Vol.45, No.1 January 2002

# JMAJ

## Japan Medical Association Journal

**JMAJ**
Japan Medical Association Journal

**Published by**
JAPAN MEDICAL ASSOCIATION
2-28-16, Honkomagome
Bunkyo-ku
Tokyo 113-8621
Japan

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Eitaka TSUBOI

*Secretary General:*
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URL: http://www.med.or.jp/english/

**Printed by** Japan Printing Co., Ltd.

**Subscription Rate:**
Single Issue: ¥600
One Year: ¥7,200

## CONTENTS

# Guidelines for the Management of Diabetic Retinopathy for the Internist

JMAJ 45(1): 1–7, 2002

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**Abstract:** Diabetic retinopathy is classified into three stages based on the stage of progression of the disease—background (simple), preproliferative and proliferative. The earliest stage is called background diabetic retinopathy and is characterized by dot or blot hemorrhages and microaneurysms associated with retinal microvascular lesions which are closely related to hyperglycemia. With the development of retinal capillary obstruction, background diabetic retinopathy progresses to the stage of preproliferative diabetic retinopathy, in which avascular zones can be detected by fluorescein angiography. In proliferative diabetic retinopathy, which develops with further progression of the disease, newly formed blood vessels, vitreous hemorrhage, and retinal detachment produce severe visual loss. Good blood sugar control is essential for preventing the development and progression of diabetic retinopathy; therein lies the important role of the internist. In the stages of preproliferative and proliferative retinopathy, patients should be referred to the ophthalmologist for laser photocoagulation and vitrectomy. Patient education is important to prevent blindness resulting from diabetic retinopathy. Diabetic patients should be aware that diabetic retinopathy may lead to blindness. It must be emphasized that diabetic retinopathy generally causes no visual symptoms in its earlier stages and that, therefore, periodic funduscopy is necessary to detect the changes of retinopathy. In patients who are at a relatively lower risk of becoming blind, funduscopy with the use of polaroid photography could be extremely useful.

**Key words:** Pathology and stages; Control of blood glucose levels; Patient education for periodic ophthalmologic examination; Frequency of follow-up and stages

## Introduction

Medical care of patients with diabetic retinopathy requires the collaboration of the internist and the ophthalmologist. I hope that this article will equip the internists with sufficient basic knowledge of the important issues related to the ophthalmologic treatment of diabetic retino-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 123, No. 3, 2000, pages 365–369).

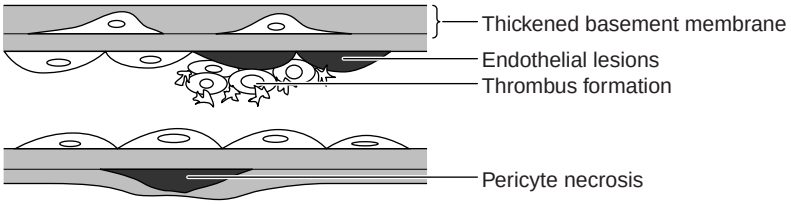


Fig. 1 Microvascular abnormalities occurring before the development of diabetic retinopathy

pathy to prepare them for patient education.

## Disease Status and the Stage of Disease in Diabetic Retinopathy

The pathophysiology of diabetic retinopathy is explained to facilitate the management and treatment of the disease.

### 1. Stage before the development of diabetic retinopathy

Diabetic retinopathy is diagnosed when abnormalities are observed on macroscopic examination by a funduscopy. However, microstructural or functional changes have already occurred before macroscopic fundus abnormalities are detected.

(1) **Microstructural abnormalities**

Diabetic retinopathy is essentially a retinal microvascular disease developing after prolonged hyperglycemia.[1)] The walls of small blood vessels are composed of endothelial cells lining the basement membrane and surrounding pericytes.

Elevated blood glucose levels promote thrombus on the surface of the endothelial cells and necrosis of the pericytes, resulting in circulatory disturbance of retinal capillary. In addition, thickening and loss of elasticity of the basement membrane occurs, inducing circulatory obstruction (Fig. 1).

(2) **Functional abnormalities**

Among the microvascular lesions described above, injury to endothelial cells may lead to breakdown of the blood-retinal barrier (BRB). BRB, which is similar to the blood-brain barrier, prevents leakage of high-molecular-weight proteins or lipids into the extravascular space and maintains intraretinal homeostasis. Breakdown of the BRB due to endothelial injury causes extravasation of plasma proteins and lipids. While severe damage to the BRB can be detected by funduscopy, even slight functional deterioration may be detected by vitreous fluorophotometry.[2)]

Neuropathy in diabetics sometimes precedes the onset of retinopathy and often involves the retinal nerve cells. In some diabetic patients, abnormal waveforms can be observed on the electroretinogram (ERG) even before diabetic retinopathy is detected.[3)]

### 2. Simple diabetic retinopathy

Chronic hyperglycemia affects the retinal microvessels and facilitates progression of the disease. The earliest manifestation is damage to the retinal vascular walls, which results in microvascular obstruction. Damage to the microvessels triggers the formation of microaneurysms and rupture of the vascular walls, observed as dot or blot hemorrhages in the retina.

Breakdown of the BRB causes the retinal edema and promotes the formation of lipid deposits, mainly consisting of cholesterol derived from the plasma. These yellow-white lesions, called hard exudates, can be identified by funduscopy. When microvessel obstruction produces focal ischemia, pallor and/or edema of the retina develops. These ischemic foci are referred to as soft exudates.

### 3. Preproliferative diabetic retinopathy

Preprolifertative retinopathy is a more severe form of diabetic retinopathy than simple retino-

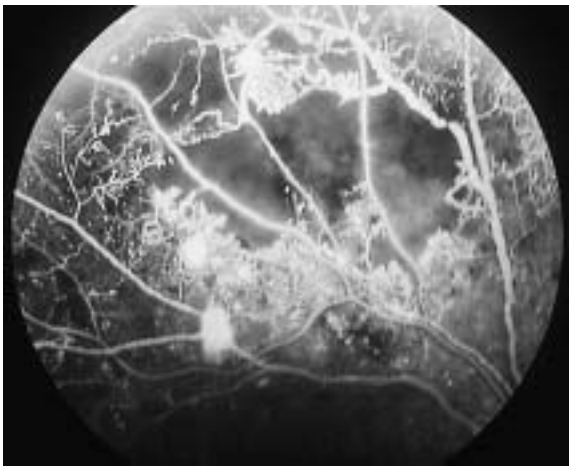

Fig. 2 Fluorescein angiograph revealing occlusion of retinal capillaries

Occluded areas are visible as blackouts surrounded by dilated or tortuous vessels (intraretinal microvascular abnormalities, IRMA)

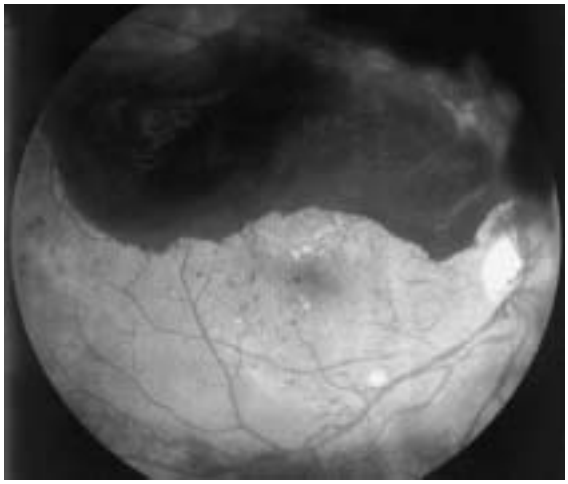

Fig. 3 Vitreous hemorrhage in proliferative diabetic retinopathy

Preretinal hemorrhage spread the upper half of the fundus.

pathy, and often progresses to proliferative diabetic retinopathy. Ischemia due to microvascular occlusion or leakage of plasma constituents stimulates the release of cytokines, particularly vascular endothelial growth factor (VEGF), which acts as an intercellular mediator in various ways.

VEGF facilitates the proliferation of endothelial cells and promotes neovascularization.[4] New vessels are thus prone to form in areas of ischemia or leakage. Preproliferative changes signify the risk of progression to the stage of tissue proliferation, or proliferative diabetic retinopathy.

In the preproliferative stage, the funduscopic findings are characterized by an increased number of soft exudates in association with microvascular occlusions and intraretinal microvascular abnormalities (IRMA), consisting of irregular segmental dilatations or abrupt reduction in vessel branching around occluded vessels. Fluorescein angiography clearly depicts areas of microvascular occlusion as blackouts, since contrast medium does not enter infarcted regions (Fig. 2).

In fluorescein angiography, the patient is administered 5 m*l* of 10% sodium fluorescein intravenously. Immediately after the injection (in about 10 seconds or less), sequential photographs are taken for up to 10 minutes. These procedures cause a sensation of glare in the eyes of the patient. The dye is hepatotoxic and fluorescein angiography should not be performed in patients with severe hepatic insufficiency. The dye should also not be administered to patients in poor general condition, since anaphylactic shock has been reported in a few cases.

**4. Proliferative diabetic retinopathy**

With the formation of new blood vessels, diabetic retinopathy shows markedly different pathological features compared to previous two stages. In this stage, lesions are seen extending from the retina to the vitreous. New abnormal vessels form in areas adjacent to occluded vessels and grow out of the retinal surface into the vitreous. These new vessels radiate throughout the vitreous, running along the posterior hyaloid membrane at the border of the vitreous and the retina or infiltrating into the center of the vitreous.

Because of their fragility, newly formed vessels easily rupture with increase in the blood

pressure or traction from the vitreous and bleed into the vitreous (Fig. 3), causing pathological myodesopsia or visual impairment when blood covers the macula. New vessels induce gradual proliferation of connective tissue, mainly consisting of collagen fibers, which proliferates along the surface of the retina as a fibrous proliferative membrane. The proliferative membrane is adherent to the surface of the retina. Contraction of the proliferative membrane causes traction on the retina, resulting in retinal detachment which may result in severe visual loss when the detachment reaches the macula.

If vitreous hemorrhage interferes with fundus examination, echography must be performed to detect retinal detachment and examine the intraocular condition.

## Treatment According to the Stages of the Disease

### 1. Stage before the development of diabetic retinopathy

Even at this stage, it is important to take measures to prevent the development of diabetic retinopathy. Control of blood glucose levels is essential and the internist plays a leading role.

Many cohort studies in the United States and Europe have shown that strict control of blood glucose levels is of critical importance in preventing the development of diabetic retinopathy and it has been recommended that the blood glucose levels be maintained within the normal range as far as possible.[5,6] In addition, diabetic patients with hypertension should receive effective antihypertensive treatment, since many researchers have indicated that hypertension greatly influences the progression of the disease in type 2 diabetic patients.[6]

Although a number of clinical studies have been conducted with a view to finding a new drug for preventing the development and progression of diabetic retinopathy,[7] at present, no drug effective for this purpose is available. This suggests that many factors are involved in the pathogenesis of diabetic retinopathy and that no single drug can solve all the problems related to the disease.

### 2. Simple diabetic retinopathy

Damage due to aneurysms, dot/blot hemorrhages, hard exudates, and a small number of soft exudates are pathological condition of simple diabetic retinopathy, and these are reversible under good control of blood glucose levels by the guidance of the internist. Drugs are available for the symptomatic treatment of hemorrhages or exudates, but no medicines, as mentioned before, have been shown to influence the disease course itself.

When retinal edema due to increased capillary permeability extends to the macula, severe visual loss becomes inevitable. While drug therapy may be somewhat useful, the ophthalmologist plays an important role in preventing the progression of macular edema and reducing its severity. At present, laser photocoagulation and vitrectomy are performed at this stage. Photocoagulation should be initiated in time, preferably before the onset of impairment of macular functions.[8]

Vitrectomy may reduce the severity of macular edema. The technique has been increasingly applied to the treatment of macular edema when the condition is too severe to perform laser surgery.[9] However, even when the edema is relieved, visual loss often does not improve in patients with severe macular edema. Some investigators have recommended vitrectomy even in the earlier stages of macular edema, but this is still controversial.

### 3. Preproliferative diabetic retinopathy

In this stage, treatment is focused on the prevention of neovascularization. As new vessels develop in areas of retinal vessel occlusion, laser photocoagulation on the occluded area has been shown to be useful for the prevention of neovascularization. This is a bloodless operation and can be performed on an outpatient

basis. The usefulness of this intervention has been demonstrated in several clinical trials and its success rate in the prevention of severe diabetic retinopathy and blindness has been reported to be 70 to 90%.[10)]

At this stage, conservative medical treatment instead of laser surgery may increase the risk of blindness and impair the chances of improvement of the disease.

**4. Proliferative diabetic retinopathy**

Even at this stage, if neovascularization is mild or moderate, laser therapy may be effective. However, when vitreous hemorrhage or retinal detachment is detected, vitrectomy is recommended. Vitrectomy requires special surgical skill and expensive equipments.

Recently, the success rate of vitrectomy has improved with technical advances and the development of elaborate devices, but the operation is still challenging and the success rate is not high enough around 80%. Several studies have demonstrated a better outcome when vitrectomy is performed at the stage of mild retinal dysfunction and have recommended early vitrectomy.

## Guide to the Management of Diabetic Retinopathy for the Internist

**1. Blood glucose levels control is the key**

Treatment of diabetic retinopathy is based on good control of blood glucose levels. It is essential to maintain good control of blood glucose levels without interruption and to never leave hyperglycemia untreated. The first step in the management of diabetic retinopathy by the internist is to make the patient aware of how serious the complications could be.

**2. Subjective symptoms are not reliable indicators for the detection of diabetic retinopathy**

The patients do not complain any symptoms until diabetic retinopathy progresses to the advanced stage. When vitreous hemorrhage, retinal detachment and severe macular edema occur, the patient may develop visual loss. Macular edema commences even at the earlier stage of simple diabetic retinopathy, and the morbidity of macular edema becomes worse and the condition becomes more severe as the retinopathy progresses.

