Such drugs include SSRIs and serotonin-noradrenaline reuptake inhibitors (SNRIs). The major pharmacologic actions of these drugs are to inhibit 5-HT<sub>2</sub> or 5-HT<sub>2</sub> and noradrenaline, respectively, targeting transporters in the pre-synaptic region.

These antidepressants cause far fewer adverse events, although nausea and vomiting may occur as a result of 5-HT<sub>2</sub> stimulation in the intestinal tract. When used with other drugs, some SSRIs may be associated with high blood concentrations owing to competition with several cytochrome P-450 molecular species or, conversely, low blood concentrations as a result of enzyme induction.

In Japan, the SSRIs available are fluvoxamine (Depromel<sup>®</sup>, Luvox<sup>®</sup>) and paroxetine (Paxil<sup>®</sup>). Milnacipran (Toledomin<sup>®</sup>), an SNRI, is available in clinics. Among the SSRIs, fluvoxamine is indicated for obsessive-compulsive disorder as well as depression, and paroxetine, which has a potent antianxiety effect in addition to its antidepressant effect, is also indicated for panic disorder. On the other hand, milnacipran inhibits the noradrenaline transporter in addition to 5-HT<sub>2</sub> reuptake inhibition, and is therefore expected to be effective for more serious depressive disorders.

## 3. Antipsychotics

Risperidone (Risperdal<sup>®</sup>), whose 5-HT<sub>2</sub> receptor inhibitory action predominates over its D<sub>2</sub> receptor inhibitory action, has been clinically available in Japan since 1996. Con-

ventional antipsychotic drugs such as chlorpromazine and haloperidol are called typical antipsychotic drugs, whereas new drugs such as risperidone, i.e., serotonin-dopamine antagonists (SDAs), are called atypical antipsychotic drugs. Drugs of this class on the market include quetiapine (Seroquel<sup>®</sup>), olanzapine (Zyprexa<sup>®</sup>), and perospirone (Lullan<sup>®</sup>), the first SDA developed in Japan based on the concept of serotonin-dopamine antagonism.

All these drugs have proved effective for negative symptoms and cognitive disorders, for which conventional typical antipsychotic drugs are much less effective, and are associated with lower frequencies of extrapyramidal side effects. Therefore, they are expected to be effective for schizophrenia, including the long-term prognosis of the disease.

Because of their lower frequencies of chronic adverse reactions, atypical antipsychotic drugs are considered to be associated with better compliance and thus better quality of life for patients. However, our 4-year clinical experience with risperidone indicated that extrapyramidal side effects occurred more frequently than expected at doses above 4 mg. Olanzapine and quetiapine are expected to be effective for refractory schizophrenia, but are contraindicated for patients who have a high probability of developing diabetes mellitus because of the reported risk these drugs have of causing diabetes mellitus. The use of quetiapine may reduce the problems of various adverse reactions common to typical antipsychotic drugs.

Although antipsychotic drug use is infrequent in primary care practice, atypical rather than typical antipsychotic drugs should be prescribed for psychotic conditions for which the use of conventional typical antipsychotic drugs had been the treatment of choice. In patients with serious complications in whom irritability and anxiety associated with insomnia and restlessness just after surgery develops into rambling conversation, unusual behavior, and, eventually, psychomotor excitability or delirium, haloperidol commonly has been employed.

However, given the adverse reactions to long-term use of this drug, an atypical antipsychotic drug would be a better choice.

## Conclusion

It is currently more common to see patients visiting a primary care clinic because of poor mental health. However, patients seen in primary care clinics often have physical complications and may have been on multiple drug therapy before psychotropic drugs are prescribed. Therefore, psychotropic drug treatment should be given as monotherapy as a rule and be based on a good understanding of the pharmacologic action of the drug. Although recent psychotropic drugs are associated with reduced side effects, it is necessary to prescribe

a proper dose, exercising due caution with regard to the possible development of adverse reactions.

In addition to drug administration, because many patients have psychosocial stress as a background to their pathologic condition, it is vital to allow patients to talk about their stress and to offer supportive psychotherapy.

## REFERENCES

- 1) Ikeda, Y. *et al.* (ed.): Beneficial and adverse effects of drugs: *How Best to Use Drugs in Patient Care*. Ishiyaku Publishers, Inc., Tokyo, 1992. (in Japanese)
- 2) Ebihara, A.: Changes in the metabolic fate of drugs in the elderly. *Geriatr Med* 1993; 31: 185–190. (in Japanese)

# Characteristics and Use of New Antidepressant Drugs

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**Abstract:** Japan has been considered at least ten years behind international standards in its use of antidepressant drugs, because selective serotonin reuptake inhibitors (SSRIs), which are mainstream antidepressants in Europe and North America, were not introduced in Japan until recently, and conventional tricyclic antidepressants had to be used instead. The first SSRI became available in Japan in 1999, followed by a newer type of antidepressant, i.e., serotonin-noradrenaline reuptake inhibitors (SNRIs), leading to more advanced treatment of depression. SSRIs are similar to conventional tricyclic antidepressants in their rate and onset of efficacy. However, since they act only on serotonin, they are associated with fewer side effects, and thus are easier for both patients and physicians to use. SNRIs potentiate the action of norepinephrine in addition to that of serotonin, and, theoretically, are expected to be more potent than SSRIs. However, their characteristics are similar to those of SSRIs. These new antidepressants are expected to be effective for anxiety disorders as well as depression, and may be useful in helping reduce the overprescription of benzodiazepine derivatives in Japan.

**Key words:** Antidepressant; SSRI; SNRI; Depression

## Introduction

Japan has been considered to be at least ten years behind international standards in its use of antidepressants, because selective serotonin reuptake inhibitors (SSRIs), the mainstream antidepressants used in Europe, North America, and elsewhere, were introduced late in Japan, forcing Japanese physicians to depend on tricy-

clitic antidepressants, an older generation of drugs for the treatment of depression.

However, in 1999, the first SSRI, fluvoxamine, was introduced in Japan, and another SSRI, paroxetine, became available the following year. Subsequently, milnacipran, a serotonin-noradrenaline reuptake inhibitor (SNRI), one of the newer antidepressant drugs, also became available, creating rapid changes and new devel-

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opments in the use of antidepressant drugs.

This paper describes the use of these antidepressant drugs according to their characteristics and side effects.

### **Properties and Problems of Conventional Tricyclic Antidepressants**

It is important to look initially at the properties and problems of antidepressant drugs of the previous generation.

Tricyclic antidepressants were first developed about 40 years ago. As mentioned above, they were the main antidepressants administered clinically in Japan until recently. Imipramine, a representative tricyclic antidepressant, was gradually improved, to produce a number of other newer tricyclic antidepressants. The basic properties of the newer derivatives are similar to those of imipramine; they inhibit the reuptake of serotonin and noradrenaline in nerve cells in the brain, thereby enhancing neural transmission and exerting an antidepressant effect.

The results of previous clinical trials indicate that the efficacy rate of tricyclic antidepressants in patients with depression is about 70%, a reasonably good rate. On the whole, tricyclic antidepressants can be regarded as effective drugs. However, the fact remains that about 30% of patients do not respond adequately to these drugs, and efforts to increase efficacy are important. In addition, tricyclic antidepressants require 3–4 weeks of uninterrupted therapy at adequate doses before their effects manifest. In other words, they are not fast-acting. Because depression is distressing to the patient and carries a high risk of suicide, the slow action of drugs in this class is a detriment to their efficacy.

However, a greater problem in the use of tricyclic antidepressants is their substantial side effects, the greatest drawback of drugs in this class. All tricyclic antidepressants block central and peripheral muscarinic receptors, histamine receptors, and  $\alpha_1$  adrenergic receptors. Blockage

of these receptors causes side effects including thirst, constipation, drowsiness, and dizziness on standing, leading patients to regard them as problematic and to take a negative attitude toward treatment. In addition, the tricyclic antidepressants induce an increase in ocular tension, making them difficult to use in patients with narrow-angle glaucoma. They may also worsen difficulty in urination in patients with benign prostatic hyperplasia, so that caution regarding their use is necessary in such patients. Thus, they can be difficult to use in the face of concomitant physical disease.

Because of these drawbacks, tricyclic antidepressants failed to gain the unmitigated trust of patients and physicians alike, despite their fairly high rate of efficacy. The attempt to overcome these drawbacks provided the impetus for the development of new antidepressant drugs.

### **Properties and Use of SSRIs**

Among the new antidepressants, SSRIs will be discussed first. Five of the drugs in this category are used throughout the world, and two of them, fluvoxamine (Luvox<sup>®</sup>, Depromel<sup>®</sup>) and paroxetine (Paxil<sup>®</sup>), are available in Japan.

SSRIs are characterized by their relatively uncomplicated chemical properties. As mentioned previously, conventional tricyclic antidepressants not only have a potent inhibitory action on the reuptake of noradrenaline and serotonin in brain cells but also have blocking actions on various receptors in the body, resulting in substantial side effects.

However, SSRIs have hardly any such blocking effects, and their chemical action serves to inhibit serotonin reuptake alone. Thus, their side effects are minimal, while their rate of efficacy is similar to that of the tricyclic antidepressants. Thus, SSRIs are considered to have none of the undesirable effects of the tricyclic antidepressants, while managing to retain their useful properties.

Although some consider an efficacy rate similar to that of the tricyclic antidepressants

insufficient, the lack of problematic side effects has led to better patient compliance; consequently, better therapeutic efficacy can be expected from these drugs. In addition, if taken in large quantities for the purpose of committing suicide, the SSRIs are relatively safe because their lethal doses are much higher than those of the tricyclic antidepressants, another definite advantage of this class of drugs.

Although they represent a great step forward, the SSRIs are not without drawbacks. Apart from side effects, they retain the main deficiencies of the tricyclic antidepressants: they are not fast-acting; their efficacy rate remains at about 70%; and there is no incremental benefit in intractable cases, an effect naturally anticipated from novel drugs. Some reports have even documented that conventional tricyclic antidepressants are superior to SSRIs in severe cases.

In addition, it is not true that SSRIs have no side effects. About 10% of patients experience rather severe gastrointestinal symptoms such as nausea in the early phase of therapy. Another reported defect of SSRIs is their interactions with other drugs. This is because SSRIs inhibit cytochrome P450, the drug-metabolizing enzyme in the liver, causing blood concentrations of other drugs metabolized by this enzyme to increase.

As an example, caution is necessary when SSRIs are used in combination with anti-anxiety drugs, other antidepressants, or hypnotics. Common drugs that should not be combined with SSRIs include the antiasthmatic theophylline, the gastrointestinal motility-enhancing drug cisapride, and the antiallergic drug terfenadine. For detailed information on drug interactions, readers are referred to the package inserts and other material on SSRIs.

In summary, while it is true that SSRIs have fewer side effects and are clearly easier to use than conventional tricyclic antidepressants, because of the chance of nausea in the early phase of therapy, it is prudent to begin with a low dose and to increase the dose weekly to a

sufficient dose. After that the same drug should be used continuously for at least 3–4 weeks to examine the patient's response. If therapy is not effective, switching to a tricyclic antidepressant or a serotonin-noradrenaline reuptake inhibitor (SNRI) should be considered. Caution should be exercised if other drugs are being used concomitantly.

### Properties and Use of SNRIs

The most recently developed antidepressants are the serotonin-noradrenaline reuptake inhibitors (SNRIs). In Japan, milnacipran (Toledomin<sup>®</sup>) has been used for two years, and currently it is the only SNRI antidepressant available.

As mentioned previously, SSRIs may be less effective for severe cases than tricyclic antidepressants because SSRIs inhibit the reuptake of serotonin alone and do not activate noradrenaline. Enhancing the function of a single neurotransmitter is not sufficient to diminish depression.

In this regard, drugs that activate both serotonin and noradrenaline, like the tricyclic antidepressants, do not have unfavorable effects such as blockade of muscarinic receptors and histamine receptors, and may be ideal in terms of potent clinical effects and minimal side effects. SNRIs were developed on the basis of this hypothesis. Thus, SNRIs are not just empirical drugs, but drugs that have been developed on the basis of a theory.

Therefore, from a theoretical point of view, a great deal is expected from the SNRIs. However, the clinical impression of SNRIs has been similar to that of SSRIs. Although it is true that SNRIs have minimal side effects and are easy to use, nausea has been a problem in the early phase of therapy. Difficulty in urination, a side effect not seen with SSRIs, has been an issue in advanced aged male patients with benign prostatic hyperplasia. Palpitation may also occur. Difficulty in urination and palpitation seem to be associated with activation of the noradrenergic system.

Table 1 Comparison of New and Conventional Antidepressant Drugs

	Tricyclic antidepressants	SSRIs	SNRIs
Efficiency rate	About 70%	About 70%	About 70%
Fast-acting property	None	None	None
Anticholinergic side effects	Strong	Almost none	Almost none
Adverse effects on digestive system such as nausea	Almost none	Rather marked	Slight
Interaction with other drugs	Almost insignificant	Significant in some cases	Not significant
Effects on diseases other than depression	Some are effective for panic disorder and obsessive-compulsive disorder.	There is corroborative evidence of efficacy for panic disorder and obsessive-compulsive disorder.	Efficacy for some anxiety disorders has been suggested.

Some studies have found SNRIs superior to SSRIs in clinical efficacy, and meta-analytical data has demonstrated this superiority. These data indicate that the aim of SNRI development has been achieved. However, most Japanese clinicians are under the impression that tricyclic antidepressants, SSRIs, and SNRIs are almost equal in efficacy, rather than considering SNRIs superior to SSRIs or tricyclic antidepressants. Nevertheless, SNRIs are reassuring because they do not carry the risk of interaction with other drugs, unlike SSRIs. This may well be considered the greatest advantage of SNRIs.

SNRIs have only a short history of use in Japan and elsewhere, and their true value, including optimal administration, remains to be established. To summarize the standard usage of milnacipran, therapy should begin with a low daily dose of 50 mg, which should be increased to 100 mg in 1 week unless there are particular adverse reactions, with maintenance at the same level for about 3 weeks. Although the package insert for this drug specifies 100 mg as the upper limit, some physicians suggest that a dose of 150 mg is more effective in actual clinical

use. Since SNRIs have almost no interactions with other drugs, it seems easier to use SNRIs than SSRIs in combination with tricyclic antidepressants when the patient has not responded favorably to the maximum dose regimen. However, sufficient data on the efficacy of this combination have yet to be obtained.

### Expansion of Indications for SSRI and SNRI Therapy

Finally, increasing indications for treatment with these new antidepressant drugs will be discussed briefly. Antidepressant drugs are, of course, mainly indicated for depression. However, it has been indicated that both SSRIs and SNRIs are effective for anxiety disorders. Thus, the indications of their use are expanding. The use of fluvoxamine, an SSRI antidepressant, for obsessive-compulsive disorder, and the use of paroxetine, another SSRI, for panic disorder are currently covered by the national health insurance in Japan. The efficacy of SSRIs for post-traumatic stress disorder (PTSD) and anthropophobia has been suggested by a number of papers published in

Europe and North America. In these regions, the efficacy of SNRIs for generalized anxiety disorder has also been emphasized.

These anxiety disorders have commonly been treated with antianxiety drugs such as benzodiazepine derivatives. However, it is likely that SSRIs and SNRIs will become the main therapeutic choice in these cases. If so, the problem of psychological dependence on benzodiazepine derivatives may be greatly reduced. Hope is being placed on the new antidepressants in this regard. Table 1 summarizes the properties of tricyclic, SSRI, and SNRI antidepressants.

