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Female Reproductive Tract and Mammary Disorders Caused by Endocrine Disruptors

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Tsunehisa MAKINO

*Professor and Chairman, Department of Obstetrics and Gynecology,
Center for Growth and Reproduction, School of Medicine, Tokai University*

Abstract: Several possible endocrine disruptors, including bisphenol A, chlorobenzenes, benzo (A) pyrene, phthalate, PCB, and chlordane, were assayed in cord blood, maternal venous blood, breast milk and ascitic fluid to investigate the mechanisms of endocrine disrupting action in human subjects. The data indicate that, once reliable techniques for quantitation are established, it may be possible to elucidate endocrine disrupting action through comprehensive studies of the real levels of endocrine disruptors in human samples and the *in vivo* presence of the receptors and their metabolisms.

Key words: Endocrine disruptors; Female reproductive tracts; Cord bloods; Ascitic fluids

Introduction

It has been some time now since endocrine-disrupting chemical substances caught the attention of society, and as reports on environmental exposure and biogenesis come out sporadically, it is only recent that the directions we should be taking to study this field are becoming clarified. The initial social confusion over endocrine-disrupting chemical substances had started in reports on abnormal biogenetic phenomena and their fleeting detection in such

natural environments as water, soil and fishes, where they were treated as “somewhat scary substances.”

The comprehensive and basic research into these substances that followed—in health sciences, for example—suggested how to proceed with research and operations. Additionally, the basic facts concerning the connection between endocrine-disrupting chemical substances and the reproductive functions have gradually been established.^{1,2)}

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Establishment of Endocrine-Disrupting Chemical Substance Assays

The first fundamental of endocrine-disrupting chemical substance research is the establishment of endocrine-disrupting chemical substance assays that are satisfactory in sensitivity and specificity. This is because, without the establishment of an assay, there can be no discussion of the effect of endocrine-disrupting chemical substances on reproductive functions.

The handling of samples must not be overlooked among the elements of an assay. All the substances are present *in vivo* only in minuscule amounts. It is especially important to establish the methodology for each step of the process, from taking biological samples to preventing background interference and admixture of contaminants during the separation and storage processes and through obtaining reliable absolute values.

We have already studied this field in cooperation with the Health Sciences Research report "Establishment of analysis of endocrine-disrupting chemical substances derived from consumer goods comprised of polymer materials" (Lead researcher: Prof. Hiroyuki Nakazawa, Hoshi University).

Biological Exposure to Endocrine-Disrupting Chemical Substances

Over 70 kinds of so-called endocrine-disrupting chemical substances are present in natural environments, but in a discussion of their effect on human health and reproductive functions, the second important issue is the exact level of biological exposure, i.e. analysis of *in vivo* concentrations of these substances.

In the Health Sciences Research report "Development of Biological Sample (Cord Blood, etc.) Analytical Methods Relating to Endocrine-Disrupting Chemical Substances and Research into Their Effects on Human Health Based on the Results of Sample Analy-

sis" (Lead researcher: Tsunehisa Makino), working in concert with the Nakazawa team mentioned above, assays were established that enabled routine obtaining of stable results, and the report identified the following substances as candidate endocrine-disrupting chemical substances that cannot be neglected in the past and current volume of Japanese industrial production.

- 1) Bisphenol A
- 2) Chlorobenzenes
- 3) Parabens
- 4) Phthalate
- 5) Benzo (A) pyrene
- 6) PCB
- 7) Chlordane
- 8) Butyl tin compounds

The human biological samples subjected to assay were primarily reproductive system samples, (a) cord blood, (b) maternal venous blood, (c) breast milk, and (d) ascites. To the extent possible, samples (a) through (d) were taken simultaneously from each case subject, and we also examined the concentration gradients among *in vivo* internal organs of individual subjects.

Our results, as previously reported in detail at several opportunities,^{1,2)} were that **bisphenol A**, still produced in volumes of 300,000 tons annually as a raw material of plastics, was detected in all such samples as (a) through (d) and was found to have *in vivo* concentrations in the range 0.21–0.79 ppb.