Vitreous hemorrhage often provokes pathological myodesopsia or blurred vision, while retinal detachment may induce visual loss or visual field defects. However, by the time the patient develops these symptoms, the disease has become far advanced and the risk of blindness is substantially high at this stage. Diabetic patients should thus be encouraged to undergo periodic ophthalmologic examination, even if they have no visual symptoms.

**3. Follow-up with polaroid photography**

Fundus photographs provide a permanent record for later evaluation and can be studied by the same ophthalmologist or other specialists. Polaroid photography offers the additional benefits of instantaneous development and printing on the spot, and the patient does not have to wait for the results till the next visit. For the internist, fundus photographs obtained immediately are very useful for clearly explaining the current status of the disease to the patient. However, this simple technique also has the following disadvantages:

The image quality of polaroid photographs is grainy and sometimes there are inconsistencies in printing. Thus, tiny lesions in the earlier stages or subtle vascular changes are often not clearly detected.

The angles at which fundus photographs can be taken are limited, and only areas of the posterior pole at 45 degrees can be photographed. Lesions in the earlier stages of diabetic retinopathy are mainly noted on the nasal side of the optic disc, and photographs limited to areas surrounding the macula often miss severe lesions in other areas.

Accordingly, polaroid photography is acceptable for excluding the disease in low-risk groups

Table 1 Frequency of Funduscopic Follow-ups in Diabetic Patients According to the Stage of the Disease

| | |
|---|---|
| 1. No diabetic retinopathy | Once a year |
| 2. Simple diabetic retinopathy | Once in 3 to 6 months |
| 3. Preproliferative diabetic retinopathy | Once in 2 months* |
| 4. Proliferative diabetic retinopathy | Once in 2 to 4 weeks* |

Note) *: When the progression of the disease is stabilized by photocoagulation or vitrectomy, fundus examination once in 2 to 4 months is acceptable.

with good control of blood glucose levels in whom no fundus abnormalities have been detected by complete funduscopy in the previous one or two years.[11)]

However, if any minor hemorrhage or lesions are detected, the patient should be referred to the ophthalmologist for a thorough fundus examination.

### 4. Frequency of the follow-up of funduscopy according to the stage of the disease

Diabetic retinopathy may progress differently according to the stages. The frequency of funduscopic follow-ups should be determined according to the stage of the disease in individual cases (Table 1). The internist should fully understand the status of the disease in each patient and refer the patient to the ophthalmologist when necessary, so as to offer timely intervention and prevent blindness.

## Conclusion

This article describes the different stages of progression of diabetic retinopathy, and provides guidelines to the internist for the management of the disease. I hope that these descriptions will equip the internist with the basic knowledge for the treatment of patients with diabetic retinopathy.

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# Glaucoma

JMAJ 45(1): 8–12, 2002

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**Abstract:** Glaucoma is a disease characterized by "glaucomatous optic disc atrophy" such as enlargement of the cupping of optic disc and retinal nerve fiber defects, with resultant visual field defect. Visual field defect gradually progresses in an irreversible manner, ultimately leading to blindness. While a high intraocular pressure (IOP) is the greatest and most decisive risk factor in its development and progression, glaucoma is not rare in patients with IOP within the normal range (21 mmHg or lower). Therefore, high IOP is not a prerequisite for the diagnosis of glaucoma. Glaucoma is roughly classified into open-angle glaucoma and angle-closure glaucoma, according to the size of the chamber angle that is formed by the cornea and the iris. Congenital glaucoma that develops immediately after birth or by the age of 2 or 3 years is classified separately. Since the cause, clinical course, and treatment policy may vary depending on the disease type, each type of glaucoma should be treated in a different way. Among these, the most common type of glaucoma is open-angle glaucoma. Open-angle glaucoma should be first treated in a conservative manner by pharmacotherapy. When pharmacotherapy fails to prevent progression of the disease, laser therapy and invasive surgical therapy should be considered.

**Key words:** Glaucoma; Optic disc; Visual field defect; Open-angle glaucoma; Angle-closure glaucoma

## Definition of Glaucoma and Its Changes

Glaucoma is a disease in which visual information obtained by retinal neurons cannot reach the brain due to damage of the retinal nerve fiber axons at the optic disc (Fig. 1), and is characterized by visual field defect (Fig. 2). Secondary to axonal damage, the death of retinal ganglion cells and ganglion cells in the lateral geniculate body is induced by the mechanism of apoptosis.

One of the most well-known causes of glaucoma is elevation of the intraocular pressure

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 12, 2000, pages 1725–1728).
The Japanese text is a transcript of a lecture originally aired on September 12, 2000, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

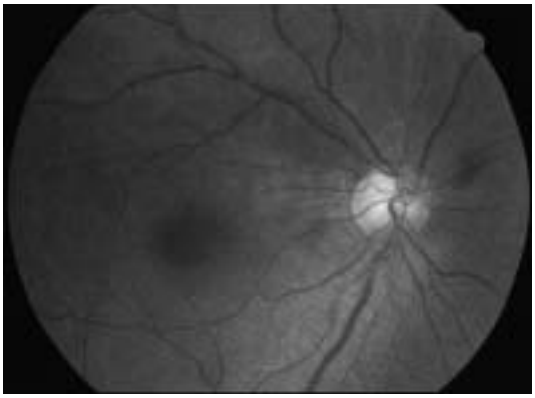

Fig. 1 Optic disc in a case of glaucoma
Enlargement of the cupping is noted.

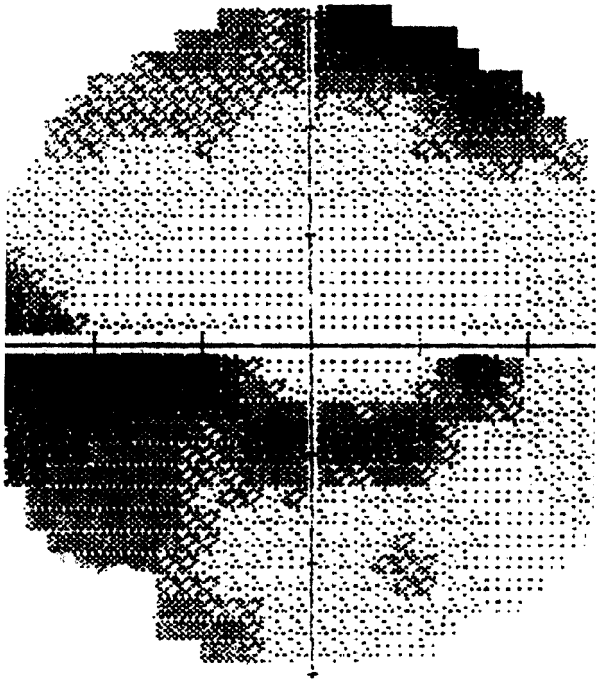

Fig. 2 Results of perimetry in a case of glaucoma presented in Fig. 1
Visual field defect (black area) corresponding to atrophy of the optic disc is noted.

(IOP). In the past, glaucoma was regarded as a condition in which elevation of the IOP elevation resulted in visual functional disorder. The term "glaucoma" is believed to have been first used by Hippocrates around 400 B.C. to refer to eyes that have turned blue-green due to high IOP and opacity of the cornea.

In recent years, however, many patients with IOP within the normal range, i.e., not higher than 21 mmHg, have been encountered who exhibit almost the same visual disc atrophic changes and resultant visual field defects as those induced by high IOP. Thus, currently, high IOP is no longer included in the definition of glaucoma.

Table 1 Prevalence of Glaucoma in the Population Aged Over 40 Years[1)]

| Disease type | Prevalence (%) |
|---|---|
| Primary open angle glaucoma | 0.58 |
| Normal-tension glaucoma | 2.04 |
| Primary angle-closure glaucoma | 0.34 |
| Secondary glaucoma | 0.32 |
| Capsular glaucoma | 0.16 |
| Others | 0.12 |

## Prevalence of Glaucoma

According to a national epidemiological survey conducted in 1988 and 1989,[1)] the prevalence of glaucoma in the population aged over 40 years is 3.56%, and the actual number of patients in Japan is estimated to be about two million. Open-angle glaucoma, or so-called chronic glaucoma accounts for three-quarters of these patients, and normal-tension glaucoma with IOP within the normal range accounts for more than two-thirds of the patients (Table 1).

After diabetic retinopathy, glaucoma is the second most common cause of blindness in advanced countries, and it is predicted that it will become the most common cause of blindness in the near future.[2)]

## Causes of Glaucoma

As mentioned earlier, high IOP is the most important cause of glaucoma. When the optic disc becomes unable to resist the pressure load-

Table 2 Genes and Loci Responsible for (Primary) Glaucoma Identified to Date

| Disease type | Loci | Position on the chromosome | Causative gene |
|---|---|---|---|
| Primary open angle glaucoma | GLC1A | 1q24.3-q25.2 | *MYOC* |
| | GLC1B | 2 cen-q13 | |
| | GLC1C | 3q21-q24 | |
| | GLC1D | 8q23 | |
| | GLC1E | 10p15-p14 | |
| | GLC1F | 7q35-36 | |
| Congenital glaucoma | GLC3A | 2p21 | *CYP1B1* |
| | GLC3B | 1p36 | |

ing of increased IOP, atrophy in a characteristic shape accompanying enlargement of the optic disc cupping develops (Fig. 1), and axonal disorder occurs. However, glaucoma may develop even when the IOP is within the normal range. Impairment of the blood flow into the optic disc and fragility of the optic disc due to some unknown reasons have also been suggested as possible causes of glaucoma other than high IOP.

The occurrence of glaucoma is relatively strongly related to genetic factors. The brothers and sisters of patients with open-angle glaucoma have a 25–35% risk of developing glaucoma, although the figures vary among reports. Primary angle-closure glaucoma is also associated with a high risk of occurrence in siblings, because this disease is related to the morphology of the eye.

As a result of recent linkage analyses, numerous genes and loci responsible for glaucoma have been discovered. While great advances in this area are expected in the future, caution must be exercised before informing the patients about the genetic risks of the disease as it may cause severe anxiety in the patients and their families. Appropriate systems for supporting the patients, such as genetic counseling, need to be established.

The genes and loci responsible for glaucoma that have been identified to date are listed in Table 2. Diagnosis by screening for genetic variations is possible in about 3% of the total number of cases diagnosed.

## Classification of Glaucoma (Table 3)

Glaucoma can be roughly classified into open-angle glaucoma and angle-closure glaucoma. In addition, glaucoma that develops immediately after birth or by the age of 2 or 3 years is distinguished as congenital glaucoma.

While primary glaucoma without specific cause accounts for the majority of the cases, glaucoma resulting from uveitis, injury or IOP elevation induced by steroid eyedrops, or other causes is classified as secondary glaucoma.

## Symptoms and Natural Course

Naturally, chronic cases and acute cases much differ in the symptoms and natural course.

In the cases with sudden IOP elevation, such as attacks of acute angle-closure glaucoma, marked ocular pain, congestion, declined visual acuity, headache, nausea, and vomiting occur. Persistent IOP elevation at such high levels for several days could lead to blindness. If immediately treated by pharmacotherapy and surgical therapy, the condition could be cured with almost no sequelae or only mild visual field impairment and irregularity of the pupil. However, severe IOP elevation may impair the aqueous outflow, and the possibility of re-elevation of IOP on a subsequent occasion should be borne in mind.

Table 3 Classification of Glaucoma

| | | |
|---|---|---|
| Open angle glaucoma | Primary open angle glaucoma | |
| | Normal-tension glaucoma | |
| | Secondary open angle glaucoma | Capsular glaucoma<br>Steroid glaucoma<br>Glaucoma associated with uveitis, etc. |
| Angle closure glaucoma | Primary angle-closure glaucoma | Acute primary angle-closure glaucoma<br>Chronic primary angle-closure glaucoma<br>Plateau iris syndrome |
| | Secondary angle-closure glaucoma | Glaucoma associated with uveitis<br>Glaucoma associated with lens subluxation, etc. |
| Mixed glaucoma | | |
| Congenital glaucoma | Primary congenital glaucoma | |
| | Secondary congenital glaucoma | Axenfeld-Rieger syndrome<br>Sturge-Weber syndrome<br>Aniridia, etc. |

On the other hand, when the glaucoma follows a chronic course without marked IOP elevation, the patients are usually unaware of the condition during the early stages. Impairment of the retinal nerve fiber axons at the optic disc progresses gradually. It is often marked at the top and bottom areas of the cribriform lamina of the optic disc that are structurally weak. The visual field impairment corresponds with this disorder. Relative scotoma appears on the superior and inferior nasal sides and in Bjerrum area 10 to 20° away from the point of foveal fixation, and gradually enlarges to progress to absolute scotoma. Patients are not aware of the visual field defect until very late stages of the disease, because the central visual field is preserved to a considerable extent until the late stage of the disease.

The visual field defect progresses gradually until only the central visual field and a small area of the temporal visual field is preserved. In the advanced stage, the central visual field is also lost and the visual acuity declines at this stage. Unfortunately, however, when the condition is discovered at this late stage, the prognosis is not good. Although some part of the temporal visual field remains until the very late stage, the visual acuity achieved by this visual field is 0.1 or less.

## Diagnosis of Glaucoma

Glaucoma is usually diagnosed on the basis of tonometry, optic disc findings, and perimetry. High IOP is an obvious risk factor of glaucoma. When the IOP is much higher than the upper limit of the normal, i.e., greater than 21 mmHg, for example, higher than 30 mmHg, a high likelihood of development of glaucoma should be borne in mind even if the optic disc findings and perimetric findings are normal, and treatment should be started.

Thus, tonometry is crucial for the diagnosis of glaucoma. However, tonometry alone is insufficient. As discussed at the beginning of this article, glaucoma is defined as impairment of the retinal ganglion cell axons at the optic disc and resultant visual field defects, and the disease is not diagnosed unless both of these abnormalities are observed. More specifically,

abnormal findings in the optic disc, such as the enlargement of optic disc cupping, and visual field impairment that can be explained by these findings should be present in order for glaucoma to be diagnosed.