## REFERENCES

- 1) Nomura, S.: Drug treatment of mood disorder. *Seishin Shinkeigaku Zasshi* 2001; 103: 1041–1045. (in Japanese)
- 2) Nomura, S.: Has a new class of antidepressant drugs caused progress in drug treatment? *Rinsho Seishin Yakuri* 2002; 5: 671–678. (in Japanese)
- 3) Nomura, S.: Combined use of multiple antidepressant drugs. *Rinsho Seishin Yakuri* 2002; 5: 863–867. (in Japanese)
- 4) Nomura, S.: Expansion of indications for psychotropic drug therapy: specificity and nonspecificity of psychotropic drugs. *Rinsho Seishin Yakuri* 1999; 2: 543–552. (in Japanese)

# The Characteristics and Application of New Antipsychotic Drugs

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**Abstract:** The characteristics of new antipsychotic drugs (atypical antipsychotic drugs) and their effective use are discussed. Atypical antipsychotic drugs can be considered modified drugs that resulted when the dopamine D<sub>2</sub> receptor-blocking effect of typical antipsychotic drugs was either lowered in affinity or combined with effects on other receptors (serotonin 5-HT<sub>2A</sub> receptor-blocking effect in particular). Such pharmacological development has contributed to an improved clinical effect and minimization of extrapyramidal symptoms (EPS). In order to reap these benefits, the high-dose polypharmacy that used to be common on the clinical scene has to be revised to the use of a single drug that keeps the D<sub>2</sub> receptor occupancy rate at a range of approximately 70%. If additional sedation or greater efficacy is required, mood stabilizers, anxiolytics or selective serotonin-reuptake inhibitors (SSRIs) may be coadministered with the atypical antipsychotic drug. Such a drug combination is practical, because it maintains the characteristics of the atypical antipsychotic drug. It is also important to not only emphasize the effects on the psychopathology, but also the gradual change in such parameters as the quality of life.

**Key words:** Schizophrenia; Atypical antipsychotics; Monopharmacy; Appropriate dose

## Introduction

It goes without saying that antipsychotic drugs play an important role in the treatment of schizophrenia. The emergence of these drugs has enabled many patients to be rehabilitated back into the society. Furthermore, in recent

years new antipsychotic drugs called atypical antipsychotic drugs have appeared on the clinical scene one after another (Table 1).

One may say that these drugs not only signify pharmacological novelty, but their clinical effect may also alter the conventional philosophy concerning treatment.

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Table 1 Atypical Antipsychotic Drugs Used in Japan

Risperidone
Perospirone
Quetiapine
Olanzapine

Table 2 The Binding Affinity of Olanzapine and Other Antipsychotic Drugs to Each Neurotransmitter Receptor

Neurotransmitter receptors Drugs	D1	D2	D4.2	5-HT <sub>2A</sub>	5-HT <sub>2C</sub>	α <sub>1</sub>	α <sub>2</sub>	musc	H <sub>1</sub>
	ki, nM								
Olanzapine	250	17	28	1.9	7.1	19	230	26	3.5
Clozapine	540	150	40	3.3	13	7	160	34	2.1
Risperidone	620	3.3	16	0.16	63	2	7.5	>5,000	2.6
Ziprasidone	330	9.7	39	0.3	13	7	390	>5,000	5.3
Sertindole	210	7.4	21	0.85	1.3	1.4	1,680	>5,000	570
Quetiapine	4,240	310	1,600	120	3,820	7	87	1,020	19
Zotepine	84	13	39	0.9	2.9	3.4	960	550	3.4
Perospirone (SM-9018)	41	1.4	ND	0.61	ND	17	408	>1,000	ND
Aripiprazole (OPC-14597)	5,100	0.8*	259	20	ND	ND	ND	ND	ND
Chlorpromazine	32	3.2	37	2	27	4.3	710	174	15
Haloperidol	270	1.4	11	25	>5,000	46	>5,000	4,670	730

ki = dissociation constant nM = 50% inhibition value ND = Not determined

\*Kikuchi, T., Tottori, K., Uwahodo, Y. *et al.*: *JPET* 1995; 274: 329–336.

(Cited from Bymaster, F.P. *et al.*: *Japanese Journal of Clinical Psychopharmacology* 1999; 2: 885–911)

In this article, the characteristics of atypical antipsychotic drugs and their effective applications are discussed.

### The Pharmacological Characteristics of Atypical Antipsychotic Drugs<sup>1)</sup>

Although atypical antipsychotic drugs are new, their central pharmacological action, like that of the typical antipsychotic drugs, e.g. haloperidol, which had been used until now, is full dopamine D<sub>2</sub> receptor blocking. Thus, atypical antipsychotic drugs may be considered improved drugs. This improvement involves potent serotonin 5-HT<sub>2A</sub> receptor blocking, which is common to all atypical antipsychotic drugs (Table 2<sup>2)</sup>). “Atypicality” is a clinical concept, and the

main pharmacological actions that identify it are as follows:

Since serotonin neurons have an inhibitory action on dopamine neurons via the 5-HT<sub>2A</sub> receptors, it can be considered that the inhibition of 5-HT<sub>2A</sub> receptors disinhibits the dopamine neurons, thus modulating the too potent dopamine D<sub>2</sub> receptor blocking (Fig. 1<sup>3)</sup>). This effect is extremely important, not only because it directly explains the decreased extrapyramidal symptoms (EPS) with atypical antipsychotic drugs, but also because it suggests that less potent D<sub>2</sub> receptor blocking produces a clinically preferable effect.

In addition, 5-HT<sub>2A</sub> receptor blocking is believed to have an anxiolytic action and to enhance deep sleep; while antihistamine H<sub>1</sub>

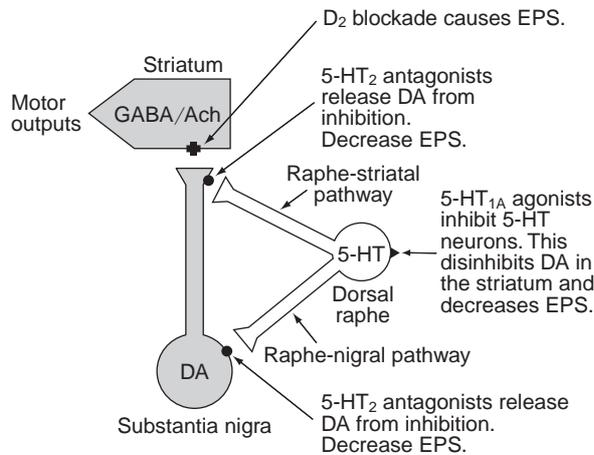


Fig. 1 Functional interactions between the serotonin-dopamine systems and their role in reducing extrapyramidal symptoms

This figure is a schematic representation of the mechanism and consequences of the interaction between serotonin and dopamine at the level of the substantia nigra and the striatum. 5-HT<sub>2</sub> antagonists and the 5-HT<sub>1A</sub> autoreceptor agonists inhibit the serotonin system and thus release the dopamine system from this inhibition (disinhibition of the dopamine system). The release of the dopamine system from serotonergic inhibition ameliorates extrapyramidal symptoms.

DA: dopamine neurons, 5-HT: serotonin neurons, GABA:  $\gamma$ -aminobutyric acid neurons, Ach: cholinergic interneurons,  $\blacksquare$ : D<sub>2</sub> dopamine receptors,  $\bullet$ : 5-HT<sub>2</sub> receptors,  $\blacktriangle$ : 5-HT<sub>1A</sub> receptors

(Japanese translation by Murphy, T.: Serotonin-dopamine interaction and its relevance to schizophrenia. *Japanese Journal of Psychiatric Treatment* 1996; 11: 1105–1118)

(Cited from Kapur, S. *et al.*: *Am J Psychiatry* 1996; 153: 466–476)

receptor blocking by olanzapine may enhance anxiolytic/sedative actions. The weak affinity of quetiapine for D<sub>2</sub> receptors in turn signifies that this drug is easily dissociated once it binds to receptors; which in turn suggests that “less potent” action is associated with higher efficacy.

## The Clinical Pharmacological Characteristics of Atypical Antipsychotic Drugs<sup>4-6</sup> (Table 3)

### 1. Effects

#### (1) Short-term effects

Reports of clinical trial results that examined the effects of atypical antipsychotic drugs over several weeks showed that the efficacy with

regards to positive symptoms was equivalent to or greater than that with typical antipsychotic drugs. Most reports also showed that atypical antipsychotic drugs show superior efficacy with regard to negative symptoms.

Furthermore, some atypical antipsychotic drugs were reported to have anxiolytic and antidepressant effects. Many also demonstrated superior efficacy to improve sleep.

#### (2) Long-term effects

It is desirable that antipsychotic drugs have excellent long-term effects, and the short-term effects of atypical antipsychotic drugs can be maintained with long-term administration. As a result, it is highly effective in preventing recurrence, lowering the re-hospitalization rate, and thus improving the quality of life (QOL) and social functions, as expressed in terms of increased work rate etc. Superior efficacy on cognitive functions is considered to form the background.

### 2. Adverse reactions

EPS effects, which define typical antipsychotic drugs, were weak with all the atypical antipsychotic drugs. Consequently, the concept that these effects are inevitable side effects of antipsychotic drugs is rapidly disappearing. In addition, not only the incidence of acute reversible EPS, but also that of tardive dyskinesia (TD) were decreased, and it was even reported that some atypical antipsychotic drugs improve existing TD. Elevation of the prolactin level is also decreased with all the new drugs, excluding risperidone.

On the other hand, the new drugs cause new problems with such adverse reactions as body weight gain and decreased glucose tolerance; thus, the new drugs are not completely free of safety issues. It was reported that, compared with haloperidol, body weight gain was greater with all the new drugs, especially olanzapine, followed by quetiapine (the data on perospirone are not available). With olanzapine, hyperglycemia, diabetic ketoacidosis, and diabetic coma were reported in 9 patients, includ-

Table 3 The Clinical Pharmacological Characteristics of Atypical Antipsychotic Drugs

1. Effects
(1) Short-term effects
• Positive symptoms: equivalent to or greater than that of typical antipsychotic drugs
• Negative symptoms: greater than that of typical antipsychotic drugs
• Anxiolytic effects, antidepressant effect, and possibility to improve sleep
(2) Long-term effects
• Maintenance of the short-term effects
• Highly preventive effect on recurrence
• Highly beneficial effect on QOL
• Highly beneficial effect on cognitive functions
2. Adverse Reactions
• Reduced the incidence of EPS (extrapyramidal symptoms) and TD (tardive dyskinesia)
• Lowered the elevated levels of prolactin (excluding risperidone)
• Risk of body weight gain and decreased glucose tolerance
(The administration of olanzapine is prohibited in patients with diabetes or a history of diabetes.)

ing 2 cases of death. The Emergency Safety Notification that was issued to prohibit patients with diabetes or a history of diabetes from taking this drug is still fresh in the memory. (The same measures have been taken for quetiapine too after this lecture was broadcasted.)

## The Effective Use of Atypical Antipsychotic Drugs

Taking the above-mentioned clinical pharmacological properties and underlying pharmacological mechanisms of the atypical antipsychotics into consideration, it is clear that, if the present treatment is exchanged for atypical antipsychotics by the mere mechanical action of changing the prescription, their benefits would not be fully reaped. The purpose of the drug therapy has to be reconsidered.

### 1. Reconsidering antipsychotic drug treatment<sup>7)</sup>

With the new drugs, the importance of D<sub>2</sub> receptor blocking as the central pharmacological action remains the same. It seems that its psychobiological significance is to recover the functions of dopamine neurons as a stress buffering system. Therefore, antipsychotic drugs help schizophrenic patients who suffer a mental crisis to recover. It can be said that this concept is supported even stronger by the new

drugs, which cause greater improvement by modulating the too potent action of full dopamine D<sub>2</sub> antagonism.

The idea of drug therapy for schizophrenia should be regarded as an aid for recovery and the principles that govern it are the same as those of rehabilitation. Also, in terms of evaluating the treatment, one should not depend on the psychopathological symptoms, but instead emphasize the gradually changing parameters such as QOL.

Some misunderstanding concerning conventional therapy has been noticed in this regard. It is known that a D<sub>2</sub> receptor occupancy rate of approximately 70% is the most effective rate for antipsychotic drugs. This is also achieved with haloperidol at doses of less than 10mg, and almost no sedation occurs at this dose. In contrast, doses that obviously cause sedation, exceed a 70% occupancy rate, increase the adverse reactions and prevent recovery. Hence, attempting to achieve sedation with antipsychotic drugs is counter-productive. This is why high-dose therapy has been criticized.

Furthermore, since the antipsychotic drug sets the recovery mechanism in motion, thus causing relief of the mental crisis which can be observed based on the disappearance of symptoms, there is absolutely no rationale for polypharmacy with several antipsychotic drugs. Until now people had various misconceptions,

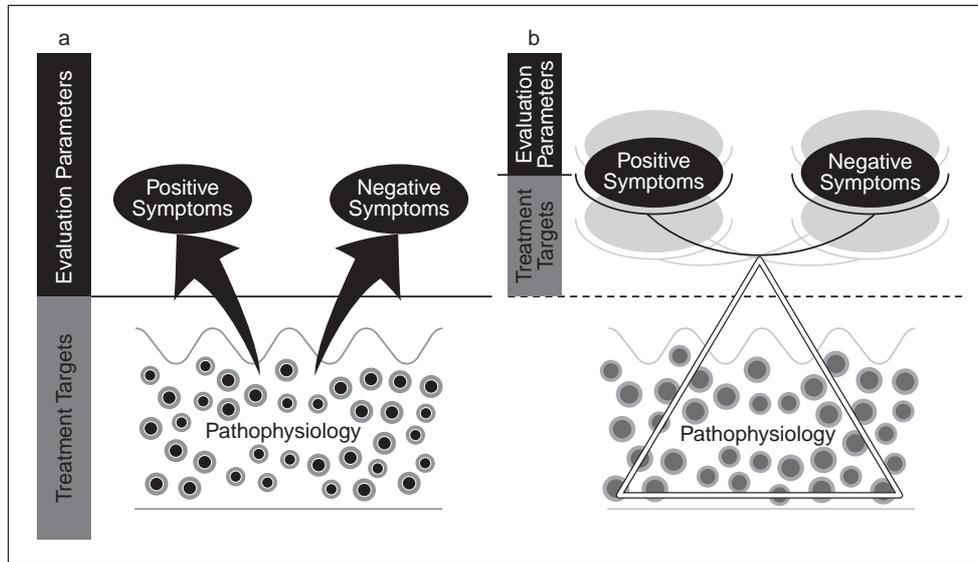


Fig. 2 Relationship between target symptoms and treatment targets

- a: The symptoms we observe are the result of the pathophysiology of schizophrenia. The target symptoms are the evaluation parameters for selecting a drug and evaluating the success or failure of the treatment, but the target of the drug itself is the pathophysiology.
  - b: However, the pathophysiology, which is the actual target of the drug, is forgotten now, and the target symptoms, which are mere evaluation parameters, are simultaneously mistaken as the target of drug treatment. Also, the concept of drug types based on sedation/activation is linked to the typifying of positive and negative symptoms, and these are believed to have a seesaw-like relationship.
- (Cited from Ishigooka, J.: *Schizophrenia Frontier* 2001; 2: 234–238)

for example, the concept of symptomatic treatment, which supposes that the target of the drugs is the symptoms; the typification of drugs as either causing “sedation” or “activation”; the idea that when negative symptoms improve, positive symptoms become aggravated; as well as the idea that therapy with typical antipsychotics is not effective against negative symptoms (Fig. 2<sup>8)</sup>).