Among **chlorobenzenes**, we assayed hexachlorobenzene and detected it in 100% of general peripheral blood and maternal peripheral blood samples and in 88% of cord blood samples, and found it to have concentrations in range of 0.03–0.10 ppb. Hexachlorobenzene concentrations in samples taken from individual subjects showed a significant positive correlation (coefficient of rank correlation = 0.722, $n = 12$, $p = 0.017$) between human peripheral bloods and ascites.

Among **parabens**, we detected methyl paraben in cord blood and maternal milk, and

inferred that parabens to which the pregnant women were exposed migrated via their blood to maternal milk and cord blood.

Phthalate, which is used as a plasticizer in plastics and the like, was detected in peripheral blood and ascites in concentrations averaging 1–5 ng/ml in the forms MBP (monobutyl phthalate), MBzP (monobenzyl phthalate), and MEHP (mono-2-ethylhexyl phthalate).

Benzo (A) pyrene, released into the atmosphere through the incomplete combustion of fossil fuels, was detected in male urines in the form OH-BaP, and we plan to go on to study the status of exposure to it in maternal milks, cord bloods, maternal peripheral bloods, and ascites.

The production of **PCB** (polychlorinated biphenyl), used as an incombustible and insulator, has been suspended since 1972, but it was detected as 35 different isomers in maternal milk, maternal peripheral blood, and cord blood in concentrations in the range, on a fat basis, of 60–99 ng/g.

The production of **chlordan**e, used in the extermination of termites and other pests, has been suspended since 1986, but trans-nonachlor was detected in 63% (0.06–0.17 ppb) and cis-nonachlor in 17% (0.03–0.05 ppb) of samples, whereas none of heptachlor epoxide, oxychlordan, trans-chlordan or cis-chlordan was detected in any of the samples at all.

For **butyl tins**, used as ship's bottom paints and fishing-net anti-contaminants and use of the open systems of which has now been partially suspended, results varied in different assays performed. They were detected (5–45 ppb) in 33% to 77% of hair samples. We reported in 1999 cases of high concentrations (41–45 ppb) detected within a single family.

Such volatile organic compounds as **toluene**, **benzene**, **xylene**, and **styrene** were detected in peripheral blood and ascites in concentrations of 0.6–4.0 ppb. 80% of samples and they were positive for toluene, 49% for P-dichloro benzene, 29% for O-xylene, and 26% for styrene. Naphthalene was not detected at all.

***In Vivo* Action and Expression**

The third important task in the study of the effects of endocrine-disrupting chemical compounds on human health and reproductive functions is the investigation of their mechanisms of action *in vivo* in human beings. Specifically, this entails the investigation of (1) whether there are **receptors** for these substances in the human body, (2) whether they display **action** and **expression** as hormones, and (3) what the mechanisms of **metabolism** and **detoxification** of these substances are in the human body.

Receptors for endocrine-disrupting chemical substances have been identified in the human body similar to such *in vivo* estrogens as human adrenocortical-derived cells (H295R) and human mammary cells (T47D). In detailed studies of receptors with human endometrial cells (HHUA) and human mammary-derived cells (MCF-7), it has been confirmed that they bound with estrogen alpha and beta receptors. In addition to known receptors, we have also decided to investigate the existence of so-called “orphan receptors” hitherto unknown.

With respect to the *in vivo* **action** and **expression** of endocrine-disrupting chemical substances, we established that they regulated the cortisol production of human adrenocortical cells. We also confirmed that they stimulated the multiplication of mammary cells and endometrial cells. We found that in mice butyl tins were active in the immune system and affect the induction of oral tolerances, and that in rats benzo (A) pyrene affected the process of differentiation of trophoblast stem (TS) cell lines.

Work that remains to be done in the study of the action and expression of these substances is a study to find out what actions, if at all, are expressed within the range of exposure in which these substances are actually present *in vivo*.