Gonioscopy is also important from the point of view of prevention of glaucoma. The chamber angle is the space created by the cornea and iris, and the aqueous humor circulating in the eye is excreted here. Since angle-closure glaucoma is likely to develop if the chamber angle is shallow, examination of the chamber angle by gonioscopy is very important for preventing acute attacks of angle-closure glaucoma. Needless to say, gonioscopy is essential for the diagnosis of angle-closure glaucoma and secondary glaucoma.

## Treatment of Glaucoma and Follow-up of the Clinical Course

At present, lowering of the IOP is almost the only way to treat glaucoma. Calcium channel blockers for improving the blood flow at the optic disc as well as vitamins are used occasionally, but their roles are only supplementary. Therefore, the main goal of treatment of glaucoma is to lower the IOP, evaluate the effects of the treatment by perimetry, and aim at further lowering of the IOP when the effects are judged to be insufficient.

The initial target IOP to be achieved by the treatment is usually set at 21 mmHg, which is the upper limit of the normal range, or 17 to 18 mmHg. If the IOP is lowered to this level, but still not associated with clinical benefits, further lowering of the IOP is attempted.

The treatment of normal-tension glaucoma is usually aimed at lowering the IOP by more than 30% from the baseline. However, a more realistic goal should be set if the baseline IOP is low, and the treatment should aim at lowering the IOP further if marked visual field defects are present and the structure of the optic disc appears to be very fragile.

Specific methods of treatment shall not be discussed here, as they are already described in numerous textbooks. As a general rule, the treatment should be started with pharmacotherapy using eye drops, and then argon laser trabeculoplasty or where indicated, surgical therapy should be attempted if the treatment effects are insufficient. In the event of surgical therapy, trabeculectomy for draining aqueous humor into the subconjunctival space is often performed. However, as a general rule, this procedure should be avoided as far as possible as it may be associated with various complications, including postoperative shallow anterior chamber, ocular hypotony, cataract development, and infection which may develop long after the operation.

## Conclusion

Glaucoma is a disease that occurs at a high prevalence (at least one in 30 people, in the population aged over 40 years). Because of the paucity of subjective symptoms, the patients may not notice the disease until the late stages. Therefore, early diagnosis through the effective use of ophthalmological examination techniques, as well as health check-ups for detecting adult diseases is important.

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# Exudative Age-related Macular Degeneration

JMAJ 45(1): 13–20, 2002

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**Abstract:** In Japan, exudative age-related macular degeneration is defined as a condition in which lesions originating from choroidal neovascularization (CNV) develop in the macular area in association with aging. The symptoms include central scotoma, metamorphopsia, and irreversible and advanced visual impairment. Serous or hemorrhagic retinal pigment epithelial detachment or retinal detachment, subretinal hemorrhage, subretinal connective tissue formation, and scar lesions are noted in the macular area. Fluorescein and indocyanine green can be used as fluorescent dyes for fluorescein angiography, and photocoagulation is performed when choroidal neovascularization outside the fovea is visible on angiograms obtained with either dye. When the CNV involves the fovea, photocoagulation of the entire subfoveal CNV, photocoagulation of the feeder vessel of the neovascularization, interferon $\beta$ therapy, low-dose radiotherapy, submacular surgery, translocation of the macula, transpapillary thermotherapy, and photodynamic therapy are attempted. Vitreous surgery is performed to remove vitreous hemorrhages originating from the CNV, and procedures for transferring or eliminating subretinal hematomas are performed to treat large subretinal hemorrhages involving the fovea.

**Key words:** Age-related macular degeneration; Choroidal neovascularization; Diagnostic criterion; Treatment

## Synopsis

### 1. Concept and definition

Age-related macular degeneration can be divided into exudative and non-exudative types.

Exudative age-related macular degeneration is a condition characterized by choroidal neovascularization (CNV). It is thought to be a hereditary disease that can be affected by aging and environmental factors and is characterized by hemorrhagic and exudative retinal and retinal pigment epithelial detachment. Atrophic scarring occurs after absorption of the blood and exudates, and severe persistent visual impairment occurs. In Europe and America, exudative age-related macular degeneration is also diagnosed if retinal pigment epithelial detachment is noted, even when no CNV is detected.[1)]

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 12, 2000, pages 1729–1734).
The Japanese text is a transcript of a lecture originally aired on September 13, 2000, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

In non-exudative macular degeneration, geographic atrophic lesions consisting of atrophy of the retinal pigment epithelium and the choriocapillaris are noted. While the incidence of this type of macular degeneration is higher than that of the exudative type, progression of the visual impairment is slower.

The prognosis of exudative age-related macular degeneration is particularly poor, and it is predicted that this may soon arise as a serious problem as the number of aged people increases in Japanese society. This type of macular degeneration is therefore discussed below in greater detail.

## 2. Epidemiology

In 1993, the Research Committee for the Designated Disease Retinochoroidal Degeneration supported by the Ministry of Health, Welfare and Labour conducted a survey jointly with Research Committee for the Epidemiological Study of Intractable Diseases. According to the results of the survey, 14,400 patients with age-related macular degeneration were diagnosed in 1993 in Japan. The overall incidence of age-related macular degeneration is estimated to be 11.5 subjects per 100,000 population (male: 16.2 and female: 7.0), and 7.9, 33.2, 76.1, and 87.2 per 100,000 population in their 50s, 60s, 70s, and 80s (Fig. 1).[2)]

## 3. Etiology

Retinal pigment epithelial cells play important roles in maintaining the retinal environment, including regulation of phagocytic activity against the outer segment of the photoreceptor cells, not only in the photoreceptor cell layer, but in the neurosensory retina. Age-related changes in the retinal pigment epithelial cells include accumulation of lipofuscin as the catabolic digestive residue, and lipogenesis. Moreover, Bruch's membrane beneath the retinal pigment epithelium thickens with aging, and the physiological environment of the photoreceptor cells layer, retinal pigment epithelium, and Bruch's membrane change.

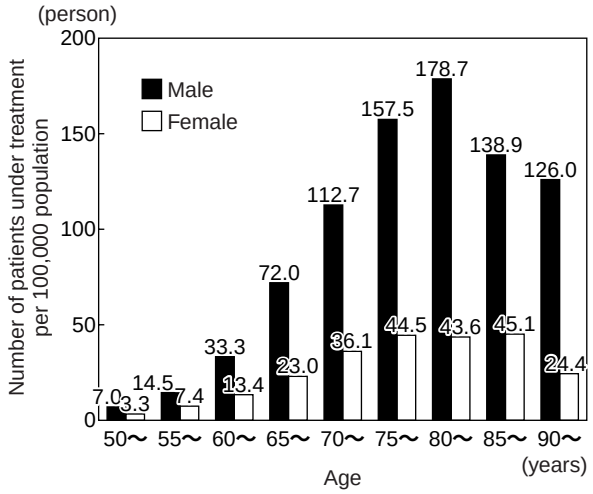


Fig. 1 Number of patients with exudative age-related macular degeneration under diagnosis (1993)

Neovascularization in the choroid is thought to occur when such excessive age-related changes are combined with an ischemic factor or chronic inflammatory reactions, and ingrowths develop through the damaged Bruch's membrane and the retinal pigment epithelium and occasionally emerge above the retinal pigment epithelium. An association with heredity[3)] and smoking[4)] has also been confirmed.

## 4. Symptoms

The symptoms include central scotoma, metamorphopsia, and progressive irreversible and advanced visual impairment.

## 5. Objective findings

(1) Since exudative age-related macular degeneration is characterized by CNV, fluorescein and/or indocyanine green angiography reveals the presence of neovascularization in typical cases. Diagnosis of exudative age-related macular degeneration is performed when CNV is related to aging as indicated by atrophy of the retinal pigment epithelium, pigmentation, and serous drusen. The following findings may also be noted in the presence of CNV:

(2) hemorrhage under the retina or retinal pigment epithelium (Fig. 2),

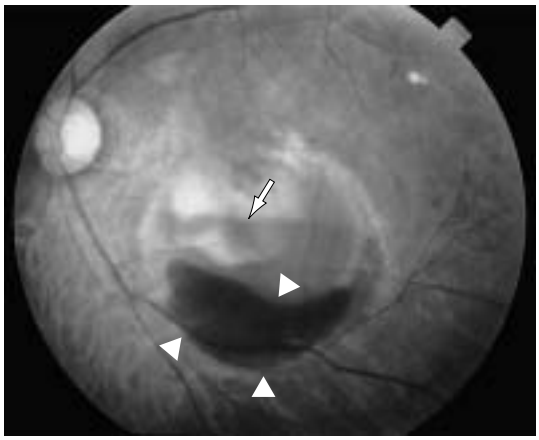

Fig. 2 Hemorrhage under the retinal pigment epithelium (arrow) and subretinal hemorrhage (arrowhead)

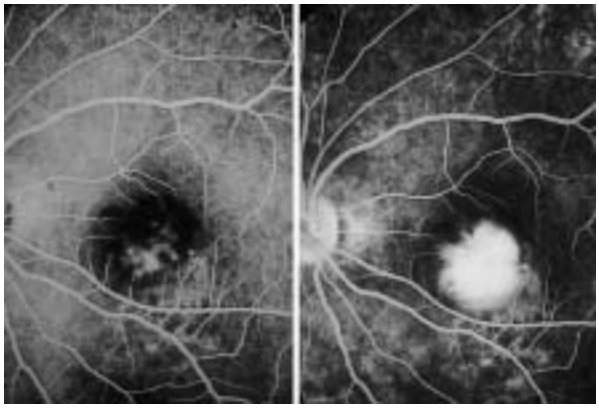

Fig. 3 Classic CNV involving the fovea detected by fluorescein angiography (left: middle phase of angiography, right: late phase of angiography)

(3) serous retinal pigment epithelial detachment, and

(4) serous retinal detachment.

Careful examination for the presence of CNV is necessary, particularly when serous retinal or retinal pigment epithelial detachment is present in patients over 50.

Even when the presence of CNV described above in (1) cannot be identified on angiograms, patients over 50 years of age who exhibit any of the symptoms described in (2) to (4) are likely to have exudative age-related macular degeneration.

**6. Treatment**

The only method of treatment whose efficacy has been established to date is photocoagulation of CNV that possesses a clear margin and does not involve the fovea. However, the indications for this method are limited, and treatment is difficult when the margin of the CNV is unclear. It is not an ideal method, because the treatment itself significantly impairs vision if the neovascularization involves the fovea.

Faced with this situation, various approaches to the treatment of neovascularization in the fovea, where photocoagulation is not a suitable approach, are currently being assessed. They include photocoagulation of feeder vessels, use of antiangiogenic agents, such as interferon, low-dose radiotherapy, surgical extraction of the CNV region, implantation of the pigment epithelium after extraction of the CNV, and translocation of the fovea.

## Diagnostic Criteria

**1. Subjective manifestations**

(1) Visual impairment
(2) Central scotoma
(3) Metamorphopsia
(4) Micropsia

**2. Objective findings**

(1) Findings in the ocular fundus
  1) Subretinal hemorrhage and hemorrhage under the retinal pigment epithelium in the macular area and its vicinity
  2) Serous retinal pigment epithelial detachment
  3) Serous retinal detachment
  4) Disciform lesions (growth of subretinal connective tissue)
  5) Cicatricial lesions
(2) Findings on fluorescein fundus angiography

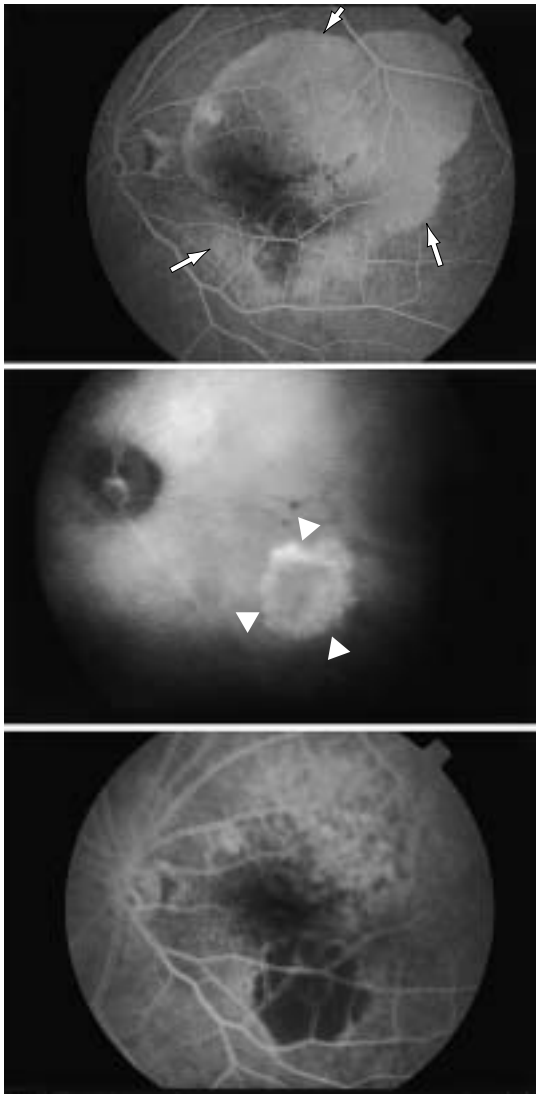

Fig. 4 Top: Occult CNV on fluorescein angiogram
Hyperfluorescence (arrow) representing retinal pigment epithelial detachment is noted, but no hyperfluorescence representing CNV is observed.
Middle: Indocyanine green angiogram
Hyperfluorescence (arrowhead) representing choroidal neovascularization is observed.
Bottom: A fluorescein angiogram obtained after laser photocoagulation of CNV detected by indocyanine green angiography. The hyperfluorescence representing retinal pigment epithelial detachment has disappeared.

1) Findings on fluorescein angiography

Choroidal neovascularization may be visualized as described below.

(a) Classic CNV (Fig. 3): Hyperfluorescence indicating choroidal neovascularization (CNV) is clearly visualized, and a vascular meshwork structure is seen in the very early phases of fluorescein angiography. In the later phase, marked extravascular leakage can be demonstrated.