## 2. Skillful polypharmacy<sup>8)</sup>

As mentioned above, in the present age of atypical antipsychotic drugs, the philosophy behind drug therapy must be modified, and if the necessary techniques are not available, it will not be possible to apply the practical medical art of treatment. In particular, the management of excitement is an urgent issue on the medical scene, but methods other than multiple antipsychotic drugs should be found.

One solution to this problem is drug ther-

Table 4 Adjuvant Therapeutic Drugs Used for Schizophrenia

1. Mood stabilizers
Lithium carbonate, valproic acid, carbamazepine, and clonazepam
2. Anxiolytics
3. Selective serotonin-reuptake inhibitors

apy called “skillful polypharmacy” that effectively employs adjuvant therapeutic drugs such as mood stabilizers, anxiolytics and selective serotonin-reuptake inhibitors (SSRIs) (Table 4). The fact that lorazepam is intramuscularly administered for sedation in Europe and the United States, may be derived from this concept.

The adjuvant therapeutic drugs mentioned here are not only known for their pharmacologically easily evaluable effects on such disorders as excitement, agitation, and unstable mood, but also for augmenting the effects of

other antipsychotic drugs when coadministered. Nonetheless, sufficient research has not been conducted on the predictors that determine which concomitant drugs are appropriate for which patients with their specific clinical attributes. At this point clinicians mostly depend on trial and error.

## Conclusion

The characteristics of the new antipsychotic drugs called atypical antipsychotic drugs and their effective use were discussed. In order to optimize the benefits of these drugs, it is necessary to see a change in the concept of drug therapy for schizophrenia and clinicians need to obtain appropriate prescription skills. I hope this article will contribute to the proper treatment of patients.

## REFERENCES

- 1) Ishigooka, J.: Pharmacological action of atypical antipsychotics. *Brain 21* 2000; 3: 332–338. (in Japanese)
- 2) Bymaster, F.P., Moore, N.A. and Nakazawa, T.: Review of the preclinical pharmacology of olanzapine: a MARTA class antipsychotic. *Japanese Journal of Clinical Psychopharmacology* 1999; 2: 885–911. (in Japanese)
- 3) Kapur, S. and Remington, G.: Serotonin-dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry* 1996; 153: 466–476.
- 4) Ishigooka, J.: Impact of atypical antipsychotic drugs on the treatment of patients with schizophrenia. *Japanese Journal of Clinical Psychopharmacology* 1998; 1: 47–59. (in Japanese)
- 5) Ishigooka, J. and Inada, K.: Trends in the clinical development of the second generation antipsychotics. *Japanese Journal of Clinical Psychopharmacology* 2001; 4: 1653–1664. (in Japanese)
- 6) Ishigooka, J. and Yoshioka, M.: QOL (quality of life)-oriented pharmacotherapy in schizophrenia. *Japanese Journal of Clinical Psychopharmacology* 2002; 5: 3–13. (in Japanese)
- 7) Ishigooka, J.: Integration of drug therapy and rehabilitation for treating schizophrenic patients. *Psychiatric Disorder and Rehabilitation* 1998; 2: 133–140. (in Japanese)
- 8) Ishigooka, J.: Skillful polypharmacy beyond monotherapy. *Schizophrenia Frontier* 2001; 2: 234–238. (in Japanese)

# Technologies in Support of Regenerative Medicine

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**Abstract:** Regenerative medicine is a method aimed at improving the patient's regenerative abilities, primarily of stem cells, or a method consisting of tissue regeneration *in vitro* with stem cells and transplantation of the regenerated tissue. This article briefly reviews engineering technologies which lend support to regenerative medicine, with illustrative examples including the following. (1) Biodegradable-absorbable materials: A mandibula-shaped mesh tray is prepared with poly-L-lactide fibers, followed by transplantation of a marrow-cancellous bone fragment autograft placed in the tray to accomplish lower jaw bone regeneration. (2) Culture technique: Incubation of chondrocytes in culture under adequate mechanical stimuli enables regeneration of cartilaginous tissue with mechanical properties closer to those of natural articular cartilages. (3) Immunoisolation: For treatment of diabetes mellitus using insulin-producing cells differentiated/induced from embryonic stem cells, a method whereby the cells are encapsulated with a high polymer membrane to avoid graft rejection and then transplanted. (4) Cell transplantation devices: Investigations for development of minimally invasive grafting devices are in progress for use in cell transplantation therapy for diabetes mellitus and for myocardial infarction.

**Key words:** Regenerative medicine; Tissue engineering; Degradable-absorbable material; Tissue regeneration; Cell arrays

## Introduction

There is a little confusion concerning terminology because of the widely different backgrounds of researchers participating in this field of science. The term regenerative medicine is preferred among physicians and bio-

logists, whereas surgeons and biomedical engineers tend to use the term tissue engineering. Embryonic stem (ES) cells have been drawing increasing attention as omnipotent cells, but tissue derived ES cells have not been used in clinical trials. On the other hand, cell sheets prepared from cultures of skin cells are already

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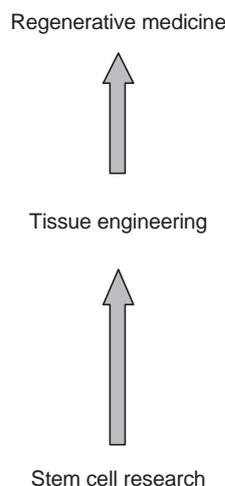


Fig. 1 Interrelation of regenerative medicine-related fields

commercially available for therapeutic use in the United States. Typically, the former exemplifies a prospective feature of this science while the latter represents an actual accomplishment.

The interrelation of regenerative medicine and tissue engineering may be envisaged as illustrated in Fig. 1. A basic scenario would be that development of stem cell research renders it feasible to obtain functional cells, which would be combined with biomedical materials by applying tissue engineering techniques and made into therapeutic devices for use in regenerative medicine.

In the case of skin, fortunately, epidermal cells are endowed with a noticeably high proliferative potential, so that epidermal cell sheets are prepared with relative ease by allowing the cells to grow in petri dishes. Consequently, clinical application of these cell sheets began as early as 1981,<sup>1)</sup> and many start-ups began merchandizing them early in the 1990s in the United States. For many other tissues and organs, however, it was not until the development of stem cell research in recent years that cells playing central functional roles became available in sufficient quantities.

This article briefly reviews the key technologies with primary reference to tissue engineering research.

## Key Technologies

Key tissue engineering technologies that are required for regenerative medicine are shown in Fig. 2.

### 1. Scaffold made of biodegradable materials for tissue construction

An actual example I would like to present here is a published clinical research on regeneration of the mandible.<sup>2)</sup> The investigators performed regeneration of the mandible in a patient. A mandibula-shaped mesh tray was prepared with poly-L-lactide fibers, a biodegradable material. Autologous iliac marrow-cancellous bone fragments were then placed in the tray, and then it was transplanted to the area of the lower jaw. The report said that satisfactory mandible regeneration was observed two years after the grafting.

Meanwhile, the poly-L-lactide mesh tray was gradually hydrolyzed and absorbed into the body. Other tissues heretofore subjected to regeneration *in vivo* by such methods reportedly include the venous vasculature, peripheral nerves, skin, and many other tissues such as cartilage of the external ear and nasal crest, meniscus, digital bones, ureter, and urinary bladder. All share the common approach of shaping the tissue or organ intended to be regenerated using a biodegradable material which eventually disappears within the body, and cells from which the target tissue or organ regenerates are then seeded, followed by return of the graft into the body to wait for proliferation of the seeded cells and regeneration of the tissue or organ.

The key to this technique is the biodegradable material. Poly-L-lactide was used for regeneration of the mandibula. Poly-L-lactide is a high polymer composed of a number of lactic acid molecules combined via ester bonds, which is gradually hydrolyzed to lactic acid when left for several months in a water-abundant milieu like the mammalian body. The lactic acid thus generated is further metabolized to

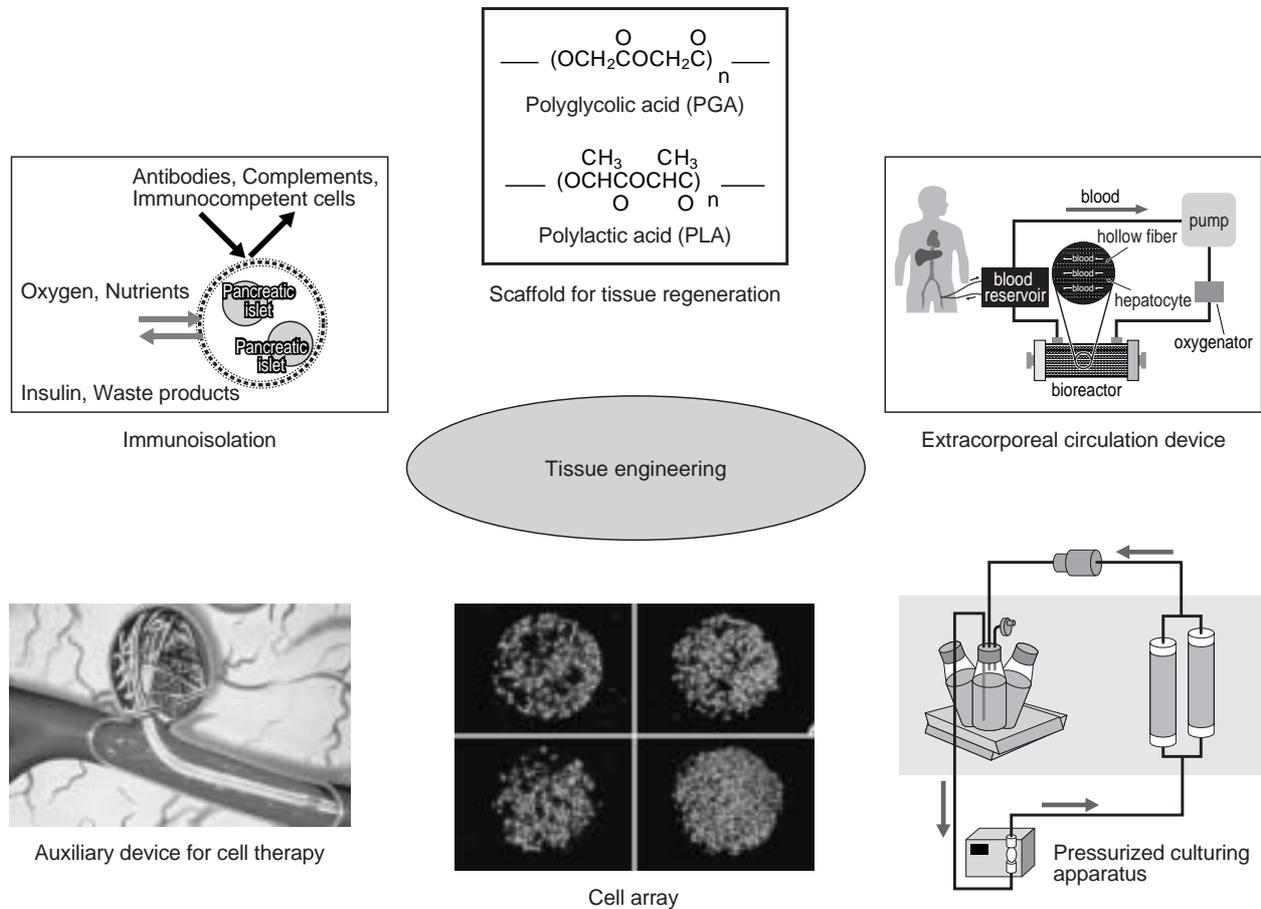


Fig. 2 Key technologies in tissue engineering

carbon dioxide gas and water, which are eliminated from the body. In the field of medical care, poly-L-lactide is not new and has been used in absorbable surgical sutures for many decades. Incidentally, poly-L-lactide has been drawing attention as an ecofriendly material and is about to be used to make daily necessities such as plastic bags. Such items for daily use will gradually decompose to lactic acid and then to carbon dioxide gas and water and will eventually disappear even when discarded outdoors.

I have given above an actual example of regenerating body tissue. Different tissues vary in softness and the rate at which they are regenerated. Copolymers of lactic acid with glycolic acid have been synthesized to control the rate

of decomposition, while copolymers of lactic acid with caprolactone are used when softness is required. Cloth, nonwoven fabrics and sheets have been manufactured from these synthetic polymers.

Synthetic polymers are suitable for mass production under uniform standards, but are problematic in terms of compatibility with the body. Materials of biological origin such as gelatin, collagen, fibrinogen, and hyaluronic acid are being used as biodegradable materials more compatible with body tissues. Recently, the human amnion has been examined in regenerative medicine as it contains a number of cell growth factors that promote cell proliferation. These materials of biological origin do possess remarkably favorable properties of

which synthetic polymers are devoid, but on the other hand, have the risk of being contaminated with viruses or prions, thus requiring scrupulous quality control.

## 2. Cultivation apparatus simulating the internal milieu formation

Attempts to regenerate tissues of the skeletal system by merely growing cells within a framework fail to yield a tissue system possessing mechanical properties sufficient to permit their use in treatment. The implication was derived from the fact that astronauts experience loss of skeletal and muscular strength if they remain in zero gravity over a long period. Adequate mechanical stimuli must be given. Figure 2 shows an apparatus used for *in vitro* regeneration of cartilaginous tissue. The apparatus enables chondrocyte culturing with pulse pressurization at 5 Mpa, mimicking the load imposed on the cartilage by walking. The cultivation of cells under the cyclic pressurization has been documented to endow the regenerating cartilaginous tissue with fine structures and mechanical properties closer to those of articular cartilages.

Bioengineering research to develop *in vitro* tissue regeneration apparatuses simulating the biological internal milieu must be promoted. Furthermore, it is also important to conduct research on how to secure the compatibility of the regenerated tissue with the host tissue after implantation.

## 3. Immunoisolation

As mentioned above, clinical evaluation of regenerated tissue is in progress for most of the types of tissues for which oxygen demand is relatively modest. The next goal of regenerative medicine is diseases that may be treated by transplanting cells that secrete bioactive substances, such as type I diabetes mellitus and Parkinson's disease.

Recently, it has been demonstrated that pluripotent stem cells are found in adult mice and in adult humans; there is increasing hope

for regenerative medicine using the patient's own cells. However, residual stem cells that would constitute the basis for regeneration usually fall short of expectations in the above-mentioned disorders, and it would be more practical to use functional cells derived by differentiation from allogeneic human embryonic stem cells or ES cells in treatment. In such instances, nevertheless, cells to be transplanted must be modified so as to prevent rejection when transplanted in the patient. One of the methods used for this purpose is immunoisolation.

Organs/tissues that anatomically are scarcely perfused with lymph drainage, such as the brain, cornea, and hamster buccal pouch, respond rather poorly immunologically and are therefore vulnerable to growth of xeno- or allogeneic tumor transplants. These organs/tissues are thus recognized as immunologically privileged sites. Studies have been undertaken to artificially prepare a privileged site within the patient's body using semipermeable macromolecular membranes and to explore the feasibility of treatment by transplanting bioactive substance-secreting cells into the said site.