Much scope remains for further research into the **metabolism** and **detoxification** of

endocrine-disrupting chemical substances. To take bisphenol A as an example, we found that in rats the bulk of the substance was glucuronidated in the gastrointestinal tract and the liver. On the other hand, it was surmised that it was not metabolized in the kidneys, but only filtered and excreted. We identified the presence of an enzyme (beta-glucuronidase) that broke down glucuronate conjugates into the original endocrine-disrupting chemical substance, and we are planning to study it in the human body in the future.

Conclusion

We have thus assayed exact levels of biological exposure on the basis of the establishment of assays for several substances derived from polymers. Through investigation of *in vivo* receptors, action and expression, and metabo-

lism and detoxification of endocrine-disrupting chemical substances, we continue further research towards our primary objective of working towards a conclusion on their effects on human health and reproductive functions.

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Health Hazards of Endocrine-Disrupting Chemicals on Humans as Examined from the Standpoints of Their Mechanisms of Action

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Tohru INOUE*, Katsuhide IGARASHI and Jun SEKIZAWA

*Chairperson**, Biological Safety Research Center, National Institute of Health Sciences

Abstract: Hormonally active compounds were first recognized in “*Silent Spring*” by Rachel Carson in 1962, which implicated pesticides, such as DDT and derivatives. Nearly four decades later, the book “*Our Stolen Future*,” by Theo Colborn *et al.*, and other pertinent publications have revisited and broadened the issue to a variety of chemicals and areas exposed. Translations of these books have just become available in Japan in the past three or four years, and since then Japan has started to join the debate and/or discussion of the global issue of endocrine disruptors—“Environmental Hormones.” Although significant numbers of chemicals possessing a hormone-mimicking action have been recognized for many years and based on biological plausibility their receptor-mediating effects strongly suggest effects in humans similar to those seen in wildlife, little is known about the experimental evidence related to human adverse effects. The key issue in resolving the dilemmas posed by the biological plausibility and poor experimental evidence may be to clarify their mechanism of actions at low levels. In other words, the mechanisms of the possible low-dose effects may be resolved simultaneously by defining three major properties threshold, oscillation, and additive-synergism.

Key words: Receptor; Hormone mimics; Homeostasis; Effects at low dosage; Human hazards

Introduction

The objective of this paper is to summarize

all the currently available information on the possible hazards of endocrine-disrupting chemicals (EDs) on human health from the stand-

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points of the mechanisms of actions of these chemicals.

It is not uncommon to come across agrochemicals and industrial chemicals that have hormone-mimicking effects. These chemicals, the so-called “environmental hormones,” often accumulate at detectable levels in the environment, and it has been feared that they may have adverse effects on living beings. Following reports of feminization and decreased colony size of wild creatures, and reports suggesting a possible association of these chemicals with abnormalities of reproductive organs and oncogenesis in human, attention has been focused on the possibility that these occurrences may be associated with exposure to EDs. In this connection, a Japanese translation of the book entitled “*Our Stolen Future*,” written by Theo Colborn *et al.*, was published some time ago.

This paper will review the problems related to EDs, the courses of arguments regarding the harmful effects of these chemicals, and current medical topics pertaining to them.

Chemicals with Hormone-Mimicking Actions

Substances with hormone-mimicking effects can be divided into four groups: (1) hormones found *in vivo*, (2) medicines with hormone-mimic actions manufactured for use in hormonal therapy, etc., (3) plant hormones known to exert phytoestrogen-like actions, and (4) chemicals found in environments that can interact with hormone receptors.

In addition, substances which do not interact with hormone receptors but exert effects on gonads by their modifying effects on steroid metabolism may be deemed as hormone-mimics in the broader sense of the term. In this paper, however, emphasis shall be placed on the hormone-mimicking actions mediated by receptors which play essential roles in the mechanism of actions of hormone-mimics.