(b) Occult CNV (Fig. 4 top): The fluorescein angiographic image of CNV is unclear. Angiographic images obtained in the early phase are ambiguous due to blockage of the CNV by hemorrhage and retinal pigment epithelial detachment. Subretinal pigment epithelial accumulation of dye is noted only in the late-phases. Punctate hyperfluorescence is observed in the middle- and late-phases in some eyes.

2) Indocyanine green angiography

There are no established standard views on the interpretation of hyperfluorescence and hypofluorescence on indocyanine green angiograms. However, it is highly likely that occult CNV, which is difficult to detect on fluorescein angiograms because of the presence of hemorrhage or retinal pigment epithelial detachment, is detected by this approach as an area of hyperfluorescence (Fig. 4 middle and bottom). Moreover, since the inflow of dye from the choroidal vessels into the CNV can be observed at an early phase, it is used to detect the vessels feeding the CNV (Fig. 5).

3) Optical coherence tomography

When CNV is present above the retinal pigment epithelium, it is visualized as a bright lesion above the red reflecting layer that represents the retinal pigment epithelium. When the lesion is present beneath the retinal pigment epithelium, differentiation is often difficult.

### 3. Staging of age-related macular degeneration

(1) Early lesions

1) Serous retinal detachment

Retinal detachment localized to the macular area is noted. A small amount of subretinal hemorrhage, retinal edema (cystoid macular edema),

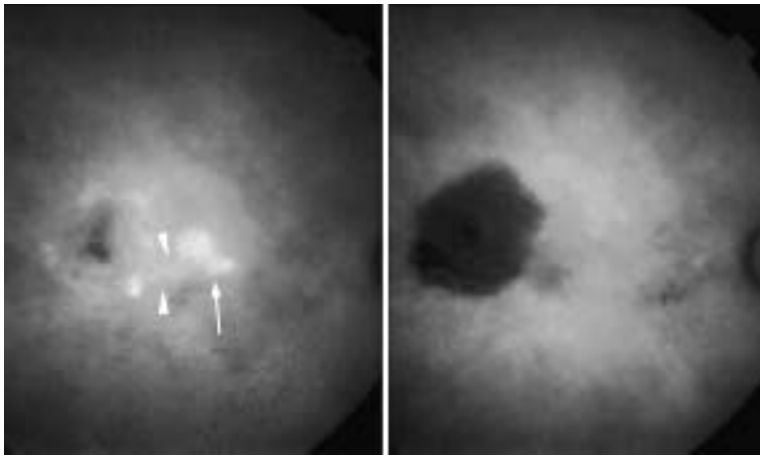

Fig. 5 An indocyanine green angiogram showed hyperfluorescence before photocoagulation, showing feeder vessel (arrowhead) of subfoveal CNV (arrow) and recurrent CNV surrounding hypofluorescence suggesting old laser scar.
Right: After photocoagulation of the feeder vessel and recurrent CNV temporal to the fovea. Hyperfluorescence suggesting foveal CNV has disappeared.

and hard exudate are occasionally present.

2) Serous and hemorrhagic retinal pigment epithelial detachment

CNV may develop beneath large retinal pigment epithelial detachment, or retinal pigment epithelial detachment may result from choroidal neovascularization. In cases with retinal pigment epithelial detachment and accompanying CNV, a condition in which the margin of the retinal pigment epithelial detachment is depressed, the so-called "notch sign", is often noted, or the retinal pigment detachment contains a hemorrhage.

(2) Lesions in the exudative stage

Retinal pigment epithelial detachment and serous retinal detachment are induced by large hemorrhages and exudation from the CNV. Retinal detachment (including cystoid macular edema) is often present. The subretinal growth of new vessels and connective tissues is marked, and so-called "disciform lesions" are noted.

(3) Lesions in the scar stage

The CNV regresses, and yellow-white fibrous vascular scar tissue remains under the retina and/or the atrophic retinal pigment epithelium remains. The retinal-choroidal anastomosis and serous detachment may persist. CNV may recur in the area surrounding the scar tissue.

## Treatment Approach

The standard approach to the treatment of this condition is photocoagulation. However, it is associated with risks, such as visual impairment induced by the photocoagulation itself, enlargement of the laser scar, and recurrence of CNV after treatment. Therefore, detailed examination by fluorescein angiography is essential.

Moreover, informed consent should be carefully obtained from patients, because the main aim of treatment is prevention of progression, rather than improvement of symptoms. Early detection and early treatment are important, because the lesions enlarge and visual impairment progresses and becomes severe.

### 1. Photocoagulation

The results of large-sample randomized double-blind clinical studies to clarify the effi-

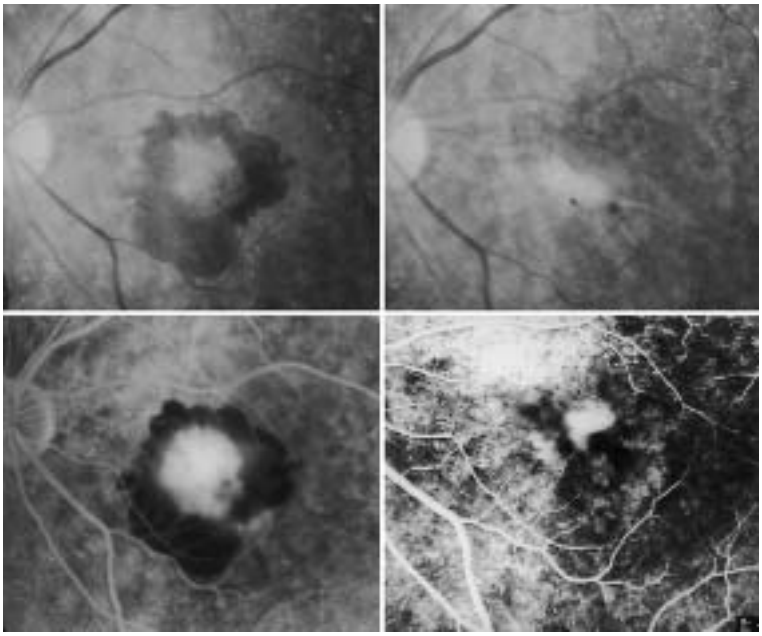

Fig. 6 Clinical course of the patient who underwent extraction of subfoveal CNV
Top left: A preoperative black-and-white photograph. Hemorrhage is noted around the CNV.
Bottom left: A preoperative fluorescein angiogram. Intense leakage suggesting CNV involving the fovea is noted.
Top right: A black-and-white photograph obtained 6 months postoperatively. Part of the sclera is exposed, but the hemorrhage has disappeared. No findings suggesting CNV are observed.
Bottom right: A fluorescein angiogram obtained 6 months postoperatively. No hyperfluorescence suggesting CNV or hypofluorescence suggesting hemorrhage are observed. Hyperfluorescence suggesting scleral tissue staining is noted.

cacy of photocoagulation have been reported in the United States, and they have shown that high intensity photocoagulation after identifying the entire CNV on fluorescence angiograms is effective for extrafoveal, and juxtafoveal CNV, except subfoveal CNV.[5] This approach is also commonly employed in Japan for the treatment of CNV, except subfoveal CNV (Fig. 4, bottom). It promotes scarring of the neovascularization in the exudative stage and absorption of the subretinal fluid and exudate, but it is not indicated in many cases associated with occult CNV, in which the extent of the neovascularization is obscure. Moreover, in eyes with subfoveal CNV, visual impairment is inevitably induced by treatment itself immediately after it is administered.[6–8] Accordingly, the approaches described below are currently employed in Japan.

**2. Photocoagulation of feeding vessels**

Photocoagulation of feeder vessels has been attempted for the treatment for subfoveal CNV. Feeder vessels extending from the choroid are identified by indocyanine green angiography, and then selectively coagulated (Fig. 5). Since the area of coagulation is small, the visual impairment induced by treatment is minimized, the fovea is preserved, and improvement of vision can be expected in some patients.[9] Since expertise is required to detect feeder vessels, this procedure is presently being performed at only a few facilities.

**3. Administration of interferon $\beta$**

Regression of small choroidal neovascular-

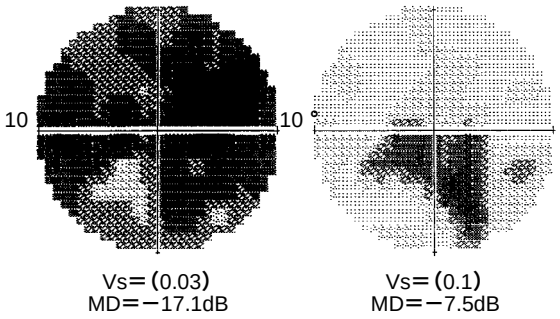


Fig. 7 Clinical course of the central visual field and vision of the patient presented in Fig. 6.
(Left: preoperatively, right: 6 months postoperatively)

izations in the fovea has been reported following administration of 6 million units of interferon $\beta$ for 42 consecutive days.[10)]

**4. Low-dose radiotherapy**

After the efficacy of low-dose X-ray irradiation for subfoveal CNV was reported in England,[11)] radiotherapy with 10 to 20 Gy was attempted in Japan. This approach has been reported to be efficacious in maintaining and improving vision in addition to inducing regression of relatively small subfoveal CNVs,[12,13)] but it has also been reported to be ineffective in a large-scale study in the United States.[14)] A randomized prospective clinical trial is currently being conducted under the auspices of the Ministry of Health, Welfare and Labour in Japan.

**5. Surgical therapy (vitreous surgery, subretinal hematoma transfer procedure, hematoma elimination procedure, and submacular surgery)**

When massive subretinal hemorrhage is present, pneumatic displacement or surgical removal of the subretinal hemorrhage is attempted, and vitreous surgery may be indicated in eyes with long-standing vitreous hemorrhage.

Surgical extraction of subfoveal CNV above the retinal pigment epithelium (Figs. 6 and 7) and implantation of the pigment epithelium after extraction have also been attempted. An operative procedure to move the fovea has also been conducted.

**6. Photodynamic therapy**

In this approach, a photosensitizer is injected intravenously in advance, and after it adheres to the endothelial cells of the CNV, low-power diode laser irradiation is conducted to induce chemical reactions that may cause thrombotic occlusion of the CNV.

Since low-power laser photocoagulation is used in this approach, retinal damage and visual impairment after treatment of the CNV are thought to be minimal. Moreover, treatment can be repeated if the CNV is not obliterated.[15)]

A clinical trial of photodynamic therapy is being conducted in Japan and is expected to show promise as a new method for treating subfoveal CNV.

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# Clinical Characteristics of Depression

JMAJ 45(1): 21–27, 2002

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**Abstract:** The epidemiology, premorbid character, diagnosis, and symptoms were overviewed regarding clinical features of depression. Depression is observed in all age groups from childhood to senescence, and its lifetime prevalence exceeds 10% and that among women is 1.3 to 1.7 times higher than that among men. Its prevalence in old age so far reported is generally low. The premorbid characters of depression known in Japan and Germany are Kretschmer's cycloid, Tellenbach's melancholic and manic types, and Shimoda's immodithymia. Recently, Ihda proposed the structural theory for immodithymic character. The diagnostics of depressive episodes (ICD-10) and the relationship between culture and depressive symptoms are discussed. Depression in non-European cultures as reported previously rarely manifested self-blame or suicidal ideas, and depressive symptoms were not severe. In Japan, there have been reports of withdrawal depression where the patient tries to escape from his/her studies or work without much self-guilt. At least some of the depressive symptoms are culturally defined, and the diversified clinical pictures of depression may reflect the cultural and social situations of the contemporary time.

**Key words:** Prevalence; Premorbid character; Comparative cultural psychiatry; Mood disorder

## Introduction

Depression is primarily characterized by depressive moods and diminished ability to think or act, accompanied by varying degrees of functional deteriorations in emotion, drive, cognition, thinking, and behavior. It is accompanied by somatic symptoms such as insomnia, anorexia, and autonomic imbalance as well as anxiety, fretfulness, and occasional delusion. Its symptoms show diurnal variation, leading to alleviation toward evening. Some patients experience several prolonged phases of depression in their life even with development of drug therapies, and may gradually recover to the premorbid level.

This paper discusses the clinical features of depression including its epidemiology, premorbid character, diagnosis, and symptoms. An attempt is made to view depression from the

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 1, 2000, pages 27–32).

viewpoint of comparative cultural psychiatry in order to gain a deeper understanding of the clinical features of depression.

## Epidemiology[1)]

### 1. Prevalence

Epidemiological surveys based on DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, third edition, revised) that have been conducted on the general population have revealed point prevalence of depression of 1–5%, one-year prevalence of 4–10%, and lifetime prevalence of 13–17%. Epidemiological studies using DSM-III that were conducted in Western countries and Korea in the 1980s, revealed somewhat lower prevalence (3.3 to 12.6% for lifetime prevalence), suggesting an increased tendency for depression in recent years.

### 2. Gender

The one-year prevalence of depression among women is 1.7 to 2.5 times higher than that among men, and the lifetime prevalence among women is 1.3 to 1.7 times higher than that among men. This indicates that more women are suffering from depression than men.

### 3. Age at first onset

In 1967 Akimoto *et al.* studied the age of first onset of primary manic-depressive illness in Japan. According to their report, onset occurs most frequently among individuals in their twenties, followed by those in their 30s, and onset occurs in a considerable number of individuals in their 40–50s. According to recent studies performed in Western countries, the average age for the first-time episode is the mid-twenties, and the first-time onset is observed in all age groups ranging from childhood to old age. Manic-depressive illness in children and youths begins to appear after approximately 11 years of age.[2)]

### 4. Senile depression

A comparatively large number of studies on senile depression have been conducted in Japan. As for its prevalence among those aged 65 years or older reported in studies conducted on the general population in Japan, Hasegawa *et al.* reported a prevalence of senile depression of 0.9% in Tokyo; Naito *et al.* reported a prevalence of 2.1 to 4.8% in three districts in Niigata; Ihara *et al.* reported a prevalence of 0.37%, and Kamahashi *et al.* reported a prevalence of 0.4% in Tochigi Prefecture. According to studies conducted in Western countries since 1980, the point prevalence of senile depression among the population aged 65 years or older is 1–4%, and the lifetime prevalence is also approximately 1–4%. Thus, the prevalence of depression reported in studies on senile depression is generally lower than that reported in studies performed on populations without age limitations.