Such semipermeable membranes must be capable of inhibiting contact between the immunocompetent cells and transplanted cells, and if possible, should inhibit entrance of patient's antibodies and complement proteins to the transplant compartment. At the same time, the membrane should permit free passage of oxygen and nutrients needed for survival of the transplanted cells, as well as bioactive substances generated and waste substances discharged by those cells. It has been reported, for example, that blood glucose levels of diabetic mice were normalized over a long period using an agarose capsule containing pancreatic islet transplants.<sup>3)</sup>

A group of researchers in the United States planned to transplant porcine pancreatic islets of Langerhans encapsulated with semipermeable membrane into diabetes mellitus patients several years ago. In Japan, the Department of

Neurological Surgery of Okayama University Medical School planned to transplant PC12 cells, mouse dopamine-producing cells, enclosed in semipermeable membrane capsules into the brains of patients with Parkinson's disease. The plan was approved by the university's institutional review board. However, neither clinical trial has begun due to safety concerns about grafting animal cells into humans.

With the recent progress of research on stem cells, represented by the establishment of the human ES cell line, it has become feasible to secure large quantities of human cells that produce insulin or dopamine. As a result, increasing attention has again been focused on treating diabetes mellitus and Parkinson's disease using these immunoisolation techniques.

#### **4. Extracorporeal circulation devices**

It has long been recognized that the liver is an organ highly capable of regeneration. In cases of fulminant hepatitis, regeneration of the patient's own liver may be anticipated if the critical stage of the disease can be weathered via assisted hepatic functions. As the liver performs diverse functions, nevertheless, the use of liver function auxiliary devices consisting solely of artificial components has not provided satisfactory therapeutic outcomes. In view of this, development of an extracorporeal circulation device containing hepatocytes as a functional component, i.e., a bioartificial liver, has been progressing. Clinical trials of a device utilizing porcine hepatocytes have been conducted on nearly 200 patients in Europe and the United States, but the detailed outcomes have not been published yet. Researchers are looking forward to the results.

One function required for a bioartificial liver is supply of proteins of the blood coagulation system. As swine liver cells supply porcine proteins, there are problems regarding their antigenicity and function. Researchers hope to develop a bioartificial liver utilizing human hepatocytes upon success in production of large quantities of human liver cells from human

hepatic stem cells or from human ES cells. Further, they hope to regenerate the liver by hepatocyte transplantation.

#### **5. Auxiliary devices for cell therapy**

The basic principle of regenerative medicine lies in enabling cures in a more natural fashion. Minimally invasive procedures are necessary in regenerative medicine. Figure 2 shows a schematic representation of minimally invasive therapy using a catheter for intracranial aneurysms. The treatment is designed to induce thrombosis within the aneurysm by placing platinum coils and to also promote progression into connective tissue to seal up the saccular dilatation. Regeneration of the vessel wall at the orifice to the aneurysm would be more desirable. Development of a device that enables vascular wall regeneration by local injection of a vascular endothelial growth factor or vascular endothelial cells *per se* is anticipated.

A little more progress has been made in the treatment of ischemic heart diseases. Attempts have been made to use regenerative medicine for myocardial infarctions by injecting a vascular endothelial growth factor gene from the cardiac lumen via catheterization.<sup>4)</sup> The device used is an electromechanical mapping system (NOGA system). The device, which has been used for other therapeutic purposes, is used because research in regenerative medicine is still in an early stage. Development of highly specialized devices for regenerative medicine is looked forward to.

#### **6. Cell array**

Fusion of stem cell research and nanotechnology is being planned. Cell arrays are shown in part as an example of the development of this fusion in Fig. 2. Viable cells are put onto numerous spots on the plate using ultra-fine processing technology (nanotechnology). This technique may possibly lead to great changes in areas ranging from gene function analysis to clinical laboratory tests, but here I would like to examine its possible use in

regenerative medicine.

With the progress in research on ES cells expected in the near future, it will become feasible to obtain important differentiated cells constituting the human body out of human ES cells. By sprinkling a drug candidate compound over an array of such differentiated cells, it may be possible to use a very minute quantity of the compound to determine effects which the compound exerts. In other words, drug screening systems with human cells can be constructed. ES cells are processed for gene modifications, then induced to develop into differentiated cells, and arrayed on plates. The cell arrays enable preparation of genetic disease model panels and single-nucleotide polymorphism panels.

## Conclusion

This article has briefly reviewed the wide spectrum of technologies in tissue engineering ranging from tissue regeneration with degradable-absorbable materials, on which clinical studies have progressed considerably, to possible cell array technology. In our country, there are few or no engineers working in the field of stem cell research essential for supplying cells for tissue engineering. Stem cell research is of vital importance to the fate of regenerative

medicine. Since stem cell research is an interdisciplinary field of science where much remains to be clarified even biologically, e.g., selection of cells, development of milieus to maintain and grow stem cells, and development of milieus to induce stem cell differentiation, engineers will have much difficulty in carrying out the research. Yet, this field of research must be pursued.

## REFERENCES

- 1) O'Connor, N.E., Mulliken, J.B., Banks-Schlegel, S. *et al.*: Grafting of burns with cultured epithelium prepared from autologous epidermal cells. *Lancet* 1981; 1: 75–78.
- 2) Kinoshita, Y., Amagasa, T., Ogura, I. *et al.*: Reconstruction of the mandible with poly (L-lactide) mesh tray/sheet and transplantation of particulate cancellous bone and marrow. *Int J Oral Maxillofac Surg* 1999; 28(Suppl 1): 161.
- 3) Iwata, H., Takagi, T., Amemiya, H. *et al.*: Agarose for a bioartificial pancreas. *J Biomed Mater Res* 1992; 26(7): 967–977.
- 4) Losordo, D.W., Vale, P.R., Hendel, R.C. *et al.*: Phase 1/2 placebo-controlled, double-blind, dose-escalating trial of myocardial vascular endothelial growth factor 2 gene transfer by catheter delivery in patients with chronic myocardial ischemia. *Circulation* 2002; 105(17): 2012–2018.

# Regenerative Medical Care for Peripheral Nerves

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**Abstract:** In case of a peripheral nerve injury that did not permit instantaneous direct anastomosis, autologous nerve grafting was the only available corrective measure, yet the clinical results were far from satisfactory. Meanwhile, studies on artificial nerve conduits have been pursued from the beginning of the 1980s, and there has been a steady development of artificial nerve conduits capable of meeting clinical needs thanks to progress in tissue engineering. In 2002, PGA-collagen composite nerve conduits filled with collagen sponge were put to clinical use. The therapeutic outcome with the new nerve conduit was far more satisfactory as compared to nerve autografting. Regarding artificial nerve conduit transplantation, further research on technical innovation and development of more improved nerve conduits are essential. Artificial nerve conduit transplantation must be performed in a large number of diverse clinical cases in the future. Important matters remain to be scrutinized in this regard, e.g., multicenter and multidisciplinary collaborative studies to explore the indications for the transplantation in individual cases and their possibilities or to probe their limits and contraindications.

**Key words:** Peripheral nerve regeneration; Artificial nerve; Collagen; Polyglycolic acid (PGA)

## Introduction

Cases of injuries to peripheral nerves of the extremities, fingers, toes or other regions caused by traumas due to traffic accidents or disasters and failing to attain repair have been increasing in recent years. There also exist no few cases where surgical resection of peripheral, i.e. somatic or autonomic, nerves is inevitable in association with such operations as cancer resection.

Bridging nerve gaps with venous segments or transplantation of cadaver nerve allografts have been clinically applied in previous years in the event of peripheral nerve severance or surgical resection permitting no instantaneous direct anastomosis. Therapeutic outcomes, however, were not satisfactory. Eventually, autologous nerve grafting was almost the only available corrective measure, yet the clinical results were not very satisfactory.

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Under this background, development of clinically usable artificial nerves has been increasingly sought. With the recent rapid progress in tissue engineering, new artificial nerve conduits have been developed and become applied in clinical settings. This article presents a brief review of this aspect of regenerative medical care.

## Regeneration of Peripheral Nerves

### 1. Structure of peripheral nerve

The peripheral nerve consists of the nerve fiber comprised primarily of an axon projecting from a hillock of the nerve cell body in the spinal cord, with covering myelin and Schwann sheaths, and Schwann cells, which constitute a basic unit of the neuron. The axon serves to conduct electrophysiological excitation of the nerve, i.e., nerve impulses, and also has the transporting function to supply various substances required for maintaining nerve functions and structure.

A bundle of nerve fibers constitutes a nerve trunk. An axon coursing peripherad out of a nerve trunk enters an effector organ, where it is branched and transmits function.

### 2. Tissue reactions at site of nerve trunk injury

In the event of an injury involving nerve trunk severance, a regenerating axon is usually inhibited by associated fibroblast proliferation. The regenerating axon consequently fails to reach the peripheral stump, eventually forms a neuroma and is deprived of its function. A regenerating axon that fortunately has reached the peripheral stump may undergo misdirection if it fails to reach its target organ.

The distal stump of a severed nerve incurs wallerian degeneration due to impaired axonal nutritive flow and loses its function.

### 3. Approaches to peripheral nerve regeneration

#### (1) Direct anastomosis

A one-stage direct anastomosis may effectu-

ate functional regeneration of a severed nerve if the nerve gap length is 5 mm or less, provided the anastomosed lesion is completely prevented from tension. Cases in which nerve anastomosis is practicable without any tension applied even if the gap is inconspicuous are rare in reality. Materials and methods to fill up nerve gaps have been sought.

#### (2) Objectives of reconstruction with the use of bridging materials

The purpose of the use of a joining device is to prevent intrusion of connective tissues from outside during the process of nerve bundle elongation or regeneration, to facilitate substance exchanges in and out of the joining device and capillary neovascularization on the joining device wall, and thereby to serve as a scaffold or to retain substances constituting a scaffold adequate for growth of the axon and Schwann cells within it. The following joining devices have been clinically applied.

##### i. Reconstruction with venous segment

A method of bridging nerve gaps by means of autologous venous segments has been applied for a long while but the regenerated nerves reported have been few because of poor vascular lumen retainability.

##### ii. Nerve autografting

The method is to transplant an autologous sensory nerve segment with relatively minor function into the lesion. In many of the cases treated by this technique, nevertheless, a fairly long period is required to recover nerve function and sensory nerve regeneration is sluggish, occasionally causing sensations of coldness and pain. Motor functional regeneration rates are often disappointing. New development of disorders at the site of an autologous sensory nerve graft presents another problem.

##### iii. Nerve allografting

In Europe and the United States, nerve grafts obtained from human cadavers are preserved frozen and used in clinical settings. With the progress in development of immunosuppressants since the 1990s, there have been considerable improvements in therapeutic out-

comes with this method. Regeneration of sensory function and motor function is evident following this procedure but requires a long period to attain it. Adverse reactions to immunosuppressants are a matter of practical concern above all, so the method has not been noticeably generalized.<sup>1)</sup>

## Peripheral Nerve Regeneration Using Artificial Nerve Conduits

### 1. Historical changes of artificial nerve tube

Attempts to regenerate severed peripheral nerves by bridging nerve gaps using nerve tubes made of artificial materials have been made for several decades. These devices have been changed and developed step by step. Significant improvement of artificial nerve tube has led to their current use in Japan.

### 2. Artificial nerve conduits made of nonabsorbable artificial materials

Beginning in the early 1980s, replacement surgery using artificial nerve conduits made of nonabsorbable materials such as silicone has been in practice for the treatment of severed nerves, and there are reports documenting partial recoveries with the technique.<sup>2)</sup> All these reports, however, are of studies demonstrating recovery in morphological continuity of a nerve with a gap as extremely small as about 10 mm in small laboratory animals such as rats, and recovery in motor function has rarely been achieved. The outcome was in no way superior to that of nerve autografting in any of the reported studies.

### 3. Artificial nerve conduits made of absorbable artificial materials

It became recognized from the latter half of the 1980s that degradable-absorbable materials in the body after attaining nerve regeneration are preferable.<sup>3)</sup> With the progress in material synthesis and bridging techniques, artificial nerve conduits made of absorbable synthetic materials have been developed. Sub-

stances such as polyglycolic acid (PGA) and polylactic acid are under investigation as biodegradable-absorbable synthetic materials.

### 4. Artificial nerve conduits made of absorbable natural materials

Since the beginning of the 1990s a number of reports describing that natural biomaterial collagen is satisfactory as a material for regeneration of various tissues/organs and is useful also for peripheral nerve regeneration.<sup>4)</sup> Thus, comparative experiments with artificial nerve conduits prepared comprising collagen extract alone versus autologous nerve grafting were performed. The results of the study with the conduits were comparable with those of nerve autografting, however, and the regenerated nerves were found much inferior to intact nerves.<sup>5)</sup>

## PGA-Collagen Composite Nerve Conduits

### 1. Hollow PGA-collagen composite nerve tube

Collagen is rich in active radicals that promote tissue regeneration but is so rapidly absorbed *in vivo* as to be unable by itself to retain its shape, tubular in this case, over a certain length of time. Therefore, novel artificial nerve tubes comprising collagen compounded with PGA, which is inferior to collagen in affinity with body tissues but capable of retaining its shape in the body for not less than 3 months, was developed to serve as a barrier against connective tissues in the mid-90s.<sup>6)</sup>

The tube applied for repairing the sciatic nerve in a cat proved to afford much improvement in surgical outcome, as compared with previous methods in terms of postoperative motor function and electrophysiological tests, along with the evidence of axonal transport beyond a nerve gap. However, the gap length was approximately 25 mm, which is insufficient for clinical application.

These experiments were carried out using

hollow tubes. As it takes a long time for a regenerating nerve to bridge a lengthy gap through a hollow tube lumen without footholds for reconstruction, the artificial nerve conduit may be biodegraded-absorbed in place and permit intrusion/growth of cicatrization tissue from outside before completing the bridging.

## 2. PGA-collagen composite nerve tubes filled with collagen fibers

For the above reason, the possibility of providing a scaffold comprising collagen for reconstruction through the hollow tube lumen was explored. A collagen fiber-filled, PGA-collagen composite artificial nerve conduit was prepared at the end of the 1990s and assessed by trying it in bridging an 80-mm gap by replacement neuroplasty of the fibular nerve in a dog.<sup>7)</sup>

The regenerated nerve was proven electrophysiologically to be virtually comparable with the intact nerves in both motor and sensory functions. Light and electron microscopic examination demonstrated morphologic evidence of regenerated thick nerve fibers and nerve trunk, and there was recovery in gait and jumping capacity.

## 3. PGA-collagen composite nerve tube filled with collagen sponge

In recent years, many published articles have stressed the importance of three-dimensional matrices.<sup>8)</sup> The present author and his coworkers developed a PGA-collagen composite nerve conduit filled with collagen sponge (Fig. 1) in 2000 on the rationale that three-dimensional structures would be superior to unidimensional structures such as fibers to serve as scaffolds for axonal elongation and Schwann cell proliferation.<sup>9)</sup> This nerve conduit has proven to be remarkably superior not only because of greater foothold and surface areas but also in industrial reproductivity.