Characteristics of the Receptor-Mediated Actions of Hormone-Mimics

The receptor-mediated actions of hormone-mimics are fundamentally characterized by the similarity in the structures of the receptors involved, crossing the barrier of species. This characteristic allows us to estimate the possibility of the actions of these chemicals exerted in nature also occurring in humans.

Secondly, since similarities in the structure to various sex steroids and hormones are also known, it is possible that each individual hormone-mimic exerts diverse effects by acting on male hormone receptors, female hormone receptors, receptors in the nuclei (including some unknown receptors), etc.

Thirdly, many of these chemicals are eliminated from the living body in the form of conjugated inactive substances instead of as degraded metabolites. They may also be eliminated in the unchanged form. Therefore, if feces and urine containing these substances are eliminated into river water, it is plausible to imagine that even inactivated hormones can sometimes become active and exert hormone-mimic actions in the environment. This is one of the characteristics unique to this class of chemicals.

Receptor-mediated responses involve many unresolved questions. Various undefined elements may be involved, including the relationship between receptor binding and signals, the relationship between receptor-ligand binding (ligand: substances that can bind to receptors) and the dissociation of ligands from receptors, signal cross-talks, involvement of unknown nuclear receptors, etc.

The actions of these chemicals add to the effects of intrinsic hormones. For this reason, these chemicals may exert their actions in a way different from that known for other chemicals which do not have structural or functional counterparts *in vivo*. For example, stimulation of hormone receptors by these extrinsic chemicals may modify homeostasis *in vivo*, leading

to weakening of the physiological stimulation of these receptors by the intrinsic substances. Therefore, the influence of the continued effects of environmental hormones needs special study.

Pitfall in the Effects of Hormone-Mimics

We must distinguish the interactions of endocrine hormone-mimics with hormone receptors from the hazards caused to endocrine tissue. Bearing this in mind, let us now summarize the problems related to the effects of hormone-mimics.

1. Antagonistic effects on the maintenance of homeostasis

The endocrine system is regulated by homeostatic mechanisms. It is not uncommon for the effects of small amounts of hormone-mimics to interfere slightly with these mechanisms, often with no adverse influence; this is well-known. However, this is not always the case. There seems to be a group of genes that act antagonistically to each other in the maintenance of homeostasis.

With the uterus growth test, which is used to check for estrogenic activity, the ovary is removed in advance and the blood level of the intrinsic female hormone is reduced to the minimum. Under the thus-created extremely undeveloped state of the uterus, the test substance (a chemical or hormone) is administered to check for its effects on the growth of the uterus. This test (checking for growth of the uterus in ovariectomized animals) is designed to evaluate the hormone activity and effects of hormone-mimics under conditions of blockade of homeostasis.

This test method itself is valid. However, there is no sufficient rational evidence that indicates that the responses observed under such indirect control conditions of the living body can serve as an indicator of the health hazards of hormone mimics. Although the ootestes seen in lower vertebrates may be used

if the effects observed were to be valid as such an indicator, there is no consensus on what is valid as an indicator of the health hazards of ED's when mammals are used as experimental animals.

2. Down-regulation of the expression of receptors

It is known that the expression of genes encoding receptors is down-regulated by stimuli, leading to reduced receptor sensitivity. This can lead to a paradoxical outcome wherein the effects observed in the presence of low levels of a substance are not seen at high levels of the same substance. If this phenomenon occurred in individual organisms, the dose-response relationship will be non-linear.

This means that extrapolation of results obtained at high levels of the chemicals to conditions where low levels of the same substance are present would be difficult. It is needed to test the validity of this hypothesis, and analysis of the mechanisms underlying this phenomenon if the hypothesis were indeed valid, are thus important. Studies to resolve these questions are now under way.

3. Data gap concerning the effects of female hormones

In mature women, there are high levels of physiological hormones *in vivo*, and these are subject to cyclic control. It has been proposed that girls with inadequate physical growth begin menstruation at lower ages and undergo sexual maturation earlier than usual, and that hormone-mimics in these subjects can precipitate breast cancer.