## Premorbid Character

As to the premorbid characters of depression, the Kretschmer's cycloid, Shimoda's immodithymic character, and H. Tellenbach's melancholic and manic types are known. Ihda *et al.*[3)] recently summarized these characters in a paper published in this journal.

Shimoda's immodithymic character[4,5)] is characterized by hard work, perfectionism, thoroughness, honesty, orderliness, strong senses of justice, obligation and responsibility, and inability to deceive or to be sloppy. Hirasawa[6)] amended Shimoda's emphasis on troublesomeness and enthusiasm of immodithymic character by pointing out that patients with depression have "apparent smooth and sociable attitude toward others with excessive sensitiveness of others' opinion of him." Kasahara[7)] reported that the melancholic type cannot be distinguished from obsessionalism (anankastic character) by merely observing orderliness or punctuality, and that one should note that a patient with the melancholic type "takes care to maintain a smooth relationship with others." By pointing out this inclination for orderliness in one's relationship with others, Kasahara em-

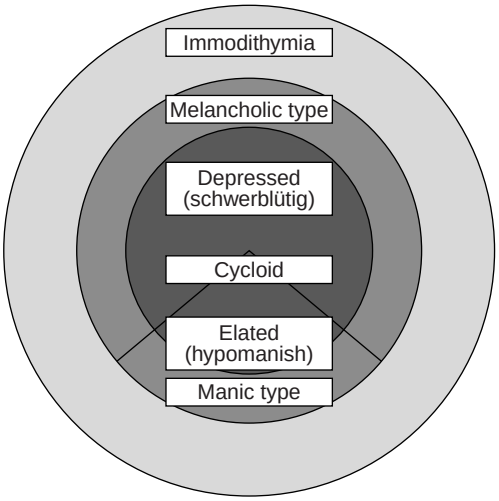


Fig. 1 Premorbid character of mood disorder (schematic drawing)

phasized that the immodithymic character is syntonic, which is a basic characteristic of the cyclothymic personality.

According to Ihda, Shimoda's immodithymic character is not only unipolar but is also a premorbid character for manic-depressive illness in general and includes both H. Tellenbach's[8] melancholic and manic types. Ihda[9,10] schematized the structure of immodithymic character as shown in Fig. 1. According to Ihda, at the nucleus of the premorbid character for manic-depressive illness (affective disorder) is Kretschmer's cycloid, which is surrounded by the melancholic type and manic type, and the immodithymic character includes both the melancholic type and manic type.

In Western countries, such temperament or character models were barely noted as premorbid characters for depression except by Titley *et al.* who published the theory in the 1930s. Although the theory of character and temperament consisting of seven-factor models proposed by Cloninger[11,12] has recently attracted attention in Western countries, it is still in a stage awaiting further development regarding its relationship with the premorbid character of depression.[13,14] According to Akiskal, the perfectionism and obsessive-compulsive traits of premorbid character are not recognized as much in the United States as in Japan or Germany. Akiskal *et al.*[15] pointed out introversion as the premorbid character of unipolar depression, and Angst *et al.*[16] pointed out neuroticism.

The following case report describes a patient who is melancholic as well as cyclothymic.

**[Case report]**

Mr. K is a 36-year-old computer engineer and the elder of two sons. Following graduation from university, he entered the company at which he is currently working, married three years ago and has a son. Although his wife complains that he spends too little time with his family, the family live harmoniously and have no problems.

He is faithful, has a strong sense of responsibility, and is capable at work with many ideas. He is proud of his supervisor's high opinion of him. Since his promotion two years ago to the position of leader of computer network structuring, he has been overworked because he could not say no to numerous jobs that were assigned to him. One year prior to the first episode, he was assigned to several large-scale projects as a leader and during the three months preceding the onset, he worked nearly every day. Looking back on those days, Mr. K mentioned that he was overworked and dissatisfied with the results of his work partly because he was a perfectionist, and that his mood might have been elevated just prior to the onset of depression.

One day, a circuit breakdown paralyzed the entire computer network. As a leader, he felt strongly responsible and became depressive following the accident. Because of easy fatigue and loss of appetite, he saw an internist thinking that something was wrong with his stomach. Gradually, he experienced depressive moods, insomnia, diminished willingness to work, and reluctance to repair the broken circuit. He became increasingly guilt-ridden and fretful.

He visited a psychiatric clinic of a nearby general hospital, accompanied by his wife and supervisor of the company. As his suicidal ideas and depressive mood were quite serious at the first interview, the physician recommended hospitalization. He was fearful of becoming socially ostracized by abandoning his work by hospitalization, and needed to be persuaded by his wife and supervisor to consent to hospitalization.

In the hospital, he was placed on drug therapy with an anti-depressant and was able to obtain good-quality rest. He recovered smoothly. At two weeks following the date of admission, he was aware of his improved condition, and two months after the start of treatment, he was discharged. He returned to work under the doctor's instructions, and had a reduced workload.

Table 1 Criteria for Diagnosis of Depressive Episodes (ICD-10)

| | |
|---|---|
| A. | Episode lasts for at least two weeks |
| B. | Typical symptoms |
| | (1) Depressed mood |
| | (2) Loss of interest or pleasure |
| | (3) Decreased energy or increased fatiguability |
| C. | Additional symptoms |
| | (1) Loss of confidence or self-esteem |
| | (2) Self-reproach or guilt |
| | (3) Suicidal thoughts or behaviours |
| | (4) Diminished ability to think or concentrate |
| | (5) Change in psychomotor activity, with agitation or retardation |
| | (6) Sleep disturbance |
| | (7) Change in appetite |
| Mild episode: | At least two items of B, and at least four items of B and C |
| Moderate episode: | At least two items of B, and at least six items of B and C |
| Severe episode: | At least three items of B, and at least eight items of B and C |

## Diagnosis and Symptoms

### 1. Diagnosis

Table 1 shows the simplified diagnostic criteria for depressive episodes according to the ICD-10 (International Classification of Diseases, 10th revision) published by the WHO.[17] By confirming the presence of several items and by elimination, the diagnosis of depressive episode may be established.

According to the ICD-10 as shown in Table 1, depressed mood, loss of interest, and increased fatiguability are typical symptoms of depression. Even without the subjective symptom of depressed mood, if additional symptoms besides the remaining two items are manifested, it is possible to diagnose a mild or moderate depressive episode. Loss of self-esteem, feeling of self-reproach and presence of suicidal ideas as well as diminished ability to think or concentrate, agitation or retardation, sleep and dietary disturbances are additional symptoms. The sleep and dietary disturbances include not only insomnia and loss of appetite, but also hypersomnia and increase in appetite.

Depressed mood, diminished ability to think and act, loss of confidence, and self-blame are frequently encountered when diagnosing depression in Japanese patients. However, some patients are in a depressive state where these symptoms can not be easily determined. While clinicians should naturally be careful not to overly increase the number of cases diagnosed as depression, it is also important not to overlook depression in patients who have few complaints but who are observed to be depressed, and in those whose depressed mood and inhibitions are not apparent, but who are hypochondriac (masked depression[18]).

### 2. Relationship between culture and depressive symptoms

The symptoms of mental disorders may present different themes according to the gender, age, and social status of the patient. The characteristics of depressive symptoms, particularly delusions in depression, are discussed from the viewpoint of comparative cultural psychiatry[19,20] referring mainly to Kondo's paper.[19]

Depression observed in non-European cultures such as in African countries used to be described as lacking self-blame and suicidal ideas, and was associated with not very serious depressive conditions. Table 2 is quoted from

Table 2 Depressions in Past Day Africa

| | | |
|---|---|---|
| 1895 | Greenlees TD | Rare examples of melancholia |
| 1936 | Gordon HL | Remarkable absence of affective disturbance except for elated type |
| 1937 | Laubscher BJF | Severe depressions and depressions with agitation are hardly ever seen, suicide is extremely rare |
| 1947 | Carothers JC | Manic-depressive insanity is relatively uncommon, ideas of guilt are consistently absent |
| 1950 | Tooth G | Rarity of depressive reactions, suicide and self-reproach |
| 1953 | Lamont AM and Blignault WJ | Rarity of depressive psychoses, not a single case with delusions of guilt |
| 1955 | Moffson A | Manics are observed but depression is very rare |

Source: Prince (1968)[21]

Prince.[21] According to Prince, depression in Africa prior to 1957 (independence of Ghana) was characterized by (1) few complaints of depressed mood, (2) rare instances of self-blame, (3) uncommon suicide, (4) and prevailing hypochondria and physical complaints.

Three major themes of delusion that depressive patients often complain about are hypochondria, sense of guilt, and fear of poverty. The hypochondriacal delusions of depression are considered to be affected by the medical knowledge shared by the society in which the patient resides. As shown by the concept of masked depression,[18] the fact that depressive patients are hypochondriac and not delusive, may be a cross-cultural phenomenon. The theme of guilt delusions may be affected by the religion and social systems defining the individual's sense of responsibility. In Japan, patients often blame themselves in view of the interests of the company they work, colleagues and their relationship with family system rather than having a religious sense of guilt. The delusion of poverty is also strongly affected by culture. The manifestation of delusion of poverty is based on the existence of a widely accepted idea in the society that each individual is responsible for his/her future financial conditions, and one might suggest that in a society lacking such an idea, delusion of poverty would barely appear.

In a world where people equally aim at economic development on the global scale, discussing the cultural characteristics of depression *per se* seems to be quite difficult. However, we should point out that the characteristics of the contemporary social system (or psychological introjection, projection and formed superego when expressed in terms of psychodynamics) that drive depressive patients to despairing self-guilt and suicidal ideation should not be disregarded. The physician's instruction for rest and guarantee of security to depressive patients may be meaningful in that they are issued by a person who is recognized as carrying out a prescribed role in that social system.

### 3. Changes in the clinical features of depression in Japan

Ihda described the following[22]: After the mid-Edo period, the so-called popular morals of diligence (or hard work), frugality, and submission became the motives for modern Japanese capitalism and the historical background for immodithymic character,[23–25] but they declined after World War II, particularly among younger generations. The new generation who are characterized by dependence and "apathy" and who grew up under overprotection and a let-alone policy, emerged. The changes in the clinical features of depression are classified into two types; the dependent type and narcissistic type. The former includes neurotic depres-

sion or somatized depression where physical symptoms are predominant, while the latter includes withdrawal depression and apathetic syndrome.[3,26,27)]

According to Hirose,[28)] melancholic-type patients fall into a depressive state as they struggle with changes in situations, whereas withdrawal- and apathetic-type patients simply abandon efforts for a solution once they realize the difficulty of overcoming the changes by conventional methods, and jump into a depressive state where they are free from uneasiness and pain. Very few patients in the latter group become self-blaming and very few manifest strong suicidal ideas or attempts.

The premorbid character and clinical features of depression change as the contemporary system of society changes.[10,25)] Alternatively, the clinical features of depression may stand on various psychological defense mechanisms. When chronic depression in Japan and Germany are compared, dependence, which develops to a neurotic tendency, becomes more apparent in Japan, while development to an autistic tendency is more evident in Germany. Clinicians should attend to patients by being aware that there are diversified types of depressed state depending on the individual's personality and the situation in which he/she is placed.

## Conclusion

The epidemiology, premorbid character, diagnosis, and symptoms of depression were reviewed with regard to its clinical features. Depression is observed in all ages from childhood to senescence at high prevalence, and is observed at a higher frequency among women than among men. The premorbid characters of depression include cycloid, immodithymic character, melancholic, and manic types. We mentioned the structural theory of immodithymic character (Ihda), summarized the ICD-10 criteria for diagnosis of depression, and discussed the relationship between culture and depressive symptoms. Based on previous reports on depression in Africa and on withdrawal depression in Japan, one may assume that the emergence of a symptom such as self-reproach is largely prescribed by the cultural situation. Clinicians should be aware of the diversified and varied clinical features of depression, which reflect changes in the social system.

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# Drug Therapy for Depression in Japan

JMAJ 45(1): 28–33, 2002

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**Abstract:** Drug therapy for depression fails in more than half of the patients receiving it because inadequate doses are given. It must be explained before starting drug therapy that its effects only appear after 2–4 weeks, but side-effects develop immediately and then begin to subside after 1 week. As a rule, a single antidepressant is administered. SSRIs are as effective as tricyclic antidepressants, but their adverse effects are far weaker than those of the older drugs. This is an advantage of SSRIs over tricyclic antidepressants. According to the American version of the therapeutic algorithm for depression (1995), the first-line drugs for moderate depression are SSRIs. For servere depression, however, tricyclic antidepressants are more effective than SSRIs. To prevent the relapse of acute depression, drug therapy should be continued for 4–6 months at the same dose. When the patients have had two or more depressive episodes in the last 5 years, drug therapy must be continued without changing the dose for 2–3 years, or for 5 years if possible, to prevent recurrence.

**Key words:** Depression; Drug therapy; Evidence-based medicine (EBM); Selective serotonin reuptake inhibitor (SSRI)

## Introduction

In recent years, drug therapy for depression has been undergoing the transition from experience-based medicine to evidence-based medicine (EBM) utilizing the findings of randomized controlled trials. To cope with the transition, the investigation of algorithms for EBM-oriented drug therapy is underway. Although it was far later than in many other countries, fluvoxamin was introduced as the first selective serotonin reuptake inhibitor (SSRI) for clinical use in Japan in 1999. Subsequently, another SSRI (paroxetin) and the first serotonin noradrenaline reuptake inhibitor (SNRI, milnacipran) have been successively released in Japan. Thus, all the types of new-generation antidepressants have now become clinically available in Japan, as in many other countries. These changes have propelled drug therapy for depression in Japan to a new level.

The prevalence of depression in the general population is 2–7%, with a lifetime prevalence of 4–19%, indicating that it is a very common

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 1, 2000, pages 33–37).