In a canine peroneal nerve 80-mm gap bridging experimental study, the author and his associates assessed the sponge-filled conduit in comparison with the fiber-filled conduit, with

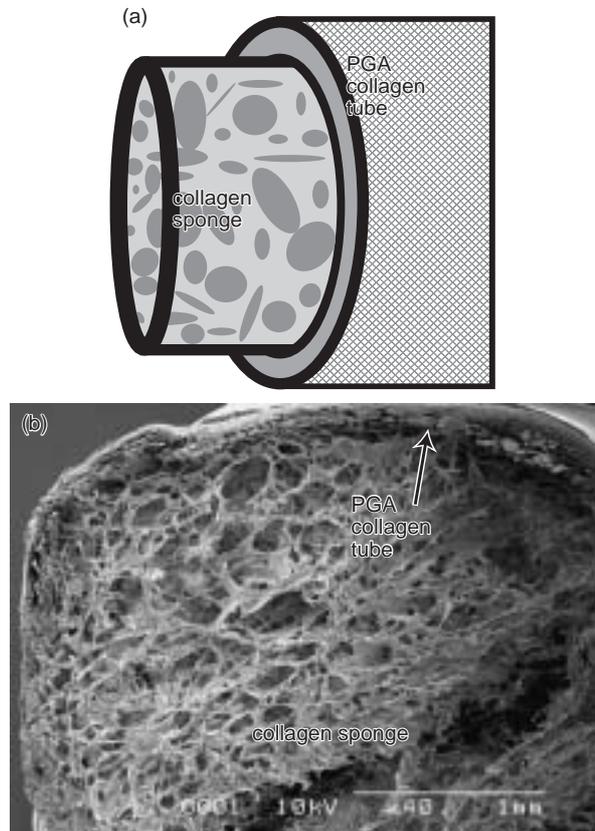


Fig. 1 PGA-collagen composite nerve conduit filled with collagen sponge  
(a) Schematic illustration (b) Electron micrograph ( $\times 40$ )  
The PGA-collagen composite conduit is filled with a three-dimensional sponge matrix.

the results demonstrating superiority of the sponge-filled conduit.<sup>9)</sup> Assessments of the regenerated nerve in various respects have shown highly potential clinical applicability of this new artificial nerve conduit.<sup>10)</sup>

## Present Status of Medical Care for Peripheral Nerve Regeneration

### 1. Controlled release of growth factors, etc.

In the event of a local injury, growth factors are released spontaneously at the site of the injury. Artificially added growth factors may accelerate tissue regeneration at the injury site. The author and his associates make it a rule to intraoperatively add laminin from the

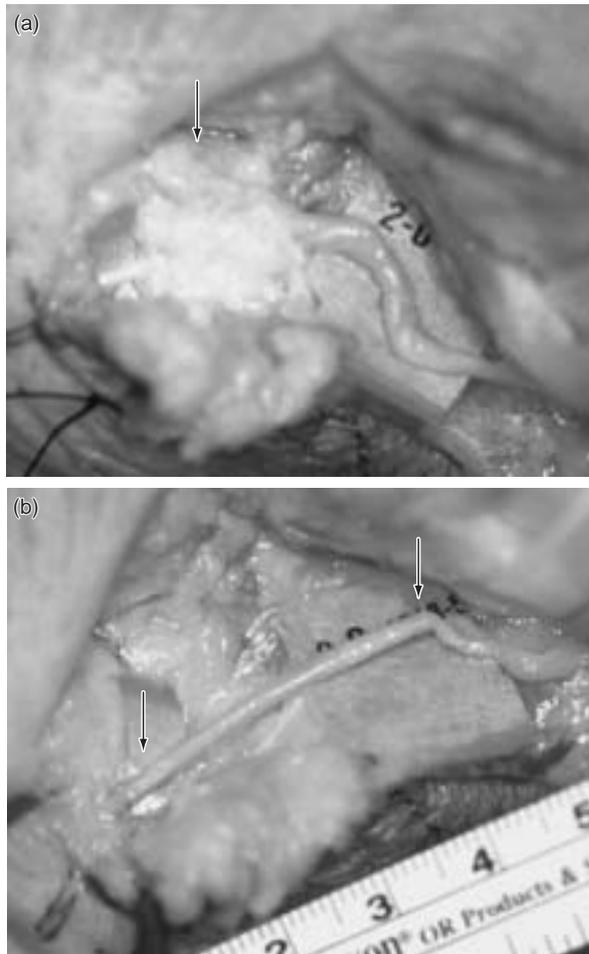


Fig. 2 An operation performed on a 53-year-old man (Courtesy of Dr. Inada, Lecturer, Nara Medical University) (a) The patient incurred an injury involving a crushed heel and severance of the posterior tibial nerve three years before. A neuroma ( $\downarrow$ ) formed in due course. (b) Upon resection of the tumor, the severed nerve lesion was replaced with an artificial nerve conduit about 3cm in length ( $\downarrow$ ). One month after the operation, the patient's nerve recovered both sensory and motor functions almost to normal, and the patient was completely free from tumor-associated pain.

human placenta.<sup>7,9,10</sup> Further investigation will be needed for administration of appropriate factors at appropriate periods.

## 2. Clinical application in humans

PGA-collagen composite nerve conduits filled with collagen sponge have been clinically used in several different specialties such as surgery, orthopedics, etc. primarily at university hospi-

tals in the Kansai Area since the spring of 2000 in this country, with satisfactory results (Fig. 2).<sup>11</sup> Further, in the Netherlands and certain other European countries, cooperative multi-center clinical trials of the device have been in progress since last year.<sup>12</sup>

## 3. Topics for future investigation

Of the studies on peripheral nerves, there has been no data published concerning regenerative treatment for autonomic nerves. In clinical application, indications of the techniques for long-standing lesions, chronic degenerative disorders, and acute phase lesions remain to be evaluated.

## Conclusion

After the early 1980s, reports began appearing in the literature of animal experiments demonstrating peripheral nerve regeneration across and beyond gaps, though only a few mm in length, bridged by artificial nerve conduits after nerve severing.

With the subsequent rapid progress in tissue engineering, development of artificial nerve conduits capable of meeting clinical needs followed. PGA-collagen composite nerve conduit filled with collagen sponge was put into clinical use in surgical cases in 2002 in Japan, and a lot of satisfactory therapeutic outcomes have been reported. It may thus be said that the era of practical application of peripheral nerve regeneration with artificial nerve conduits has come true.

As artificial nerve regeneration has been just realized in its clinical application, further technological innovation including the use of growth factors and development of more improved artificial nerve conduits are now considered to be growing importance.

There has been no study data published concerning regenerative treatment for autonomic nerves bearing importance in the function after visceral surgical intervention, though being likewise peripheral nerves. This, as well as clinical

indications of the techniques and their potential, remain as problems that need to be resolved.

### REFERENCES

- 1) Mackinnon, S.E.: Nerve allotransplantation following severe tibial nerve injury. *J Neurosurg* 1996; 84: 671–676.
- 2) Lundborg, G., Dahlin, L.B., Danielsen, N. *et al.*: Nerve regeneration in silicone chambers: Influence of gap length and of distal stump components. *Exp Neurol* 1982; 76: 361–375.
- 3) Madison, R.D., da Silva, C., Dikkes, P. *et al.*: Peripheral nerve regeneration with entubulation repair: Comparison of biodegradable nerve guides versus polyethylene tubes and the effects of a laminin-containing gel. *Exp Neurol* 1987; 95: 378–390.
- 4) Mackinnon, S.E. and Dellon, A.L.: A study of nerve regeneration across synthetic (Maxon) and biologic (collagen) nerve conduits for nerve gaps up to 5cm in the primate. *J Reconstr Microsurg* 1990; 6: 117–121.
- 5) Kitahara, A., Suzuki, Y., Shimizu, Y. *et al.*: Evaluation of collagen nerve guide in facial nerve regeneration. *Int J Artif Organs* 1998; 1: 22–27.
- 6) Kiyotani, T., Teramachi, M., Takimoto, Y. *et al.*: Nerve regeneration across a 25-mm gap bridged by a polyglycolic acid collagen tube: a histological and electrophysiological evaluation of regenerated nerves. *Brain Res* 1996; 740: 66–74.
- 7) Matsumoto, K., Ohnishi, K., Kiyotani, T. *et al.*: Peripheral nerve regeneration across an 80-mm gap bridged by a polyglycolic acid (PGA)-collagen tube filled with laminin-coated collagen fibers: a histological and electrophysiological evaluation of regenerated nerves. *Brain Res* 2000; 868: 315–328.
- 8) Mikos, A.G., Sarakinos, G. *et al.*: Laminated three-dimensional biodegradable foams for use in tissue engineering. *Biomaterials* 1993; 14(5): 323–330.
- 9) Toba, T., Nakamura, T., Shimizu, Y. *et al.*: Regeneration of canine peroneal nerve with the use of a polyglycolic acid-collagen tube filled with laminin-soaked collagen sponge: a comparative study of collagen sponge and collagen fibers as filling materials for nerve conduits. *J Biomed Mater Res* 2001; 58(6): 622–630.
- 10) Toba, T., Nakamura, T., Lynn, A.K. *et al.*: Evaluation of peripheral nerve regeneration across an 80-mm gap using a polyglycolic acid (PGA)-collagen nerve conduit filled with laminin-soaked collagen sponge in dogs. *Int J Artif Organs* 2002; 25(3): 230–237.
- 11) Toba, T., Nakamura, T. and Shimizu, Y.: Peripheral nerve regeneration using a polyglycolic acid (PGA)-collagen nerve conduit filled with collagen sponge: experimental research and human application. *Connec Tissue* 2003; 35(1).
- 12) Meek, M.F.: A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. *Plast Reconstr Surg* 2001; 108(4): 1087–1088.

# Tissue Engineering for Blood Vessels

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**Abstract:** The artificial vascular grafts currently in clinical use still have problems with respect to late calcification, restenosis, antithrombotic property, durability, biocompatibility, and safety, and no ideal artificial vascular graft has been developed to date. In view of this, we have been continuing basic experimental studies and their clinical applications in an attempt to develop tissue-engineered regenerative blood vessels. Tissue-Engineered Vascular Grafts (TEVG) autologous cells have no graft rejection potential, and as they are comprised of viable autologous cells, a longer sustained durability can be expected. Eventually, no foreign matter remains, and the lumen becomes completely endothelized. Therefore, no long-term anticoagulant therapy is required post-implantation, and the implanted graft, being autologous tissue, may have higher growth potential: Such artificial grafts are considered ideal blood vessels. We will continue to seek methods that enable less cumbersome treatments that are less stressful for patients in the future.

**Key words:** Tissue engineering; Blood vessel; Autogenic cell implantation

## Introduction

Cardiac surgery has spread explosively throughout the world since J. H. Gibbon succeeded in performing open heart surgery using a pump-oxygenator in 1953. With the Westernization of lifestyles in Japan, open heart surgery for valvular diseases or congenital heart diseases, bypass surgery for ischemic heart diseases and operations on greater blood vessels have been increasing rapidly. In the field of cardiovascular surgery, revascularization using artificial vascular grafts has been undertaken to

treat congenital defects or hypoplasia and to correct acquired vascular stenosis or occlusion due to atherosclerosis.

Especially in cases of low-pressure or small-caliber artificial vascular graft implantation, however, anticoagulant therapy is required and reoperations are inevitable due to late calcification, stenosis, and the non-growth nature of the graft. As many as some 80 different types of artificial vascular grafts are currently in clinical use in this country, but there is no ideal artificial vascular graft developed/available to date. There is great need for development of vascu-

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lar prostheses with higher biocompatibility such as greater antithrombotic property, durability, and safety.

In view of this, we have been continuing basic experimental studies aimed at development and clinical application of TEVG as ideal artificial vascular grafts. We make it a rule to use "autologous cells" for preparation of regenerative blood vessels to ward off potential graft rejection. Viable autologous cells exist within the tissue regenerated. Therefore, a longer sustained durability can be expected, and eventually, no foreign matter remains, and the lumen becomes completely covered by endothelial cells. Thus, no long-term anticoagulant therapy is required post-implantation, and the implanted device, being autologous tissue, may have a higher growth potential.

This article describes the method of regenerative vascular graft preparation we perform with tissue engineering techniques and the present status of its clinical application.

## Basic Research and Results

Basic experiments designed to construct a large-caliber blood vessel from peripheral vascular cells and to determine whether the constructed vasculature might withstand surgical grafting at its acute phase and continue to function satisfactorily in the long term were conducted on large animal models (pulmonary artery: sheep; and inferior vena cava: dog).<sup>1,2)</sup>

### 1. TEVG construction (i. cell collection, ii. mass cell production, and iii. seeding on polymer graft)

An approximately 2-cm segment of the femoral artery was obtained from an animal and trypsinized to prepare isolated vascular cell cultures using the simple explant technique. The resultant mixed cell cultures were grown over a period of about 6–8 weeks for mass production of cells. A concentrated cell suspension was made up from the mass culture about one week prior to implantation, and then

seeded on a biodegradable polymer conduit. The biodegradable polymer is hydrolyzed non-enzymatically and has been verified in many clinical studies to be safe not only early after implantation, but its degradation products *in vivo* have been shown to be safe as well. As the rates of biodegradation vary with the types of polymer, the polymer graft was designed to set a degradation/absorption period of 6–8 weeks by combining a plurality of different polymers. The cells disseminated on the polymer carrier continued to divide and proliferate to form a three-dimensional confluent growth during incubation, preceding its implantation.

### 2. TEVG implantation procedure

Implantation in animals was performed between Days 7 and 10 after cell seeding. A conduit prepared from vascular wall cells was implanted in the same animal from which the cells had been collected (autografting). Extracorporeal circulation was established with the animal placed under general anesthesia, and TEVG was implanted at the main pulmonary artery in sheep. Replacement of the inferior vena cava by TEVG was carried out under general anesthesia.

Tissue engineering for the cardiovascular system provides a condition favoring the seeded cells: the implanted cells/structure can be in direct contact with intravascular blood and can thus be supplied with oxygen, nutrients, and humoral factors from just after the implantation. Therefore, the cells on the structure implanted further differentiate, enabling reconstruction of the tissues.

### 3. Late (follow-up) evaluation

The diameter of each artificial vascular implant was evaluated at 10–36 weeks after the implantation. In every case, the implanted polymer was completely absorbed and the TEVG presented features similar to intact vascular tissues (Fig. 1). These implants were subjected to histological, biochemical and biodynamic assessments.