The weak links in this hypothesis have been pointed out, and it has been shown experimentally that estrogen by itself may be teratogenic, although this tendency has been shown to be weak. It is known that organisms are programmed such that excessive exposure to estrogens during the intrauterine period or other developmental stages is avoided.

There are many open questions as to the

mechanism by which mature females remain physiologically stable, even when exposed daily to high levels of estrogen (400 pM/l). Some dramatic effects are probably needed to disturb this physiology.

4. Multi-generation tests and effects on fetuses

It has been shown that exposure to hormones or hormone-mimics during intrauterine or early neonatal periods can lead to irreversible changes in the pattern of development. This susceptibility period is short, extending from the 13th gestational day to about one week after birth. These effects are the so-called "intrauterine window effects."

In animal studies involving observation of experimental animals for two or more generations, no effects of EDs have been demonstrated. The question therefore arises as to why window effects are observed during the short period mentioned above. It is unknown whether or not these effects really do occur, and if they do, how are they produced.

Delayed growth of the thalamic nucleus specific to males (called sexual type II nucleus) is seen in male rats treated with female hormones. We may say that under conditions of homeostasis of the physiological hormones in mature individuals, exposure to dose levels that usually cause only reversible changes can lead to irreversible changes, if the exposure occurs during genesis, morphogenesis or functional development. However, there are no ample data endorsing this view in humans.

Considering the biological plausibility inferred from the experimental data accumulated to date,^{*1} we may say that there are no sufficient data that clearly rule out this view. Close attention has therefore been paid to these effects in children.

New theories of methodology, focusing on the effects in fetuses and children, are now

being developed, primarily in the United States, within the framework of children's program, etc.

Health Hazards at Low Levels of Exposure

Chemicals used for agriculture or industrial purposes are marketed, in general, only after their effects on living beings have been investigated. We may therefore understand that they are used on the premise that the possibility of these chemicals exerting hazardous effects on health at relatively high dose levels has been almost ruled out. Nevertheless, problems with EDs have begun to be highlighted. These problems may be not confined to those related to the accumulation of these substances through food chains in the ecosystem, but also to the possibility additionally that these chemicals may exert effects at low dose levels even if they have been declared safe at high dose levels. The latter possibility may apply, however, only to some cases and not to others.

We may say that a major issue pertaining to EDs that must be resolved urgently is whether or not they pose health hazards at low dose levels. This issue can be summarized into the following three questions: (1) presence/absence of threshold level, (2) presence/absence of synergistic or additive effects, and (3) possibility of extrapolation of high-dose effects to low-dose levels (i.e., presence/absence of a linear dose-response relationship). No clear-cut answers have as yet emerged to these questions. Considering the above-mentioned characteristics of the effects of hormones, it is plausible to imagine how difficult it may be to resolve these questions.

To determine if these chemicals exerted hazardous effects on health at low dose levels, the following basic questions may need to be considered; their biological plausibility is hardly denied.

^{*1} Biological plausibility: Likelihood of a phenomenon as judged by considering the difference or similarity of elements of reactions in individual organisms, on the basis of the results of a series of a related biological experiments. (cf. probability)

- (1) Regarding the presence or absence of threshold levels, it seems likely that many chemicals suspected of being EDs can easily permeate across the cell membrane, which is composed of phospholipids. Therefore, assuming that one receptor molecule reacts with one chemical molecule, the lower limit of the dose level exerting the chemical's effects would be very low.

Of course, since the probability of the binding of a ligand to the receptor will be low if the dose level is low, we cannot say that there is no threshold level for the effects seen in the low dose level range. In fact, for bisphenol A, which has been attracting close attention because of its hazardous effects on health at low dose levels, the presence/absence of a threshold level has not yet been reported. It seems rational, therefore, to assume that these health hazards occur in a very low dose level range.