Table 1 List of Antidepressants Clinically Available in Japan and Their Daily Doses

| Nonproprietary name | Daily dose (mg) |
|---|---|
| Tricyclic antidepressants | |
| Imipramine | 25–300 |
| Amitriptyline | 30–300 |
| Trimipramine | 50–300 |
| Nortriptyline | 20–150 |
| Clomipramine | 50–225 |
| Amoxapine | 25–300 |
| Lofepramine | 20–150 |
| Dosulepin | 75–150 |
| Tetracyclic antidepressants | |
| Maprotiline | 30–150 |
| Mianserin | 30–60 |
| Setiptiline | 3–6 |
| Others | |
| Trazodone | 75–200 |
| Sulpiride | 150–600 |
| Selective serotonin reuptake inhibitors (SSRIs) | |
| Fluvoxamine | 50–150 |
| Paroxetine (2001～) | 20–40 |
| Serotonine noradrenaline reuptake inhibitors (SNRIs) | |
| Milnacipran (2001～) | 50–100 |

disease. Among all patients, about one third seek attention at psychiatric clinics, with another one third being seen at other types of clinics. The remaining one third do not seek any medical assistance. Even at psychiatric clinics, depression is often overlooked. In addition, drug therapy fails to control depression in more than half of the patients receiving it because of inadequate doses. In the end, only one tenth of all patients with depression receive appropriate drug therapy.[1,2)]

This article provides an outline of drug therapy for depression following the introduction of the first SSRI in Japan, with the factors described above being taken into consideration.

## Pharmacology of Antidepressants (Tables 1–3)

Antidepressants can be divided into two major classes: one is drugs that selectively inhibit the reuptake of monoamines such as serotonin and noradrenaline at the synapses and the other is tricyclic and tetracyclic antidepressants, which not only inhibit the reuptake of monoamines but also block various neurotransmitter receptors such as adrenergic $\alpha_1$ and $\alpha_2$, muscarinic (cholinergic), histamine $H_1$ and dopamine $D_2$ receptors. Antidepressants of the former class can be further divided into two subclasses, which are selective serotonin reuptake inhibitors that have a much stronger inhibitory effect on the reuptake of serotonin than that of noradrenaline (SSRIs) and drugs that inhibit the reuptake of both serotonin and noradrenaline (SNRIs).

Selective monoamine reuptake inhibitors have as strong an antidepressant action as tricyclic or tetracyclic antidepressants, but cause much less severe side-effects. This is an advantage over the older antidepressants, particularly during long-term treatment to prevent relapse or recur-

Table 2 *In vitro* Short-term Biochemical Activities of Selected Older and Newer Antidepressants. Adapted from Potter *et al.* (1991) and Pirmohamed *et al.* (1992), plus data from Richelson & Nelson (1984) and Lancaster & Gonzalez (1989a,b)

| Drug | Reuptake inhibition | | | Receptor affinity | | | | |
|---|---|---|---|---|---|---|---|---|
| | NA | 5-HT | D | $\alpha_1$ | $\alpha_2$ | $H_1$ | MUSC | $D_2$ |
| Older drugs[a] | | | | | | | | |
| Amitriptyline | ± | ## | 0 | ### | ± | ### | ### | 0 |
| Clomipramine | ± | ### | 0 | ## | 0 | + | ## | ## |
| Desipramine | ### | 0 | 0 | + | 0 | ± | + | 0 |
| Dothiepin | ± | ± | 0 | ± | 0 | ### | ### | 0 |
| Doxepin | ## | + | 0 | ### | 0 | ### | ## | 0 |
| Imipramine | + | + | 0 | ## | 0 | + | ## | 0 |
| Nortriptyline | ## | ± | 0 | ## | 0 | + | ## | 0 |
| Trimipramine | + | 0 | 0 | ### | ± | ### | ## | ## |
| Newer drugs | | | | | | | | |
| Amfebutamone (bupropion) | ± | 0 | ## | 0 | 0 | 0 | 0 | 0 |
| Amoxapine | ## | 0 | 0 | ## | 0 | + | 0 | ## |
| Citalopram | 0 | ### | 0 | 0 | 0 | 0 | 0 | 0 |
| Fluoxetine[b] | 0 | ### | 0 | 0 | 0 | 0 | 0 | 0 |
| Fluvoxamine | 0 | ### | 0 | 0 | 0 | 0 | 0 | 0 |
| Lofepramine | ### | 0 | 0 | + | 0 | | + | ## |
| Maprotiline | ## | 0 | 0 | ## | 0 | ### | + | + |
| Mianserin | 0 | 0 | 0 | ### | ## | ### | 0 | 0 |
| Paroxetine[b] | 0 | ### | 0 | 0 | 0 | 0 | ± | 0 |
| Sertraline[b] | 0 | ### | 0 | 0 | 0 | 0 | 0 | 0 |
| Trazodone | 0 | + | 0 | ### | ± | ± | 0 | 0 |

a: Tricyclic antidepressants.

b: Selective serotonin reuptake inhibitors.

*Abbreviations and symbols:* NA = noradrenaline (norepinephrine); 5-HT = 5-hydroxytryptamine (serotonin); D = dopamine; $\alpha_1 = \alpha_1$-adrenergic receptor; $\alpha_2 = \alpha_2$-adrenergic receptor; $H_1 = H_1$ histamine receptor; MUSC = muscarinic (cholinergic) receptor; $D_2 = D_2$ dopamine receptor; 0 = no effect; ± = equivocal effect; + = small effect; ## = moderate effect; ### = large effect; #### = maximal effect.

Source: Rudorfer, M.V. *et al.*: Comparative tolerability profiles of the newer versus older antidepressants. *Drug Saf* 1994; 10(1): 18–46.

rence, because poor compliance can be avoided. In addition, because of adverse effects on the central nervous system and cardiovascular system, these drugs are relatively safe even for elderly and/or debilitated patients. Unlike tricyclic antidepressants, these drugs are rarely lethal even when an overdose is taken for attempted suicide.

Fluvoxamine may cause side-effects such as gastrointestinal disorders (including nausea and decreased appetite), anxiety and irritation, tremor, impaired ejaculation, and the serotonin syndrome. Therefore, this drug should be used with careful consideration of such side-effects. The co-administration of drugs to potentiate gastric defensive factors may be effective in preventing the gastrointestinal side-effects of fluvoxamine, although the value of such combinations is largely unproven. Care must be taken when fluvoxamine is used because it is a potent inhibitor of cytochrome P-450(CYP)1A2 and thus blocks the metabolism of propranolol, theophylline, and warfarin. It also causes moderate inhibition of CYP3A4, and hence blocks the metabolism of antiallergic drugs (such as terfenadine or astemizole) and cisapride (a gastrointestinal prokinetic drug). Fluvoxamine should not be used in combination with any of

Table 3 Antidepressants Side-effects and Possible Clinical Consequences of Neurotransmitter Receptor Blockade by Antidepressants

| |
|---|
| Antihistamine $H_1$ |
| Potentiation of central depressant drugs |
| Sedation, drowsiness |
| Weight gain |
| Hypotension |
| Antimuscarinic |
| Blurred vision |
| Dry mouth |
| Sinus tachycardia |
| Constipation |
| Urinary retention |
| Memory dysfunction |
| Anti-$\alpha_1$-Adrenergic |
| Potentiation of the antihypertensive effect of prazosin (Minipress) |
| Postural hypotension, dizziness |
| Reflex tachycardia |
| Anti-$\alpha_2$-Adrenergic |
| Blockade of the antihypertensive effects of clonidine (Catapress) and $\alpha$-methyldopa (Aldomet) |
| Anti-dopaminergic |
| Antipsychotic effects |
| Extrapyramidal movement disorders: dystonia, parkinsonism, akathisia, tardive dyskinesia |
| Endocrine effects: increase of prolactin (galactorrhea, gynecomastia, and menstrual changes) |

Source: Kanba, S. and Richelson, E.: Antidepressant interactions with neurotransmitter receptors *in vitro*; Prediction of potential side effects. Ed. O'Brien, R.A. In *Receptor Binding in Drug Research.* Mircel Dekker Inc., New York, Basel, 1986; pp. 429–477

these drugs because the inhibition of metabolism may result in QT prolongation and ventricular arrhythmia.

## Acute Therapy

As a rule, acute therapy of depression is treated at outpatient clinics. When anxiety, irritation, or suicidal ideation is severe or the patient is unable to eat, hospitalization is necessary. Before starting drug therapy, it should be carefully explained to the patient and the family that: 1) depression is a brain disease that can be cured by drug therapy and rest, 2) the family should make allowance for the disease and should not encourage the patient to do too much, 3) drug therapy begins to have an effect after 2 to 4 weeks, and 4) side-effects develop immediately, but begin to subside gradually after about 1 week. In order to assess the effectiveness of drug therapy, a single antidepressant is usually administered. In the case of antidepressants, combined drug therapy has rarely evidenced an increase in efficacy.

When the treatment of moderate depression is tried from the perspective of EBM, there is no evidence that one antidepressant is superior to another in effectiveness. On the basis of antidepressant activity, consequently, drug therapy can be started with any antidepressant, but it is better for one having minimal side-effects be selected. According to the American version of the therapeutic algorithm (1995), the first-line drugs for initiating therapy are SSRIs.[3] Based on this policy, fluvoxamine and paroxetine become the drug of choice in Japan. According to the Japanese algorithm (1998) produced before the introduction of fluvoxamine, sulpiride and

the tricyclic or tetracyclic antidepressants are all regarded as first-line drugs.[4)]

Fluvoxamine is initially administered at a dose of 25–50 mg/day, which is increased to 75–100 mg/day after 1–2 weeks, if necessary. If the condition shows a tendency to improve after 2–3 weeks, treatment is continued without a further increase of the dose. If not, the dose can be increased to 150 mg. If the drug is ineffective despite administration at a higher dose for 4–6 weeks, fluvoxamine should be replaced with another antidepressant. If the alternative drug is one of the tricyclic antidepressants, the initial dose should be 75–100 mg/day. The dose is increased gradually once every two weeks if there is no response and an absence of side-effects or tolerable side-effects. It is desirable for the drug to be administered for 4–6 weeks or longer at an adequately high dose exceeding 150 mg or around 250 mg, if possible (see Table 1). Because antidepressants can lower the threshold for tremor at high doses, the patients should undergo electrocardiography and electroencephalography. When an antidepressant is given at such a high dose and fails to elicit any effect, it can be regarded as having failed and an alternative antidepressant should be used.

For severe depression, tricyclic antidepressants are more effective than SSRIs.[3)] Amitriptyline and clomipramine are the drugs of choice. Intravenous infusion of clomipramine and electroconvulsive therapy are used in some cases.

When depression is refractory to antidepressant monotherapy, the drugs are administered in combination with lithium, thyroid hormone, or bromocriptine (an antiparkinson agent) for potentiation of efficacy. The effectiveness of such combinations has been documented.[3,4)]

Remission is achieved with first-line drugs in 38% of patients. This rate increases to 61% and then 77% when therapy is continued by replacing the first-line drug with a second-line and then third-line drug, respectively. If fourth-line drugs and alternatives are given subsequently, remission is only achieved in another 9% in total. Depression resolves completely within 6 months after the start of drug therapy in 79% of all patients treated. During the subsequent 12 months, remission is only achieved in 2%.[5)] If depression is associated with psychotic features, the remission rate is even lower. For depression of this category, a combination of antidepressants and antipsychotic drugs is effective.

When depression is associated with insomnia, anxiety, and irritation, the combination of an antidepressant with a benzodiazepine is effective, particularly soon after the introduction of antidepressant therapy. When the response is inadequate, however, treatment should not be continued for more than 2–4 weeks. Generally, drug therapy is discontinued step-wise when the symptoms have been stabilized.[4)]

## Continuation Therapy and Maintenance Therapy

### 1. Continuation therapy: To prevent relapse before the termination of a depressive episode

Drug therapy for a first episode is continued for 4–6 months without changing the dose. For second and subsequent episodes of depression, treatment is continued the same period as for the previous episode.[6-9)]

### 2. Maintenance therapy: Prevention of recurrence and new depressive episodes

After a first depressive episode, depression will recur within one, five, and ten years in 28%, 68%, and 75% of patients, respectively.[10)] Among patients receiving long-term drug therapy with fluvoxamine at an average dose of 100 mg/day for 2 years, the recurrence rate was 20%.[11)] The rate for patients receiving imipramine at a dose of 200 mg/day for three and five years was 21%[12)] and 9%,[13)] respectively. If a patient has had two or more depressive episodes in the previous five years, it is desirable for prophylactic therapy to be continued for 2–3 years at the same dose as that used during

acute treatment and for 5 years, if possible.[11,13)]

## Conclusion

Drug therapy for depression fails to work in more than half of the patients receiving it. In particular, tricyclic antidepressants are very likely to cause adverse events, and have failed to elicit a sufficient clinical response in patients receiving these drugs at inadequate doses because of such adverse effects. This has been partly responsible for the frequent occurrence of therapeutic failure. Because two SSRI drugs (fluvoxamin and paroxetine) and an SNRI (milnacipran) have now become clinically available in Japan, more patients with depression can receive adequate doses of antidepressants at present. With the advent of this new stage in the treatment of depression, it is hoped that psychiatrists will not overlook depression and depressive states that can easily be improved by drug therapy, even if the response is not perfect. In other words, it is important to identify patients with the indications for aggressive drug therapy as completely as possible.

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# Expectations of a Low Birth Society
## —From the Perspective of Historical Demography—

JMAJ 45(1): 34–44, 2002

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**Abstract:** Fertility in Japan has fallen under the population reproductive standard for the past quarter century and it continues to decline. The low birth rate has precipitated the demographic aging of Japanese society which has produced projections of a population decrease. Studies on the merits and demerits of a low birth rate vary, but the general concern is that a low birth rate is debilitating to both society and the economy and will lead to the eventual ruin of the country. This unprecedented transition is very alarming, but it is not necessarily an abnormal phenomenon in terms of historical demography. The objective of this presentation is to evaluate Japan's low birth rate from a historical demographic perspective. Firstly, the long-term population wave over the past 10,000 year period, which is closely linked to systematic changes in Japanese civilization, will be discussed. Secondly, the trend toward late marriages and low child births that occurred during the latter half of the pre-modern Tokugawa period will be discussed. Lastly, if Japan achieves the status of a prosperous, aging nation with a low birth rate, its accomplishment will contribute greatly to resolving the global population, environmental, and resource issues.