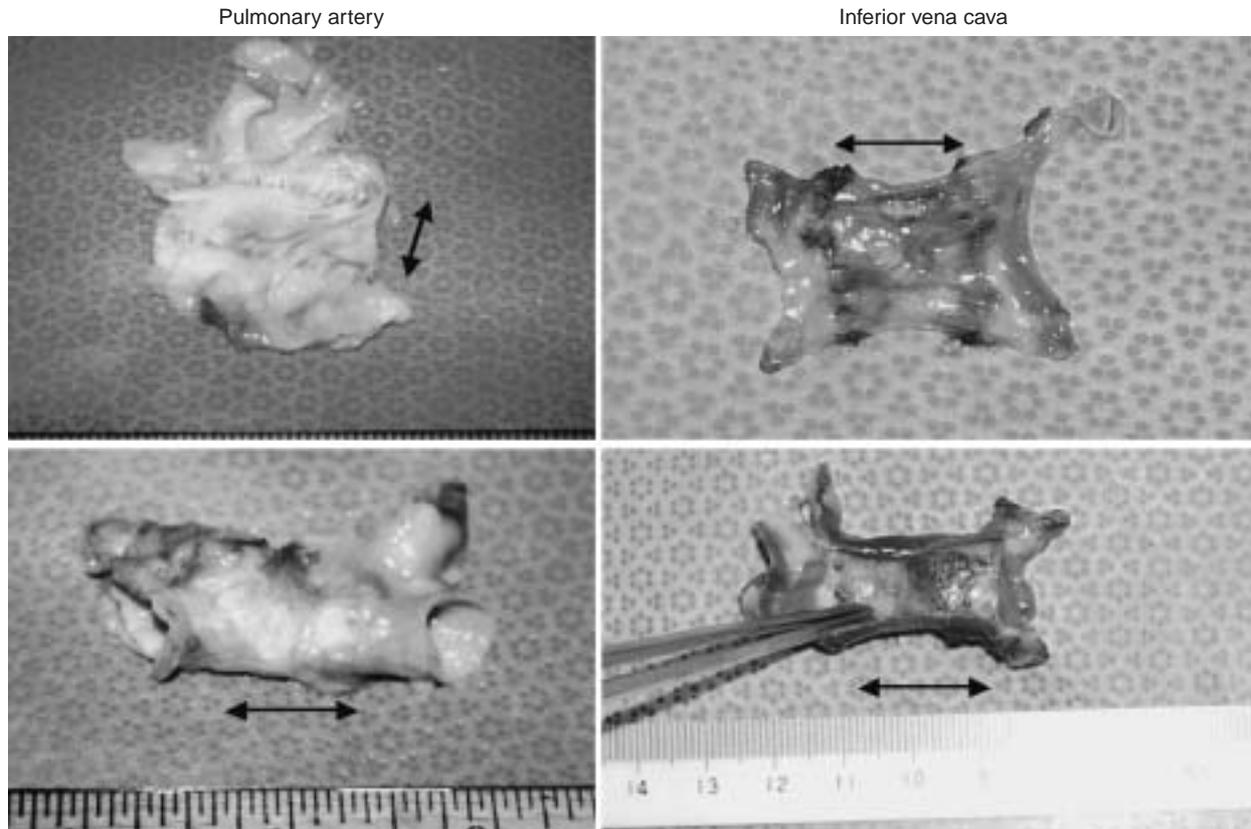


Fig. 1 Left panel: Six months (top) and 9 months (bottom) after ovine pulmonary artery replacement  
Right panel: Six months (top) and 9 months (bottom) after canine inferior vena cava replacement

The tissue collagen content tended to increase progressively with time, and this suggested a tissue remodeling *in vivo*. There was also an increase in tensile strength with time as assessed by the biodynamic test. An immunohistological study with the factor VIII and anti- $\alpha$ -smooth muscle actin verified that the vascular tissue prepared was covered with endothelial cells, and there was evidence of the presence of smooth muscle cells in the tunica media. Vascular diameter increased progressively with the growth of the recipient host.

### Cases of Clinical Application

Cell collection from humans began with the approval of the Tokyo Women's Medical University Ethics Committee in April 1999. Clinical applications began upon obtaining fully

informed consent from patients/their family members. The first case was of a 4-year-old child who received a regenerative vascular implantation for reconstruction of the pulmonary artery in May 2000, with satisfactory results.<sup>3,4)</sup>

This method is used at present only in cases where it is obvious that correction with conventional techniques will result in a poor outcome, as no satisfactory biomaterials are currently available in cardiac surgery. We plan to extend clinical applications through accumulation of experience in clinical cases. The method of clinical application is described in detail below.

#### 1. Preparation of grafts with tissue engineering techniques

##### (1) Collection of venous segment and cell culture

A 3 cm segment of the great saphenous vein

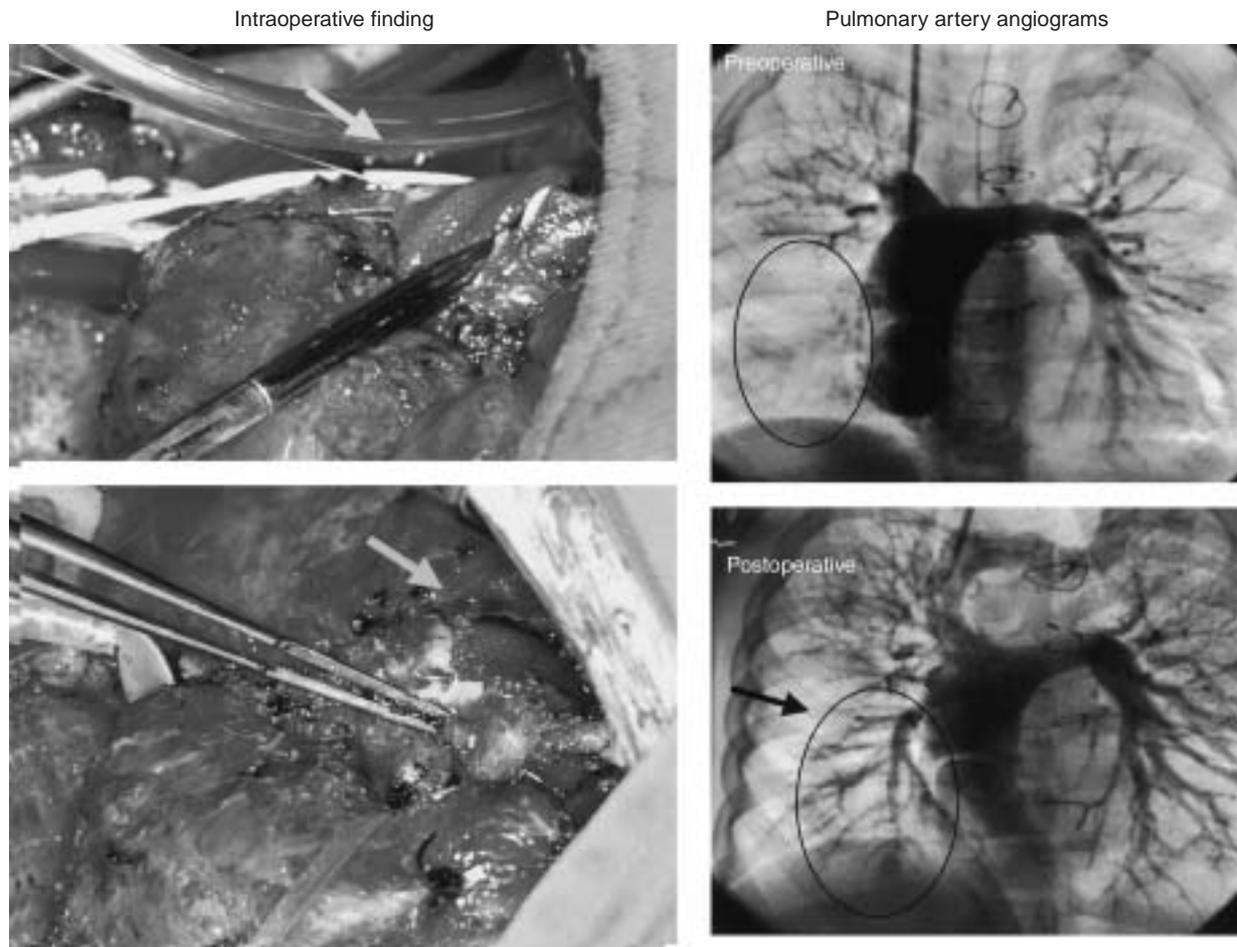


Fig. 2 Case 1. Left panel: Operative finding at regenerative vascular graft implantation  
Right panel: Pre- and post-operative angiographic findings for the pulmonary artery

was cut from the patient. It was then placed in a dish for culture in a clean bench, cut into 1 to 2-mm pieces with a knife, and incubated with an added culture medium in a 5% CO<sub>2</sub>-95% air atmosphere at 37°C. The medium was changed at intervals of 2–3 days. The tissue fragments began to grow about 10 days after the start of incubation, and continued to proliferate to form confluent growths in the dish about 2 weeks later. The growths were then trypsinized and transferred to culture flasks for further incubation. The cells grew confluent in the flasks in about 4 weeks. When examined by immunostaining at this stage, the cell population that had grown was found to be a mixture of about 10% endothelial cells, about 20–30% smooth

muscle cells and about 60–70% fibroblasts.

#### (2) Seeding on polymer graft

The cell sheets grown in flasks were trypsinized and prepared into a cell suspension, which was then centrifuged to obtain 1 to 2 ml of a concentrated cell suspension, discarding the supernatant. This suspension was spread for seeding on a bioabsorbable polymer graft system to complete a graft. The graft was cultured by incubation for about one week and subsequently used in a surgical operation. Scanning electron microscopic observation of the graft surface showed that the seeded cells adhered to the polymer surface, entering polymer interspace. The polymer graft was comprised of spongy polycaprolactone-poly(lactic acid) high

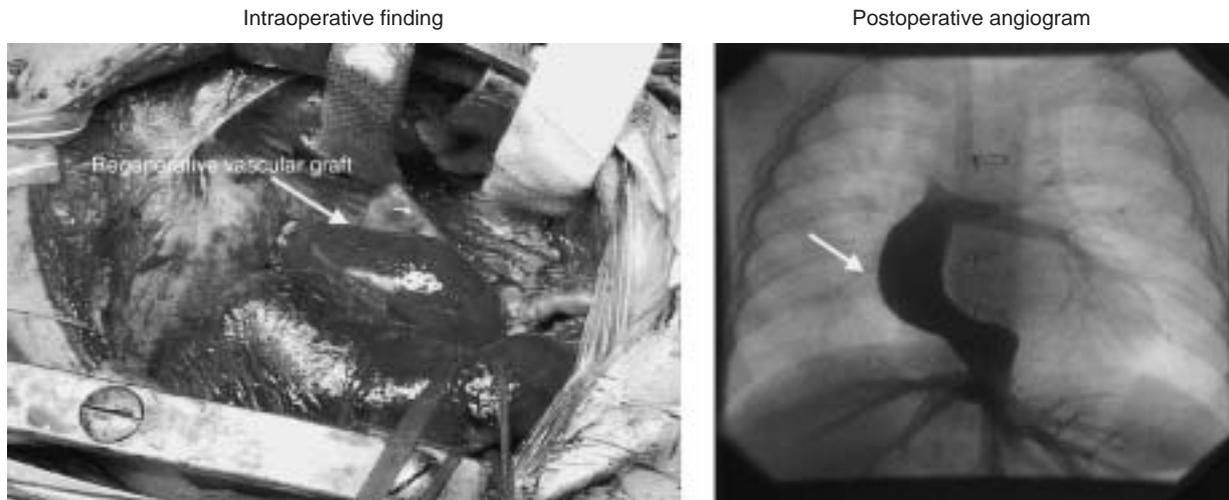


Fig. 3 Case 2. Left: Intraoperative finding at completion of graft implantation Right: Postoperative angiogram

polymer reinforced with polyglycolic acid fibers.

## 2. Case 1: A 4-year-old girl

The patient had previously undergone Fontan operation (right atrium-pulmonary artery anastomosis), but occlusion of the right inferior pulmonary artery occurred postoperatively. In view of the child's QOL, we judged that her condition would be indicated for pulmonary artery reconstruction using TEVG. It took about 3 months from vascular cell collection until graft implantation.

**Operative findings:** Upon approach through a midsternal incision, a cardiopulmonary bypass was established. The right pulmonary artery was completely occluded at the site of the entrance to the middle and lower lobe branches, forming a cord about 1 cm in length. The uniform segment of the pulmonary artery was then resected, an incision was made in the anterior aspect of the pulmonary artery wall, and while securing the arterial lumen, the posterior wall was directly anastomosed. The incised anterior aspect was patched up with a piece that had previously been cut out of a tissue-engineered tubular graft to complete the pulmonary artery reconstruction (Fig. 2).

**Postoperative radiographic examination:** The

operation produced improvement in blood flow to the middle and lower lobes of the right lung. On examination by selective angiography of the pulmonary arteries, the wall of the TEVG was uniformly even and the graft was satisfactorily patent with no particularly significant stenosis (Fig. 2).

## 3. Case 2: A 2-year-old male infant

The infant had received a palliative operation at infancy with the diagnosis of asplenia, atrial ventricular septal defect, common atrium, bilateral discontinuous central pulmonary artery, partial perfusion abnormality of the pulmonary vein, and bilateral superior vena cava. The patient was admitted to the hospital for reconstruction of the left and right pulmonary artery continuity and total cavopulmonary connection (TCPC; the superior vena cava and inferior vena cava are respectively anastomosed directly to the pulmonary artery).

**Operative findings:** TEVG, 17 mm in diameter, was prepared and used to bridge the inferior vena cava and the pulmonary artery.

**Postoperative radiographic examination:** The postoperative course was uneventful, and postoperative angiographic examination verified a satisfactory patency of the TEVG (Fig. 3).

## Current Problems and Future Development

The vascular tissue we constructed and used with the tissue engineering technique is applicable, but only under medium or lower blood pressure such as the pulmonary artery, and its use is limited in corrections of blood vessels bearing higher systemic blood pressure. This is because the durability of the graft to stress by systemic blood pressure after disappearance of the polymer is questionable. It would be possible to use the TEVG even within the blood pressure of greater vessels provided absorbability of the polymer is improved or the strength of the graft is augmented by early introduction of stromal (interstitial) protein after *in vitro* seeding.

Bioreactors functioning to create the pulsating circulation of the culture medium have been put to practical use to permit *in vitro* "conditioning" of the cell/polymer structure under more physiological conditions. We have been pursuing studies to seek methods of TEVG preparation that are less cumbersome and less stressful on children, taking note of

marrow stem cells and peripheral blood stem cells as the source of autograft cells.

Development of engineering techniques to produce flexible, elastic biodegradable polymers with long-term absorption periods as well as polymers capable of sustained release of cytokines is considered essential to bring about advances in tissue engineering for the cardiovascular system.

## REFERENCES

- 1) Shin'oka, T., Shum-Tim, D., Ma, P.X. *et al.*: Creation of viable pulmonary artery autografts through tissue engineering. *J Thorac Cardiovasc Surg* 1998; 115(3): 536–545.
- 2) Watanabe, M., Shin'oka, T., Tohyama, S. *et al.*: Tissue-engineered vascular autograft: inferior vena cava replacement in a dog model. *Tissue Eng* 2001; 7(4): 429–439.
- 3) Shin'oka, T., Imai, Y. and Ikada, Y.: Transplantation of a tissue-engineered pulmonary artery. *N Engl J Med* 2001; 344: 532–533.
- 4) Hibino, N., Imai, Y. and Shin'oka, T.: Reconstruction of pulmonary artery using tissue-engineered vascular autograft. *Kyobugeka* 2002; 55(5): 368–373. (in Japanese)

# Regenerative Medicine for Jawbone

JMAJ 47(6): 294–297, 2004

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**Abstract:** This paper outlines tissue engineering of the jawbone and introduces a new method of jawbone regeneration using poly[L-lactide] (PLLA) mesh and bone marrow grafting. This method utilizes particulate cancellous bone and marrow (PCBM) from the ilium as the source of bone precursor cells and a PLLA mesh tray as the scaffold or framework for bone formation. The PLLA mesh tray is gradually degraded and absorbed after bone formation by PCBM. The procedure has been clinically applied in 62 cases, with a success rate of 84%. Resorption of regenerated bone was relatively rare, rather, ossification tended to progress among patients having achieved an early recovery in occlusion as a result of denture insertion or dental implantation. This method is preferable in that it enables regeneration of the physiological mandibula and is minimally invasive, but is awkward to indicate in post-radiotherapy patients and elderly subject who usually have diminished bone precursor cells. Concomitant use of bioactive factors that stimulate angiogenesis and bone formation is advisable in such cases.

**Key words:** Jawbone regeneration; Tissue engineering;  
Poly-L-lactide (PLLA) mesh; Bone marrow

## Introduction

Usually, repair and reconstruction by bone grafting or use of artificial materials are undertaken in case of a mandibular defect so large as to be non-self-restorable, such as defects caused by tumor, inflammation or trauma. Any such attempt, however, has its merits and demerits and has limitations with respect to morphologic and functional restoration. The ultimate goal of jawbone reconstruction consists in regeneration of a physiological bone

permitting insertion of dentures or dental implantation. The recent advent of tissue engineering has made such goals more achievable. This paper outlines the tissue engineering of the jawbone and introduces a method of jawbone regeneration using bioabsorbable poly-L-lactide (PLLA) mesh and bone marrow grafting.