- (2) If we consider not only the affinity of each substance for the receptor, but also the non-linearity of responses (e.g., waveform responses as a result of reduced receptor expression following an increase in dose level), it is possible to assume that there are U-shaped or reverse U-shaped reactions or oscillational dose-response curves. *Interim* data endorsing such a view are being accumulated.
- (3) Regarding the possibility of synergistic or additive effects, the observation of additive effects among different nuclear receptors has been reported. Data yielded by analysis of interactions between receptor signals also suggest such a possibility. In fact, the dose-response curves for some composite materials were reported to be additive, but not synergistic.

Thus, the questions on health hazards at low dose levels have several aspects: (1) the type of receptor-mediated actions of the hormone mimics, (2) diverse reactive characteristics on the part of the receptors, (3) diverse modification during expression of intracellular signals,

and (4) factors involved in irreversible changes related to morphogenesis and functional development. Resolution of all these aspects of the question will lead to clarification of the mechanism of actions of the substances from each of the aforementioned standpoints. While these questions are among the hottest research themes at present, they are certainly unlikely to be resolved easily.

At a workshop held in North Carolina, USA, in October 2000, health hazards of chemicals at low dose levels were discussed. Investigators for and against the possibility of these substances posing health hazards at low dose levels gave detailed accounts of their studies, and no definitive conclusions could be reached, as the arguments of both sides appeared to be tenable.

This means that reports affirming the plausibility of these substances posing health hazards at low dose levels in animal experiments cannot be immediately rejected. The workshop concluded by pointing out the necessity of paying attention to the possible hazards on fetuses and neonates.

Health Hazards of Hormone-Mimics on Humans

The possibility of health hazards of hormone-mimics on humans have not been supported by adequate epidemiological data, and the number of cases for which the data clearly endorse such effects is quite small. The US National Research Council emphasizes the necessity of conducting further epidemiological studies on this topic (National Research Council, 1999).

In conclusion, this paper summarizes the current knowledge concerning the health hazards of hormone-mimics on humans. Reports dealing with the effects of these substances on humans are confined to those pertaining to the effects of dioxins and PCB, and the validity and usefulness of these results have not yet been established.

The following are based on case studies conducted to date.

1. Health hazards of dioxins

Regarding health hazards of dioxins, two-year dosing studies revealed weight loss and liver damage, and three-generation reproductive studies in rats disclosed intrauterine death and a decrease in litter size. Onset of endometriosis in rhesus monkeys has also been reported.

A causal relationship of EDs to the following episodes in humans has been suggested: biased male-to-female ratio in children born in the dioxin-exposed Seveso area of Italy, and increased incidence of cleft palate in the Diemerzeedijk district of the Netherlands, probably due to steroids. In both of these cases, the Environmental Protection Agency (EPA) of the United States did not affirm a causal relationship, and treated classified them as cases requiring special attention.

No consensus has been reached concerning the relationship of hypothyroidism observed in the inhabitants along Lake Michigan to the ingestion of PBB (polybrominated biphenyls)-contaminated fish.

2. Effects on mature females, e.g., increased incidence of breast cancer

No reports affirming the effects of dioxins on mature human females (e.g., effects on breast cancer or endometriosis as discussed below). There are many unresolved questions on this topic. However, none of the studies conducted in mature experimental animals revealed data endorsing the plausibility of occurrence of such effects. On the other hand, it is known that the age at menarche is lower and the incidence of breast cancer higher in females exposed to dioxins. Some investigators cite these data when discussing the health hazards of dioxins.

It is also known that females exposed to dioxins are often taller.

In European countries, a height increase of about 3.5 mm per year and an approximately one-year decrease in the age at menarche have been reported during the past 30 years. It is difficult to identify the influence of extrinsic endocrine factors on these changes, and no studies addressing this issue have been reported to date. Although a number of studies have been published concerning the effects of female hormone preparations, including pills used for contraception and hormone replacement therapy in postmenopausal women, no studies have provided data that establish the effects of EDs.