**Key words:** Low birth society; Population decline; Demographic transitions; Civilization system; Historical demography

## Presentation of the Issues

It is an honor to be present at this prestigious symposium and I am grateful for the opportunity to address the many academically renown colleagues assembled here today. However, despite this fact, I am slightly apprehensive that I may not be an appropriate speaker in terms of the paper I am presenting and I hope that my presentation will serve as a useful source of reference.

The first major underlying reason for my concern is that I am not a population analyst or an expert on economic issues. My field is historical demography, which is centered on research pertaining to the populations in pre-modern

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 122, No. 2, 1999, pages 213–221).
The paper is a transcription of a lecture in the Health Policy Symposium on A Low Birth Society — A View of the 21st Century — held at the JMA office in Tokyo on February 6, 1999.

society that predates the establishment of population dynamics or the population census that is characteristic of the study of modern demography. As one who is constantly viewing the history of populations from the standpoint of past societies, I am concerned as to what suggestions about the present and the future can be proposed.

Secondly, I view the low birth rate and the approaching population decline in a positive light. It is my understanding that I was invited to speak at this symposium because one of the trustees happened to read an article of mine that was published in a journal. The following quotation from that article largely summarizes my standpoint. "The national and the local governments are desperately trying to forcibly raise the number of births, but they do not have the time, revenue, nor the ideas to squander ... the time has come to seriously endeavor to formulate a plan on land usage and to create a social framework suited to the needs of a society with a declining population, in order to allocate production facilities and social capital prudently within limited financial resources. As one of the foremost nations faced with a low birth rate and aging population, establishing a prosperous society characterized by a declining population will be Japan's contribution to the international community." Therefore, I am afraid that by proposing that the low birth rate is a welcome phenomenon before my distinguished colleagues, whose energies are dedicated entirely to resolving the issue of Japan's low birth rate, I do so at the risk of being tarred and feathered.

Japan's fertility rate has continued to drop, which has driven the country's low birth rate and aging population. Moreover, it has been predicted that a decreased population will become a reality within the next ten-year period. One of the series of transitions, which is anticipated to occur, is the debilitation of Japanese society and the ensuing ruin of the country. This unprecedented transition is most certainly very foreboding and studies on the merits and demerits of a low birth rate vary. But the overall consensus has been an emphasis on the negative aspects produced by this phenomenon; and this symposium is one means of addressing these fears and apprehensions for the future. However, this is not a phenomenon which requires our acknowledgment, denial, or our attempts to raise the birth rate.

Although the current low birth rate and decreased population is an unprecedented occurrence in recent Japanese history, it is not an abnormal phenomenon from the standpoint of historical demography. There has been a stagnation in population growth throughout different periods of human history. Additionally, the issue of population decline is a problem that is not restricted to Japan alone, but it is an issue that confronts most of the European nations as well.

The objective of my presentation is to assess the issue of a low birth rate from the perspective of historical demography and the study of civilizations. The report is divided into the following three sections. In section one, demographic transitions that occurred in the Japanese archipelago 10,000 years ago will be discussed. The close link between the wave of populations that have occurred over an extended period of time and the shift to a civilization system will be explained. The second section of the report will discuss the trend toward late marriages and a low birth rate that occurred during the Edo period. It is a well-known fact that population growth stagnated during the 18th century which proceeded an era of high population growth in the 17th century. The characteristics that distinguish this period will be described from the historical perspective of civilizations. Lastly, the low birth rate that characterizes contemporary Japan will be discussed from the context of historical demography.

## A History of the Demographic Transitions in the Japanese Archipelago

The demographic transitions that occurred in the Japanese archipelago during the last 10,000

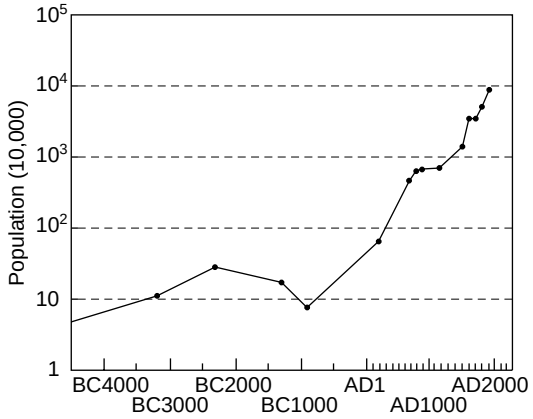


Fig. 1 Long-term Trends of the Japanese Population (Early Jomon period~2100)

years are characterized by continuous growth followed by a period of population decline or stagnation. As shown in Fig. 1, population growth is seen in large waves. The first growth wave occurred during the Jomon period. The population grew from 20,000 people in the early Jomon period to 260,000 by the middle Jomon period and declined from a population of 160,000 in the latter Jomon period to 80,000 people in the late Jomon period.

The second population growth wave occurred during the Yayoi period (population 590,000) to the Nara period (7th century, population 5 million) and stagnated or declined from the Heian period (10th century, population 6 million) to the Kamakura period.

The third growth wave began in the period of the Northern and Southern Courts (14th century). Although clear population statistics from this period are nonexistent, it is hypothesized that it is linked to the population explosion that occurred during the early Edo period (17th century) when the population, estimated at about 12 million in 1600, grew to 31 million by 1721. However, as can be seen from the statistics obtained from a nationwide population survey taken by the Tokugawa government, the national population was only 32 million in 1846, which is indicative of a stagnant population growth which lasted for over 100 years from the mid-Edo era.

The fourth wave began during the early 19th century. From the final days of the Tokugawa government-Meiji Restoration period to present day Japan, the population has greatly increased. However, this large population growth rate, which occurred in tandem with modernization, was not permanent and was predicted to level off at the beginning of the 21st century. The underlying causes of this population growth wave are firstly, environmental changes, and secondly, contact with other civilizations which in turn, triggered the shift to a civilization system.

## 1. Environmental changes

The environmental changes which contributed to the fourth population growth wave will be explained very briefly. The large population decrease or devastation which occurred in the latter half of the Jomon period is attributed to climatic changes. In the aftermath of the glacial period, the early Jomon period was distinguished by a warm climate which reverted back to a colder climate by the middle Jomon period. The marked decrease in population occurred mainly in the Tohoku, Kanto, and Chubu mountainous regions. According to one theory, the population is surmised to have been drastically reduced due to contact with ethnic groups from China and Korea that contributed to the onset of new diseases.

The underlying cause for the static growth in population during the Heian and Kamakura periods is not known. It is said that the study of medieval Japanese history is presently in vogue and the prevailing concept promulgates "an illuminated medieval age" supported by an active populace. Unfortunately, from the standpoint of population history, the Japanese medieval period is categorized as the Dark Age. The static population growth rate of this period is not due to the advent of a cold climate, but a warm climate accompanied by dry weather, which is believed to have led to unstable conditions in rice cultivation. National management of the rice fields based on an ancient legal system was destroyed and the establishment of the

manor system may have also affected population growth. These climatic changes may have also indirectly caused the fall of the Taira government centered in western Japan and the victory of the succeeding Genji clan which moved the seat of government to eastern Japan.

Stationary population growth in the latter half of the Edo era may also have been affected by climatic changes. The period from the 18th to the 19th centuries is also known as the little ice age due global cooling. The three great famines which occurred from the 1730s to the 1830s stemmed from long, rainy spells in the summer, the lack of sunlight, lowered temperatures, and floods which devastated the rice crop. The situation was further compounded by the onset of disease. The atmospheric conditions that prevailed during the crop failure of 1993 were similar to the conditions that occurred 200 years ago.

Then why is the growth in population becoming static despite the continued onset of global warming? Because the static population growth in the past and the decline in population are not due solely to climatic changes.

The French historian, Braudel, who greatly influenced the study of history, claimed that the changes in population were the progressive outcome of a materialistic civilization and the foremost index that reflected progress. This definition aptly describes the long-term population growth wave seen in the Japanese archipelago. Japanese civilization is based on a cumulative 10,000 year history. It is comprised of at least four segments when analyzed in terms of the long-term population growth wave.

## 2. Transition to a civilization system

The civilization system refers to the human collective or community lifestyle and the term is used to signify culture or a living system. We devise tools, machines, buildings, customs, institutions, laws, and a variety of other components to help us create a life of comfort and convenience. These components have become the second environment for human beings. Just as we refer to an ecosystem to describe the relationship of an individual or groups of living organisms with the external environment, the relationship of human beings with all of the components that have been created by and surround human beings is called the civilization system.

The characteristics of the four civilization systems that developed in the Japanese archipelago in conjunction with the population growth wave are shown in Table 1. Various factors such as the largest population, population density, stage of civilization, the major energy resources that supported the society, and the predominant economic system that comprised each civilization system have been listed. Additionally, energy usage, the type of social community, and the predominant staple foods have also been given. Although there are many more factors which need to be reviewed, these are the factors that have been included in this paper.

The first population growth wave, known as the Jomon civilization system, was based on the natural environment and the basic activities were hunting, collecting, and fishing. The lives of the Jomon people were deeply linked to and greatly affected by the natural environment.

The second population growth wave spans the Yayoi, Nara, and Heian periods. Triggered by the development of the rice field farming system, it represents the transition to an agricultural society. A national legal government structure also developed in conjunction with the spread of rice field farming and a legal system, construction of capital(s), the family register, a government system of land distribution, a written language system based on Chinese characters, Buddhism, Taoism, Confucianism, and other institutions were introduced from China (T'ang dynasty).

The third population growth wave is believed to have occurred during the Northern and Southern Courts period. The period from the 14th to the 17th centuries was a major transitional period in the history of Japan comparable in significance to contemporary times. The advent of a socioeconomy was the underlying cause of this

Table 1 A Comparison of Civilization Systems

| | 1<br>Jomon System | 2<br>Paddy Cultivation System | 3<br>Socioeconomic System | 4<br>Industrialization System |
|---|---|---|---|---|
| Population density [1/km$^2$] (pop/10,000) | 0.9[1)]<br>(26/middle Jomon period) | 24[1)]<br>(700/10th century) | 112[1)]<br>(3,258/year 1828) | 350<br>(13,044/year 2011) |
| Civilization stage | Natural environment (hunting, fishing, collecting food) | Agrarian society (direct consumption of farm products[2)]) | Agrarian society (Indirect consumption of farm products[2)]) | Industrialized society |
| Major energy resources | Plants and animals + manual labor Natural energy | Plants and animals + manual labor Natural energy | Plants and animals + manual labor Natural energy | Mineral Natural energy →electricity |
| Wrigley's categorization[3)] | Organic economy | Organic economy | Advanced organic economy | Mineral energy-based economy |
| Major economic systems[4)] | Traditional economy | Traditional economy + command economy | Traditional economy + command economy + market | Market economy |
| Social community[5)] | Band society | Clan society | Stem family society | Industrialized community |
| Staple foods[6)] | Nuts, fish, shellfish | Rice | Rice and minor grains | Rice, minor grains, sweet potato→ diversification |

[1)]Excluding the Ainu, Ryukyu (Okinawa), [2)]Van Bart, 1980, [3)]Wrigley, 1991, [4)]Heilbroner, 1972, [5)]Murakami, Sato, Kumon, [6)]Koyama, Goto, 1985

transition in the civilization. A market economy, which grew within the framework of an agrarian society, accelerated productivity and triggered economic growth. This socioeconomic chain of events is called the making of an economic society. The impact of the market economy on the rural community created narrow areas of cultivated land, and established small farm management centered on family labor, which was an integration of labor intensive farming technology and diligent labor. Some researchers have called this phenomenon an industrious revolution.

Wrigley has referred to pre-industrial England as an advanced organic energy-based economy and Japan with its advanced socioeconomy fits this description as well. Although it was an agrarian society that was dependent on the land (natural environment), it was a society with high productivity and an advanced system of land usage. Japan's mode of behavior, sense of values, and social structure underwent a major transition. The country was influenced by the Chinese, Portuguese, and Dutch civilizations. Japan's traditional culture and many familiar aspects of the Japanese lifestyle evolved and developed at this time.

The fourth population growth wave occurred in tandem with the establishment of the industrialized system. In the 19th century, the population growth rate in Japan, which had remained static for about one century, gradually began to accelerate. During the final days of the Tokugawa government, the energy supply was nearly

at a bottleneck in conjunction with a rise in living standards. The European and American system was introduced following the opening of Japan to the West and its entrance into the prevailing global system of that time. The Japanese economy which incorporated the framework needed for modernization began to industrialize at the end of the 19th century. However, like the three preceding population growth waves, the current growth in population is anticipated to become stationary in the future and industrialization is nearing maturity.

### 3. A static population growth society and a mature society

Let us assume that the population approaches the maximum carrying capacity of a society or civilization following a long-term growth in population. It gradually becomes difficult for productivity and the population to quantitatively increase based on the current system and technology. This type of society is defined as a mature society. When society reaches this stage of maturity, tension develops between civilization (living standards), the environment, and the population and it becomes vulnerable to climatic changes. A mature society at first glance is a static society. Certainly, development is difficult in a mature society since it represents the aftermath of an expanded population, cultivated land, residential areas, and productivity. It is also a period of prosperity and thriving culture.

In studying the Jomon culture of the Sannai Maruyama ruins, it has been deduced that the culture was based on a fairly advanced social structure and technology for a society rooted in the natural environment. The Nara period, which introduced the ancient legal codes, literature (Chinese characters), religion (Buddhism, Taoism, Confucianism), and various other productivity related technology from China, has a strong foreign cast. In contrast, Japanese culture flourished during the Heian period when the legal system was more relaxed and less stringent. The kana writing system evolved and "The Tale of Genji", the famous literary work, was written in this period; and in the area of religion, all Buddhist sects which developed after the Tendai sect were Japanized. This was truly an ancient mature era.