## Tissue Engineering of the Jawbone

The basic strategy of bone regeneration is to

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incorporate into the target site one or more of the basic elements necessary for bone formation, i.e. 1) osteogenic cells (bone precursor cells/stem cells), 2) scaffold for bone formation and 3) bioactive factors (biologically active substances) or genes that induce proliferation and differentiation of osteoblasts, while guiding the tissue-repairing function of the subject.<sup>1)</sup> If the bone defect is inconspicuous in quantity, a mere scaffolding may suffice for induction of cells and bioactive factors from surrounding tissues to effect regeneration. This method is used as guided tissue regeneration (GTR) in regenerating the alveolar bone in paradental diseases or guided bone regeneration (GBR) in increasing bone mass of atrophied alveolar ridges (footholds for dentures or implants).<sup>2,3)</sup> In case of a larger bone defect, it is necessary to introduce bioactive factors or bone precursor cells/stem cells from the outside. Bone morphogenetic proteins (BMPs) are the best known bioactive factors. There have been many reports on BMPs since their discovery by Urist *et al.* as proteins inducing ectopic bone formation in 1965,<sup>4)</sup> but their application to humans is still extremely rare. For clinical application of these proteins, it is indispensable to provide a carrier or sustained-release system to have BMPs remain and continuously exert their effects at the target site.<sup>5)</sup> Human recombinant BMP-2 and BMP-7 (OP-1) are currently used along with absorbable biomaterials including collagen and poly lactic-co-glycolic acid (PLGA) as the carrier in such operations as maxillary sinus floor augmentation and alveolar ridge augmentation, but outcomes have not always been consistent.<sup>6,7)</sup> A considerable amount of BMPs is required to attain regeneration of a human bone, so unpredictable reactions may occur. This as well as the technique's costliness pose problems. Application of BMP-transfected cells or concomitant use of undifferentiated mesenchymal cells may be necessary.

The introduction of cells may be accomplished by implanting bone precursor cells/

stem cells that have previously been proliferated to a certain extent *in vitro*, or by directly implanting tissues containing these cells. The former is rational as it requires a rather small quantity of tissue to be taken, but problems such as scaffold and culturing conditions remain to be solved in order to put it to clinical application. The latter utilizes particulate cancellous bone and marrow (PCBM). This technique's advantages are: PCBM contains bone precursor cells/stem cells and various bioactive factors, its collection is relatively less invasive, and the site of its collection can thus be self-restored. To apply it to jawbone regeneration, however, it is essential to mold the bone into the desired shape and to provide a scaffold (support or framework) that can withstand external force until completion of the intended bone formation. Such a scaffold should ideally be absorbed and disappear from the graft site after bone regeneration. The present authors, giving attention to bioabsorbable poly-L-lactide (PLLA), have developed PLLA mesh and established a jawbone regeneration technique using the mesh and PCBM.<sup>8)</sup>

## Jawbone Regeneration with PCBM and PLLA Mesh

### 1. PLLA mesh

PLLA mesh is made of monofilaments ( $\phi 0.30\text{--}0.60\text{ mm}$ ) spun from PLLA of molecular weight  $20.5 \times 10^4$  that is elongated and woven into mesh, and is moldable at  $70^\circ\text{C}$ . When implanted, the mesh undergoes a gradual degradation and absorption over a few to 5–6 years via non-enzymatic hydrolysis and macrophagic phagocytosis without any adverse effect on tissues. Poly-L-lactide retains its initial strength for 3 months after implantation and then gradually loses its strength. PLLA mesh provides full support until bone formation by PCBM and subsequently is absorbed; hence, it is preferable as a scaffold for bone formation in that it casts a physiological weight load upon the regenerating bone.<sup>6)</sup>

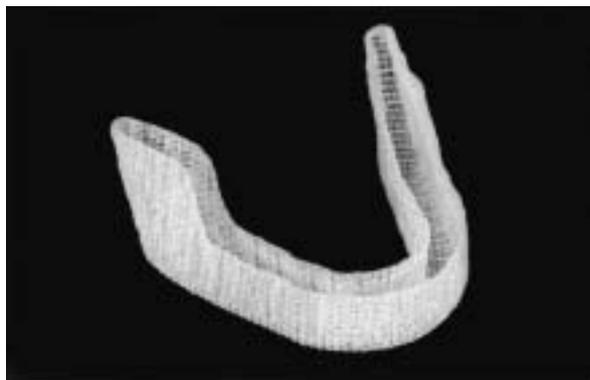


Fig. 1 Poly-L-lactide mesh tray (for lower jawbone)  
The tray may be cut with scissors and is moldable at 70°C.

## 2. Clinical application

The treatment was clinically applied in 62 patients (age range 15–76 years; mean: 47 years) who gave informed consent upon approval by the ethics committee at eight dental institutions between April 1995 and September 2001. The study population comprised 22 patients with malignant tumors of the mandible, 30 patients with benign tumors, 5 with cysts, 2 with osteomyelitis, 1 with atrophy of the alveolar ridge, and 2 with trauma. The operative procedure was as follows: molding of a PLLA mesh or tray (Fig. 1) to fit the defect, adjustment, wire anchorage, and finally filling the mesh or tray with PCBM harvested from the ilium.

The therapeutic outcome, as assessed radiographically in terms of degree of bone regeneration at 6 months post-operation, was excellent (markedly effective) in 35 cases (56.5%), good (effective) in 17 cases (27.4%), and poor (not effective) in 10 cases (16.1%). Of the 10 poor responders, the mesh and PCBM were removed postoperatively due to local infection in 6 patients. Of these 6 patients, 3 patients underwent concurrent reconstruction of both soft tissue and jaw bone due to malignant tumor in this study.

There was only one patient who experienced late inflammatory reactions among 38 patients who were followed for 1–7 years (mean: 3.3 years) post operation. Twenty-one patients

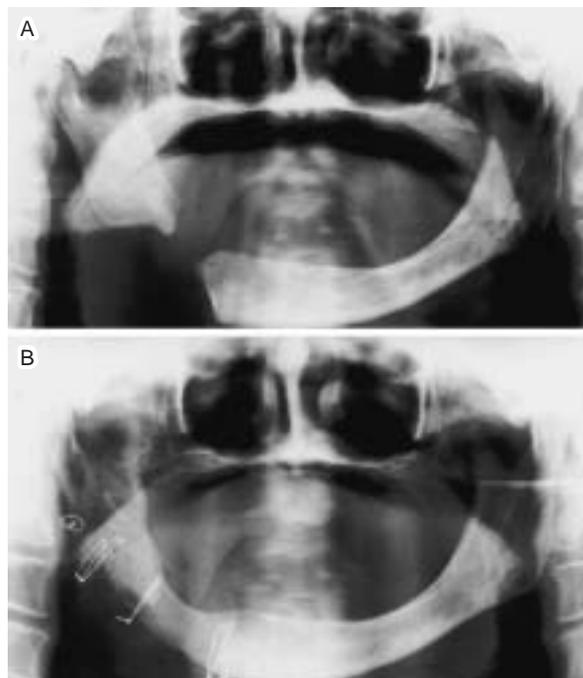


Fig. 2 A 75-year-old man. Panorama radiograms before (A) and after (B) operation for mandibular regeneration with the use of poly-L-lactide mesh and particulate cancellous bone and marrow

A: The patient underwent resection of the jaw for treatment of mandibular tumor. The mandible is discontinuous and markedly malposed.

B: 18 months after reconstruction. Regeneration of jawbone showing normal trabeculae and recovery to practically normal shape are evident in the formerly defective region.

received insertion of dentures into the regenerated bone and 4 patients dental implantation. A satisfactory recovery in occlusion was attained in all these cases. On X-ray examination of the regenerated bone, there was 0–10% bone resorption in 31 cases, 10–20% in 6 cases, and 20–30% in 1 case. Among the patients having achieved an early recovery in occlusion, bone resorption was inconspicuous, rather, ossification progressed (Fig. 2).

This method is superior to the conventional jaw bone reconstruction in that it enables mandibular regeneration that permits insertion of dentures and dental implantation with minimal invasion. However, it has limitations as an indication in post-radiotherapy patients with poor regional blood circulation and elderly

subjects with fewer bone precursor cells/stem cells. Concomitant use of bioactive factors that induce angiogenesis and promote bone formation is necessary in such cases.

Whitman *et al.* reported that concurrent use of PCBM and platelet-rich plasma (PRP) hastened bone formation.<sup>9)</sup> Furthermore, basic fibroblast growth factor (bFGF), which has recently been used for treatment of refractory skin ulcer, is also a potential candidate as a bone formation promoter.<sup>10)</sup> Gelatin microspheres impregnated with bFGF (bFGF-GMS), where acid gelatin serves as a carrier, proved to slowly liberate bFGF as gelatin degrades to accelerate bone repair in experimental canine mandibular defect.<sup>11)</sup> Its efficacy when used in combination with PCBM is anticipated.

## Conclusion

The tissue engineering of the jawbone has been briefly reviewed and jawbone regeneration using bone marrow (particulate cancellous bone and marrow) and bioabsorbable poly-L-lactide has been introduced. This surgical method is minimally invasive, procedurally simple, and enables regeneration of the physiological mandibula to permit insertion of dentures and dental implantation. Regional blood flow at the site and sufficient bone precursor cell/stem cell population are important for success in this treatment.

In post-radiotherapy patients with poor regional blood circulation and elderly subjects, concomitant use of bioactive factors that induce angiogenesis and promote bone formation are advisable to accomplish the treatment.

## REFERENCES

- 1) Bruder, S.P. and Fox, B.S.: Tissue engineering of bone. Cell based strategies. *Clin Orthop* 1999; (367 Suppl): S68–S83.
- 2) Nyman, S., Lindhe, J., Karring, T. *et al.*: New attachment following surgical treatment of human periodontal disease. *J Clin Periodontol* 1982; 9: 290–296.
- 3) Nyman, S., Lang, N.P., Buser, D. and Bragger, U.: Bone regeneration adjacent to titanium dental implants using guided tissue regeneration: a report of two cases. *Int J Oral Maxillofac Implants* 1990; 5: 9–14.
- 4) Urist, M.R.: Bone: formation and autoinduction. *Science* 1965; 150: 893–899.
- 5) Winn, S.R., Uludag, H. and Hollinger, J.O.: Carrier systems for bone morphogenetic proteins. *Clin Orthop* 1999; (367 Suppl): S95–S106.
- 6) Howell, T.H., Fiorellini, J., Jones, A. *et al.*: A feasibility study evaluating rhBMP-2/absorbable collagen sponge device for local alveolar ridge preservation or augmentation. *Int J Periodontics Restorative Dent* 1997; 17: 124–139.
- 7) Boyne, P.J., Marx, R.E., Nevins, M. *et al.*: A feasibility study evaluating rhBMP-2/absorbable collagen sponge for maxillary sinus floor augmentation. *Int J Periodontics Restorative Dent* 1997; 17: 11–25.
- 8) Kinoshita, Y., Kobayashi, M., Fukuoka, S. *et al.*: Functional reconstruction of the jaw bones using poly (L-lactide) mesh and autogenic particulate cancellous bone and marrow. *Tissue Eng* 1996; 2: 327–341.
- 9) Whitman, D.H., Berry, R.L. and Green, D.M.: Platelet gel: an autologous alternative to fibrin glue with applications in oral and maxillofacial surgery. *J Oral Maxillofac Surg* 1997; 55: 1294–1299.
- 10) Yamada, K., Tabata, Y., Yamamoto, K. *et al.*: Potential efficacy of basic fibroblast growth factor incorporated in biodegradable hydrogels for skull bone regeneration. *J Neurosurg* 1997; 86: 871–875.
- 11) Yokoya, S., Kinoshita, Y., Fukuoka, S. *et al.*: Tissue engineering in jawbone — Potential efficacy of bFGF-incorporated gelatin microspheres for bone formation of mandibular defects —. *J Jpn Stomatol Soc* 2002; 51: 324–334. (in Japanese)

# Professional Autonomy: A New Perspective for Relating with Clinical Practice Guidelines

JMAJ 47(6): 298–304, 2004

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**Abstract:** The relation between physician discretion and clinical practice guidelines is a typical issue in malpractice lawsuits, however, little attention has been paid to this issue in terms of general context. Due to this limited perspective, the relationship has been seen as opposing. To propose a new perspective with which these guidelines are viewed, we historically review the terminology on physician discretion. Secondly, we analyze usages of the terms, focusing on the concept of freedom, the essence of professionalism, and the bibliometric data of the terminology. Thirdly, the findings are explored to show that the relationship can be restructured from one of opposition to a mutually indispensable relationship through the medium of professional autonomy.

**Key words:** Professional autonomy; Positive freedom; Self-governance and self-regulation; Clinical practice guidelines; Mutually indispensable relationship

## Introduction

Funded by the Ministry of Health, Labour and Welfare (MHLW), clinical practice guidelines in Japan started to be developed for five diseases in 1999. Guidelines for seven diseases were added in 2000, four in 2001, four in 2002, and two in 2003.<sup>1)</sup>

In the task of compiling these guidelines, discussion about the issue on how to coordinate clinical practice guidelines with the discretion-

ary authority of physicians was nonexistent, though there existed political discussion which organization would lead the EBM movement in Japan.<sup>2)</sup> Historically in Japan, the former issue on physicians and guidelines has been discussed within the limited context of medical malpractice, i.e., in negative and specific cases where physicians have been sued for negligence. Thus, it was quite natural for this issue to remain unaddressed in the discussions about developing guidelines at that time.

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However, the issue of clinical practice guidelines versus physician discretion should not be limited within the context of litigation. This is because the guidelines greatly affect clinical medicine. How physicians balance the guidelines against their discretion is critical in their daily practice as they are disseminated. Therefore, it is meaningful to study the relationship between clinical practice guidelines and the discretionary authority of physicians in a more positive and general context.

The objective of this paper is to propose a new perspective for restructuring the relationship between the discretionary authority of physicians and clinical practice guidelines in the general context. Our proposal is that the concept of professional autonomy is one of perspective. To make this proposal, one of the commonly used terms on physician discretion in Japan, “*purofesshonaru furiidamu*,” will be historically reviewed in comparison with professional autonomy. Secondly, using the concept of positive freedom, the essence of professional autonomy will be analyzed. Thirdly, a new relation between the medical profession and clinical practice guidelines will be identified based on the result of our review and analysis.

## Historical Review

### 1. “Professional freedom” in Japanese

Physicians have used the term, professional freedom, to denote noninterference by government authorities or external parties. The late Dr. Taro Takemi, former JMA president, translated and utilized this English term to support his viewpoints; and subsequently, the translated Japanese term, “*purofesshonaru furiidamu*” took on a significance of its own and it has continued to be used by many in Japanese health care circles to this day.