3. Endometriosis

Endometriosis is a disease of unexplained origin that is seen in primates with sexual cycles. It has been pointed out that this disease tends to be more severe in individuals exposed to dioxins (TCDD/PCBs). Data yielded from experiments in rhesus monkeys are used as evidence to corroborate the causal relationship between dioxins and endometriosis. We cannot thus rule out the biological plausibility of these effects. However, no reports affirming the causal relationship in humans have been published.

4. Possibility of other effects on humans

Biological plausibility has been pointed out also on the following effects of hormone-mimics on humans: qualitative dysfunction of human sperm, effects on neurobehavior of neonates, and immune functions. The effects on immune functions have been suggested by reports of cases with Yu-sho (PCB intoxication).

Effects of Bisphenol A on Human Health

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Yozo NISHIKAWA

*General Manager, Environment and Safety Department,
Mitsubishi Chemical Corporation*

Abstract: When examining substances suspected to be endocrine disruptors, it is important to recognize that these can be divided into persistent organic pollutants and estrogenic chemicals. Beside bisphenol A, estrogenic chemicals include synthetic estrogens and phytoestrogens in food. Most estrogenic chemicals have many properties in common; they are biodegradable and not bioaccumulable. However, estrogenic potencies vary largely from substance to substance. Many animal experiments, including multigenerational reproductive toxicity studies, have been conducted on bisphenol A, and the no-observed-effect level (NOEL) in humans is estimated to be 0.05 mg/kg/day. The NOEL can be estimated for synthetic estrogens and phytoestrogen because they have frequently been used in humans. Based on the current situation regarding usage, I believe bisphenol A is safe to use.

Key words: Endocrine disruptors; Bisphenol A; Estrogenic chemicals; Tolerable daily intake; No observed effect level

Introduction

Approximately 0.35 million tons of bisphenol A are produced in Japan each year, and most are used as raw materials for polycarbonate resin and epoxy resin.

Bisphenol A might be ingested by humans through polycarbonate used as milk bottles and as dishes used at schools or through epoxy resin used for cans. Such cans are usually coated with epoxy resin on the inside, from which very low levels of bisphenol A may migrate.

I believe it is safe to use bisphenol A for these uses based on the reasons explained below.

Tolerable Daily Intake of Bisphenol A

The tolerable daily intake (TDI) that will not adversely affect humans is 0.05 mg/kg/day. So for someone who weighs 50 kg, the total daily intake is 2.5 mg, which means that bisphenol A will be ingested at concentration of 2.5 ppm in a food if a person were to eat 1 kg of food in a day.

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When bisphenol A is detected in dishes used at schools, as we occasionally hear on the news, the levels are usually no more than 1/1,000 of 2.5 ppm.

The TDI for bisphenol A was established as follows. First, various types of studies, such as chronic/carcinogenicity studies and reproductive toxicity studies, were conducted. Based on the results of these studies, the no-observed-effect level (NOEL) was estimated to be 5 mg/kg/day. Since TDI in humans is calculated by multiplying the NOEL in animals by uncertain factor of 1/100, the figure 0.05 mg/kg/day is obtained as the TDI for bisphenol A in humans.¹⁾

However, people frequently ask the question, "Shouldn't the TDI be lowered since the current TDI was established long ago, and since bisphenol A acts as a estrogen?"

To this I respond that the TDI for bisphenol A was determined also based on reproductive toxicity studies, which are the most appropriate test for assessment of the toxicity caused by estrogenic actions.

Moreover, the same TDI is used in the United States and Europe, and there have been no indications that this might change.

Achievements in Occupational Health

It is reasonable to assume that people who work at companies that manufacture bisphenol A are exposed to bisphenol A at a much greater level than others are, especially since bisphenol A exists as a powder, and people are likely to be exposed to it at high levels when packaging it into bags or pouring it out of bags into reactors.