Japanese society in the Edo period around 1700 had become a stationary. This became a confirmed reality during the 1720s and population growth for the next 100 years or more remained static. Although the people were not materialistically blessed as today, the culture flourished — it was a time when artists exhibited their talents, the populace enjoyed the theater and hobbies, pleasure-seeking activities, trips, and other aspects of an active culture. Scholars and other intellectuals were earnestly engaged in absorbing knowledge from the West. The educational facility for the populace, the temple schools, increased from the 1780s and experienced an explosive boom during the final days of the Tokugawa government. In tandem with the rise in the literacy rate, there was an increase in the number of published books. The restaurant industry flourished in the urban areas of Edo, Osaka, and Kyoto and the populace enjoyed an abundant food culture. These social conditions are far removed from the image of a populace eking out a destitute living.

## The Population in the Latter Half of the Edo Period

I would like to discuss in detail the latter half of the Edo period as exemplar of a mature civilization with a static population. There is an accumulation of historical demographic research findings on the population phenomenon of this period, based on the religious investigations that were conducted to contain the spread of Christianity, the death registry of Buddhist temples, and other sources of information.

The contradictions within the Tokugawa government are said to have erupted during the latter half of the Edo period, which is better described as the collision between the developing market economy and the prevailing economy based on feudal directive. The feudal lords who

were levied a land tax and faced with financial difficulties were drawn into the commodity economy. The situation was further compounded by bad harvests which caused a large number of farmers to starve to death, in addition to miscarriages and the practice of killing unwanted children which cumulatively contributed to the static population growth. The commonly held opinion is that static population growth was caused by a rising mortality rate and the functioning of what Malthus referred to as the positive check.

## 1. Analysis of the Malthus population theory

The year 1998 was the 200th anniversary of the publication of "An Essay on the Principle of Population" by Malthus. In this paper, Malthus advocates that the population is constantly striving to increase, but the limited production of living resources inevitably produces social confusion such as famine and war which leads to a rise in the mortality rate and static population growth. In view of the life ethics and technological limitations of that time, the solution was to restrict population growth through restrictive measures such as marrying late or remaining single throughout one's life, in order to prevent the occurrence of war, famine, and other tragic events. It is self-evident that if population growth was disregarded, living standards would fall to survival levels.

When Malthus's essay was published in Europe, Japan was recovering from the aftermath of the volcanic explosion of Mt. Asama and the great famine of the 1780s. Farmland was devastated and population growth was at rock bottom levels. The conditions matched the criteria described by Malthus. In addition, climatic cooling began in the 17th century. However, the impact of bad harvests ended within a relatively short period of time and population growth continued to be sustained. In contrast, when the population surpassed 30 million in the 18th century, the carrying capacity within the Japanese archipelago had reached its limits, thus producing static population growth. Excessive development caused by economic growth had debilitated the capacity to absorb unexpected traumas. The cooling climate raised the population carrying capacity which triggered the occurrence of tragic events.

The agrarian society of the Edo period was dependent on agricultural products. Due to the nonexistence of modern scientific technology to prevent disasters, disease and insect damage, Japanese society was strongly affected by the natural environment. It was not a society that had an adequate system of information, transport means, and policies to cope with famine and other disasters. Subsequently, some regions in Japan were case examples of the gloomy prognoses made Malthus. In cities where the population density was high and the social capital was inadequate, the mortality rate was high in contrast to a low birth rate. As a result, population growth could not be sustained and there was a constant need for a population inflow from the rural areas. This is known as the grave-yard theory in Europe and the United States and the ant lion theory among Japanese researchers.

## 2. Late marriages and a low birth rate

Contrary to common opinion, the comparatively high living standards that prevailed during the latter half of the Edo period are attributed to what Malthus called the preventive check, namely the existence of a population control factor that lowered fertility. In contrast to general supposition, the mortality rate was declining and the average life expectancy had risen. Improved nutritional intake, easy access to physicians and medicine, a higher public awareness of child care, and other factors reflected a higher living standard. One underlying cause of the drop in the fertility rate in conjunction with a lower mortality rate was the trend toward late marriages. This became especially pronounced when women became engaged in sericulture, weaving, domestic help, and other non-farming activities, thus raising their importance as income earners. As a result, women

were prolonging their marriages by three years throughout the nation. Another underlying cause was a lower marital fertility rate — women were having fewer children. The number of children that a woman had throughout her lifespan averaged six to seven children throughout the 17th century when the annual population growth rate was near 1 percent. But this figure dropped to five or less in the middle of the 18th century with the advent of a lower infant mortality rate, since there was less need to have added children to replace the male heir in the event of death. The increased population in the 17th century also reduced the area of cultivated land per household, thereby curtailing the fertility rate of branch families with lowered economic prospects. Nonetheless, both in the East and in the West, the practice of fertility control was essential. Unfortunately, in addition to long-term breast-feeding and abstinence, miscarriages, abortions, and infanticide were also practiced. However, this situation can also be assessed from a different perspective. Thomas Smith, who conducted his research on a village in Nobi Plain, and others have raised the high possibility that abortions and infanticide were conducted systematically based on such factors as the balance between the genders and the scope of available resources.

Susan Hanley has called the high qualitative living standard that prevailed during this time as "the Tokugawa legacy", namely the rich culture, effective utilization of resources in the form of recycling, adequate nutritional intake relative to the Japanese physical constitution at the time, and a respectable life expectancy for a preindustrialized society. This high qualitative living standard was realized through planned fertility control, which was a vital precondition to Japan's modernization. By the early 19th century the components of popular society, specifically mass production, mass consumption, and mass advertising, were already evolving. The energy crisis that would inevitably result from the pursuit of national wealth by the clans and the populace's aspirations for wealth was narrowly avoided through recovery of the forests due to a warmer and more humid climate, population control, recycling, and economization. The decision to open the country to the international community and pave the way to a free economic system was timely and occurred just before the ecosystem's equilibrium was destroyed by the economic growth of the Tokugawa period. The immediate start of Japan's industrialization saved the country from the restrictive civilization system of the Tokugawa period.

## Expectations of a Low Birth Society

### 1. Conditions in Japan

In the aftermath of the oil shock, the Japanese government published the white paper, Japanese Population Trends, in June 1974. The subtitle, "Aiming for a Stationary Population" left an indelible impression. The term, stationary population, refers to a population that neither increases nor decreases and maintains a consistent size and a zero population growth rate. During this time the fertility rate, which was rapidly dropping, showed slight signs of increasing. It also coincided with the period when the baby boomer generation was marrying and entering parenthood. The developing countries were in the midst of a population explosion. Under the consignment of the Rome Club, the Massachusetts Institute of Technology had just published the "Limits to Growth" in 1972 which propounded the theory that countries would face shortages in food and resources stemming from increased populations and economic growth; and warned of the potential devastation of civilization. The oil supply was propitiously decreased at this time as part of the tactics related to the Fourth Mideast War that occurred in the fall of 1973. Oil prices skyrocketed and the global community was forced to confront the reality of limited growth. The total fertility rate (TFR) was barely able to sustain the population size at this time and the net reproductive ratio was near 1.0. However, just as

it is difficult to instantaneously stop the speed of an ongoing giant oil tanker, it is estimated that it takes approximately 40 years for population growth to actually cease. Meanwhile, the mass media was propounding in unison a zero population growth rate. Although I do not know whether this was an effective factor, the fertility rate began to fall from that year and continued its downward slide. The 1.57 fertility rate, that shocked the nation, occurred in 1990 and Japan's TFR has recorded new lows annually from that year.

The decline in fertility is an issue that is shared by the advanced industrialized nations. European nations have fallen under the population reproductive line since the 1970s. The fertility rate has also fallen under 2 in North America as well. The fact that the fertility rate, which indicates the number of children one women is expected to have throughout her life, continues to fall under 2 for an extended period of time signifies that population growth is declining. Perhaps this phenomenon represents the first step toward the realization of a society with a static population that was touted during the oil shock. The fact that this goal is about to be realized 25 years later has been a source of national apprehension.

## 2. Global conditions

In contrast, the fertility rate in developing countries remains high. In particular the TFR in Africa continues to be over 5. However, in contrast to the fertility rate which exceeded 6 in the latter half of the 50s in Southeast Asia and other developing countries, the rate is steadily declining. This is due to successful economic growth and the spread of education. Another important factor is the active national policy adopted by many developing countries to control the fertility rate.

In view of these conditions, the United Nations has adopted lower figures in their revision of future population statistics recently. For example, the average estimate of the world population in 2050 in 1992 was 10 billion, but the revised statistic projected in 1998 for 2050 was lowered to 8.9 billion.

However, the situation is not optimistic. The average statistics are in anticipation of the gradual decline of the fertility rate to below the population reproductive line (2.05). If the fertility rate does not change (high statistics), the population is estimated to reach 10.7 billion. If the world population increases according to the average statistics projected by the United Nations, the population will have nearly doubled to 10 billion by the end of the 21st century.

## 3. Global population capacity

Will the earth be able to support a world population of 10 billion people? American demographer, Joel Cohen, addresses this question in his book, "How Many People Can the Earth Support?", published in 1995. He introduces and evaluates more than 65 theories regarding the potential population capacity which the earth can support. The methodology used to support these theories are very diverse and include unfounded theories to system models. The majority of the theories support a maximum figure of 8 billion to 16 billion, the minimum figures were concentrated in the 4 billion to 8 billion range; and the maximum average estimate was 12 billion and the minimum estimate was 7.7 billion people, which was similar to the high estimations of the world population for 2050 given by the U.N. in 1992.

But this does not mean that the population will continue to be sustained without undue problems. Firstly, there is no guarantee that the world population will remain at 12 billion people. The high estimations given by the U.N. signify that the world population will exceed this figure.

Secondly, there is no guarantee that the estimated global population capacity will remain permanently at sustainable levels. The Medows, *et al.*, system model which includes population, food, industrialization, nonrenewable energy resources, and the environmental pollution variable, postulates that a global population of 7.7 billion people can be sustained. However, even

the most elaborate statistic guarantees sustainability only until the year 2100. According to the supplementary studies of other researchers, the population and economy will be destroyed before 2300.

Thirdly, an universally accepted, standardized concept regarding the global population capacity does not exist. When oil imports ceased following the 1974 oil shock in Japan, the population capacity of the Japanese archipelago was debated. According to one calculation, if all level land was converted to rice fields and cultivated without pesticides, fertilizers, or farming machinery, the land would be capable of sustaining a maximum population of only 40 million people. This is comparable to the population of the latter half of the Edo period. Will we be able to tolerate a situation where the majority of the population had to be engaged in food production activities? If we want to enjoy an urban lifestyle with an abundant supply of meat and fruits and to enjoy sports and nature, an immense amount of land is needed. According to this definition, many countries, including Japan, clearly support an excess population at present and it would not be inaccurate to state that the global population will shortly exceed the limit.

## Establishing an Prosperous Society with a Reduced Population

Recently, the burden of a low birth rate and aging population on the Japanese economy and society has been accentuated and debates centered on raising the fertility rate have been prominent. It is indeed a fact that an increased population in the developing countries has contributed to food shortages, poverty, population movement across international borders, and environmental destruction. Additionally, mass production, mass consumption, and mass disposal that occurs in advanced countries with high living standards can not be ignored as well. Stopping the population growth in developing countries and decreasing the population growth in advanced countries can be likened to the hero Kandata who sought his salvation from a spider's thread.

Simon Kuznitz has defined modern economic growth as the simultaneous, sustained increase of per capita income and population growth. However, when the economy and population growth become stationary, it does not automatically mean that per capita income and living standards become static. Advanced countries with an industrial civilization that has entered a maturation stage must abandon the idea of an economy where growth is expected and taken for granted. Post modern economics must embrace the concept of a stationary political economy aimed at establishing a high living standard within a decreased population.

Since the end of the Tokugawa period, Japan has taken economic and population growth for granted. However, the country is entering an age when a population decline will be a commonplace reality. Both the national and local governments are desperately and forcibly trying to increase the birth rate, but do they really have the time, budget, and ideas to dedicate to this endeavor? In conjunction with a decreased population, the population distribution will also greatly change. In a breakdown of the population statistics according to the urban and rural prefectures and metropolis (May 1997), a population decline is predicted in 33 urban and rural prefectures from 1995 to 2025. In order to allocate production facilities and social capital from limited financial resources, it is now the time to seriously build a social organization and to utilize the land in ways that are suited to a society with a declining population. As the front runner nation in terms of a low birth rate and aging population, Japan's contribution to the international community is to establish a prosperous society with a declining population.

## Conclusion

Stationary population growth is another characteristic of a mature society. A society with a

static population growth rate is not necessarily a poor society. The issues which we must address is how to guide the population toward a certain living standard and to determine what kind of mature society should be built. The foremost issue is not the fact that the population will decrease. The average life expectancy during the latter half of the Edo period was 36 or 37 years of age, but the average life expectancy of contemporary Japanese has doubled. A nationwide life expectancy of 50 years was realized only after WWII in 1947. The majority of Japanese children born after WWII live to see their 61st birthday and become senior citizens. The Japanese of today live very different lifestyles from their counterparts 50 years ago and it would not be erroneous to state that they have evolved into a different species of people. There are many problems that must be resolved and building a new social system and fostering new perspectives and values will take time. But we should remember that in every era, changes in the civilization system were realized after much painstaking effort. We should strive to be prudent, while optimistic and remain modest and confident in our endeavor to achieve simple prosperity.

Former Prime Minister Obuchi advocated the need to make the change in our perspectives by figuratively referring to a glass of water in his inaugural speech in January 1999. Fortunately, economists have begun to advocate the view that if measures are taken to build a society that qualitatively adapts an aging, declining population and a low birth rate, regaining balanced economic growth is not an impossibility. When tadpoles evolve into frogs, their gills and tails disappear. Similarly, in order to change an existing system, apoptosis, a resorption of unnecessary organs, is also required for human society to undergo a transformation in civilization. We should not emphasis the pessimistic negative aspects of a low birth society, but look to the positive aspects as well; and confront the reality that was forecasted 25 years ago with strong convictions.

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