Dr. Takemi became the president of the JMA in 1957 and served in that office for 25 years. During his tenure, he also served as the WMA president from 1975 to 1976. The term,

“*purofesshonaru furiidamu*,” first appears in his report entitled, “Development of Health Care, Professional Freedom and the Law,” which was written in 1979.<sup>3)</sup> This report pointed out that the classical definition of professionalism was diminished in malpractice lawsuits and that the health insurance system was put into effect largely because of the passive sense of professionalism. It stated, “The law has strengthened its control without hesitation, thereby infringing on a classical profession . . . . The modern medical profession should not remain in a position of unassertiveness, but should actively pursue creative activities . . . .”<sup>3)</sup>

The report interpreted any interference of physicians’ practices as unfair control of physician discretion. Dr. Takemi recognized that the conventional means of realizing professionalism were insufficient to eliminate this control and it was necessary to pursue true medical professionalism. Dr. Takemi described this situation in his report as “the need for ‘*purofesshonaru furiidamu*,’” where he was specifically referring to the need for active pursuit of freedom in the medical profession. In 1982, his report was revised and published by the Legal Department of the JMA.<sup>4)</sup>

### 2. Original usage of the term by Dr. Takemi

For a quarter of a century, the term “*purofesshonaru furiidamu*” has been used in Japan, notably in situations where the MHLW has interfered in the medical profession or where the physician has refused to be dictated to by the patient. Some Japanese physicians even deny the need for clinical practice guidelines based on the concept of this term. But as explained in the previous section, the original meaning of this term did not signify negative freedom, which denoted escape from interference. It meant something active and positive.

In the 1982 article, “*purofesshonaru furiidamu*” was defined as follows. “The classical definition of freedom in the medical profession was diminished in the name of public welfare. We must reinterpret freedom as the

source of positive activities that will enable us to fulfill our responsibilities . . . . This is what ‘purofessionaru furiidamu’ is all about.”<sup>4)</sup> Therefore, it is clear that the original usage of the term did not refer to negative freedom, but *positive freedom*.

However, “purofessionaru furiidamu” has been mainly used to indicate negative freedom rather than positive freedom since its initially use. Part of the reason for this is apparent. Although Dr. Takemi pointed out the importance of positive freedom, he tried to promote measures in his actual suggestions to eliminate external interference. Consequently, many physicians in Japan interpreted the term to refer to negative freedom.

### What Is Professional Autonomy?

We have shown that “purofessionaru furiidamu” has an original and present meaning, i.e., positive freedom and negative freedom. Then, how does it differ from the English term, professional autonomy? To answer this question, we firstly detail the differences between negative and positive freedom to find the essence of the latter. Secondly, we examine the essence of professionalism. Thirdly, comparative usages of “professional freedom” and “professional autonomy” are investigated to quantitatively augment our argument.

#### 1. Two concepts of freedom

Since the time of ancient Greece, innumerable philosophers and thinkers have discussed two concepts about freedom, namely negative freedom and positive freedom. They are generally differentiated according to the following.

Negative freedom is defined as the act of escaping the interference of external parties. It focuses on the range of choices that can be made by an individual without any interference. In contrast, positive freedom focuses on whether the choices are truly made by the individual. Positive freedom is defined as acting on rationale rather than impulse. In other words,

when action is based on rationale, the individual indeed makes that choice and can enjoy positive freedom. Thus negative freedom can be summarized as noninterference and positive freedom as self-control.

Negative freedom can also be defined as the availability of choices, and positive freedom as the ability to make choices. When viewed in this way, negative freedom is freedom that protects an individual from those who impede his choices, whereas positive freedom is freedom that enables an individual to be governed by his self by limiting the range of choices.

According to the commonly held interpretation of freedom by Immanuel Kant, positive freedom is decision-making that is governed by the universal laws of self-reasoning.<sup>5,6)</sup> Since the individual is governed by the self, this becomes “Autonomie” through practical reasoning.<sup>7,8)</sup> Thus, the essence of positive freedom is self-reasoning or self-governance, and it can be plainly described using the term, *autonomy*.

#### 2. Self-governance and self-regulation

It is well-known fact that professions are organized into groups. These groups foster and qualify their members as professionals; and they are self-governing. These groups also take disciplinary action against the misconduct of members; and they function as self-regulating entities. They are seen as autonomous based on these two characteristics.

Despite the differences which existed between countries, the self-governing and the self-regulating characteristics of these groups were especially conspicuous prior to the modern age.<sup>9)</sup> With the advent of the modern age, the national governments have granted certifications or licenses to the professions in many countries, and the educational function of the professional groups has been limited to fostering the technical skills of their members after they acquired their credentials. The power to take disciplinary action against professionals has also increasingly fallen under the control of the government.

To this day, however, the professions are responsible for creating and abiding by their ethical standards. In this respect they continue to be autonomous. According to Eliot Freidson, autonomy is the only element that separates the professional and the nonprofessional.<sup>10)</sup> He states that from autonomy or self-direction, all other elements that encompass the definition of the professional are, in truth, deductive.<sup>11)</sup>

The essence of *positive freedom* is autonomy and autonomy can also be clearly found in the essence of *professionalism*. Autonomy represents positive freedom and autonomy is the validation of the professional. The term, professional autonomy, is symbolic of this fact. Thus in principle, professional autonomy denotes positive freedom or self-control, while professional freedom denotes negative freedom or noninterference.

It can now be understood how Dr. Takemi's original usage of the term "purofesshonaru furiidamu" is relevant. It is rational for professional groups such as a physicians' organization to extol its positive freedom due to the very nature of the organization. Moreover, it is also desirable in terms of public interests for the profession to be aware of their role in society and to remain unflinching in their autonomy. An example of this is the JMA approval of public disclosure of patient records and the establishment of relevant ethical standards in 1999.<sup>12)</sup> In short, "purofesshonaru furiidamu" equals professional autonomy in its original usage of positive freedom. If Dr. Takemi had paid attention to the English term, professional autonomy, and translated and utilized this term as "purofesshonaru otonomii," it would have been more straightforward and easier to understand; and a more far-reaching understanding of the terminology would have been cultivated in Japan.

Nevertheless, due to the flexible usage of professional autonomy, this term is also used to denote the concept of negative freedom partly because the self-governance often requires noninterference. To understand the significance of

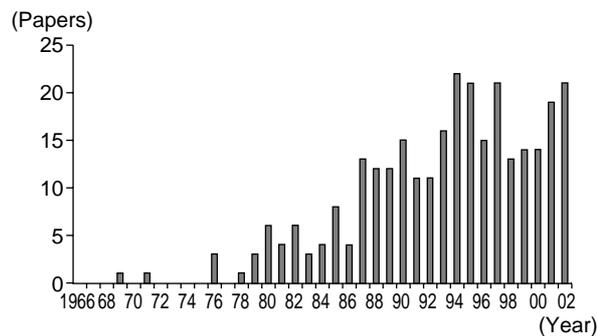


Fig. 1 Number of papers found in the search using "professional autonomy"

this term more accurately and to strengthen our argument, it is necessary to utilize quantitative data.

### 3. Quantitative data

We investigated the global usage of the term, professional autonomy, in comparison to the term, professional freedom. The frequency with which the two terms were used in health care was observed by investigating the number of papers published in academic journals that have used these terms. Using the method known as the bibliometric analysis of time series, the number of academic papers for each year was searched. MEDLINE of Ovid Co. was used in the search starting from January 1, 1966 to December 31, 2002. Our search was conducted on May 2, 2003.

In using MEDLINE, attention was paid to the search field. The search thesaurus known as Medical Subject Headings (MeSH) does not list the term "professional freedom," while the term "professional autonomy" has been listed since 1992. Thus, if a paper which did not contain the term "professional autonomy" broadly related to the subject of professional autonomy, it was assigned the MeSH and counted. Consequently, when the MeSH was included in the search field, a total of 4,415 papers for "professional autonomy" and a total of 29 papers for "professional freedom" were observed.

The search field was then restricted to only

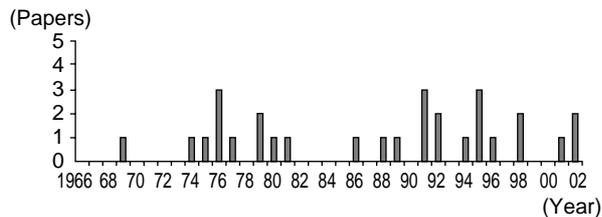


Fig. 2 Number of papers found in the search using "professional freedom"

title (ti) and abstract (ab). Fig. 1 shows the number of papers whose title or abstract contained the term "professional autonomy." Fig. 2 shows the number of papers whose title or abstract contained the term "professional freedom." The total number of papers for each figure was 295 and 29, respectively. There was thus a ten-fold difference in the frequency of usage between the two terms.

The primary factor for this difference is believed to be due to the double meanings as referred to in the previous section. If professional freedom denotes only negative freedom and professional autonomy denotes both negative and positive freedom, then it stands to reason that the number of papers shown in Fig. 1 is greater in number. In actuality, when all the papers from Fig. 2 and the equivalent number of randomly sampled papers from Fig. 1 were selected and their contents were examined, this difference in terminology usage was confirmed.

In studying the distribution patterns for both figures, Fig. 1 shows an overall tendency to increase and a distinct peak is seen from 1994 to 1997. Fig. 2 shows uniform movement. To investigate the cause of the pattern in Fig. 1, the content of the papers for the four-year period from 1994 to 1997 and every fifth year prior to and after this four-year period (1979, 1984, 1989, 2002), for a total of eight years was studied.

It was found that the number of papers on medical ethics and managed care was relatively high during the four-year period from 1994 to 1997. It firstly signifies that many papers during

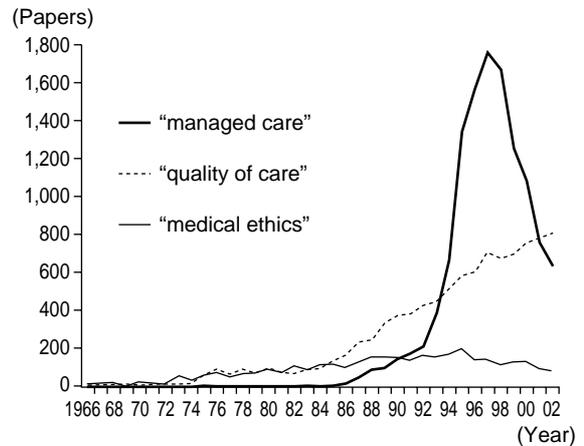


Fig. 3 Number of papers found in the search using "medical ethics," "managed care," "quality of care"

this period supported medical ethics or self-regulation by using the term, professional autonomy. Secondly, the term, professional autonomy, was used to combat the inroads made by managed care and advocate physicians' self-governance. This result squares with the fact that managed care began to thrive in the United States at the end of the 1980s and strengthened its advance in the health care sector during the first half of the 1990s.

It was also found that the number of papers discussing the issue on how to secure quality care was relatively high from 1979 to 2002 and the number has been rising. We observed that the term, professional autonomy, in the selected papers was used to explain the theme on improving the quality of care by self-regulation. Papers about the autonomy of the nursing profession in the health care sector were also occasionally found.

These findings suggest that the topics on medical ethics and managed care are the major cause in the increased number of papers from 1994 to 1997 and the topic on the quality of care is the major cause in the overall increased number of papers. To make certain of this theory, a search using the terms of "medical ethics," "managed care," and "quality of care" was carried out and the number of papers for

each term was investigated. The results were plotted in Fig. 3. The number of papers containing the term “medical ethics” peaked from 1994 to 1996; the number of papers containing the term “managed care” peaked from 1996 to 1998; and the number of papers containing the term “quality of care” showed an overall increase.

## The Physician and Clinical Practice Guidelines

Our review and analysis thus far clearly indicate that positive freedom is vital to the profession and the term, professional autonomy, signifies this fact. Based on this result, how is the issue of clinical practice guidelines to be addressed? It is evident that the relationship between the physician and clinical practice guidelines can be restructured from the perspective of professional autonomy. “Purofessionaru furiidamu” has hitherto served as the physicians’ theoretical justification to cast off the guidelines. However, the direction of this justification would be reversed, if we substitute the term “professional autonomy” in place of “purofessionaru furiidamu.” This can be explored from the side of responsible for formulating clinical practice guidelines and from the side of that will use them.

### 1. Formulated by the medical profession

Positive freedom denotes freedom that can be achieved only when decisions are made by the self. It is suggested that physicians enjoy this freedom only when they actively participate in the decision-making process with regard to clinical practice guidelines. From the perspective of autonomy, it is also desirable for the profession to formulate guidelines to regulate its members, to improve professional quality, and to earn the trust of society.

Since clinical practice guidelines affect society in general, the process of formulating guidelines must be kept transparent. The participation of methodologists, clinical epidemiolo-

gists, biostatisticians, pharmacotherapy specialists, librarians, informationists, patients, public institutions, and other relevant parties is advisable. Nevertheless, from the perspective of professional autonomy, the contribution of the medical profession is a requisite. The attitude of physicians who are against formulating guidelines is inappropriate as a professional.

### 2. Used by the medical profession

All physicians cannot be directly involved in the task of formulating guidelines. Thus, what becomes significant is their application. Autonomous decision-making is also achieved when physicians use these guidelines in their daily clinical practice. Repeated critical study of the guidelines through their actual use by physicians will expedite the revision process. This process will enable decisions to be made by the rationale self rather than by fixed ideas and biases.

The more revisions will require the more involvement of medical professionals in formulating guidelines. Thus, the guidelines can be advanced through these two stages. Skillful coordination between the formulators and users will be the key to the future evolution of clinical practice guidelines.

## Conclusion

In this article, we have attempted to restructure the opposing relationship between physicians and clinical practice guidelines that currently exists. By reviewing and analyzing terminology usages, we found that the attitude, “guidelines aren’t needed because we’re professionals,” is irrelevant, and the mindset, “because we are professionals, we must act as the nucleus in developing guidelines,” is relevant. Physicians are recognized as professionals because they have autonomous guidelines. Clinical practice guidelines do not become meaningful until they are formulated and used by physicians. Hence, we conclude that the relationship between physicians and clinical

practice guidelines can be restructured to become mutually indispensable through the medium of professional autonomy. The future of clinical practice guidelines depends on the professional awareness of physicians.

#### REFERENCES

- 1) Accessible at <http://www.ebm.jcghc.or.jp>.
- 2) Tsutani, K.: Policy and politics of evidence-based medicine in Japan. *In: Health Sciences Research Grants Report 2000-S-009* (ed. by Tango, T.). National Institute of Public Health, Tokyo, 2001; pp.51–68. Accessible at <http://cochrane.umin.ac.jp/pp.pdf>.
- 3) Takemi, T.: Development of health care, professional freedom and the law. 1979. (in Japanese)
- 4) JMA Legal Department: Introduction to professional freedom and the law. *In: Research Report for 1980–1981* (ed. by JMA Committee on Medical Law and Social Legislation), JMA, Tokyo, 1982; pp.1–24. (in Japanese)
- 5) Kant, I.: *Grundelgung zur Metaphysik der Sitten*, 1785; Der Begriff der Freiheit ist der Schlüssel zur Erklärung der Autonomie des Willens.
- 6) Kant, I.: *Die Metaphysik der Sitten*, 1797; Einleitung in die Metaphysik der Sitten I.
- 7) Kant, I.: *Grundelgung zur Metaphysik der Sitten*, 1785; Von dem Interesse, welches den Ideen der Sittlichkeit anhängt.
- 8) Kant, I.: *Die Metaphysik der Sitten*, 1797; Einleitung zur Tugendlehre II.
- 9) MacDonald, K.M.: *The Sociology of the Professions*. Sage Publications, London, 1995; pp.72–94.
- 10) Friedson, E.: *Profession of Medicine: A Study of the Sociology of Applied Knowledge*. Univ. Chicago Press, Chicago, 1970; pp.71–84.
- 11) Freidson, E.: *Professional Dominance: The Social Structure of Medical Care*. Atherton Press, New York, 1970; p.134.
- 12) JMA: *A Guide on Providing Medical Information (2nd edition)*. JMA, Tokyo, 2000. (in Japanese)