However, despite the fact that bisphenol A has been manufactured and used for more than 40 years, only several cases of impairment in such employees have been reported. These were only cases of irritation to eye, nose, and throat due to exposure to high levels of dust and photosensitization in skin. Systemic impairment, such as reproductive toxicity and liver

toxicity, have not been reported.²⁾

Thus, it can be said that bisphenol A will pose no hazard to humans as long as the current TDI and handling instructions are observed.

There are Two Types of Endocrine Disruptors Suspected

When examining substances suspected to be endocrine disruptors, it is important to recognize that these can be divided into persistent organic pollutants and estrogenic chemicals.

Persistent organic pollutants include PCB, DDT, dioxin, and tributyl-tin compounds.

Estrogenic chemicals are substances that possess estrogenic activity, and include diethylstilbestrol, synthetic estrogens, genistein, which is contained in soybeans, as well as bisphenol A and nonyl phenol.

Persistent organic pollutants are not biodegradable, and will remain in the environment for a long time once they are released in the environment. Since they are bioaccumulable, they can adversely affect birds and humans that eat fish in the food chain even when the levels in the environment are very low.

The harmful effect of these persistent organic pollutants has been known even before the endocrine disruptors issue began to attract attention, and these pollutants has been strictly controlled. As a result, the pollution has already being improved.

Estrogenic chemicals, on the other hand, are biodegradable and not bioaccumulable. Adverse effects through the food chain are, therefore, not a threat. When absorbed in the body, they are easily metabolized, and most are excreted within a day.

The only thing people need to be careful concerning estrogenic chemicals is the fact that they may exhibit estrogenic actions, and that some of them, like bisphenol A, are commonly used in our daily life.

There are some that fuel nervousness among people by causing them to think that estrogenic chemicals might also cause like incidents that

were associated with dioxin and PCB.

It is important that people understand that bisphenol A is an estrogenic chemical that possesses completely different properties from dioxin.

Estrogenic Chemicals

Estrogenic chemicals have the following in common.

- (1) They have similar chemical structures. Molecular weight ranges from 200 to 300, and the structures contain one or more phenolic hydroxyl groups.
- (2) When absorbed into the body, they are rapidly excreted after becoming water-soluble through glucuronidation.
- (3) They bind with estrogen receptors, and exhibit estrogenic actions.
- (4) They lose their estrogenic activities through glucuronidation.

While these chemicals share many properties, as shown above, there are great differences among their estrogenic potencies. Results of a

comparison of the estrogenic potencies that were made in rats using uterotrophic assay are shown in Table 1.³⁾ Lowest-observed-effect level (LOEL) is the dose at which the weight of the uterus increased significantly, and is based on the results of oral administration studies. Relative activity is the inverse number of the relative LOEL.

Estrogenic action does not necessarily lead to toxicity. Whether or not the estrogenic actions might be toxic must be examined through reproductive toxicity studies. Minimum toxic dose in reproductive toxicity studies and those in any studies are compared in Table 2.³⁾ "Any studies" are toxicity studies, such as chronic tests and reproductive studies, and the values for "any toxicity" in the table represent the lowest value among all minimum toxic doses. As suggested in Table 2, the toxicity of a substance with strong estrogenic potency, for example, diethylstilbestrol, is caused by the estrogenic actions. With respect to bisphenol A, general toxicity, such as adverse effects on the liver, is observed at levels lower than those at

Table 1 Comparison of the Estrogenic Potency³⁾

Name of substance	LOEL (mg/kg/day)	Relative potency (E2 = 1)
Diethylstilbestrol	0.001	50
Ethinyl estradiol	0.002	25
Estradiol (E2)	0.050	1
Genistein	28	0.0018
Bisphenol A	200	0.00025

Table 2 Comparison of the Minimum Toxic Dose in Animal Studies³⁾

Name of substance	Reproductive toxicity (mg/kg/day)	Any toxicity (mg/kg/day)
Diethylstilbestrol	0.0075	0.0075
Ethinyl estradiol	0.010	0.010
Estradiol	0.16	0.16
Genistein	67	67
Bisphenol A	437	50

Table 3 NOEL and Intake in Humans³⁾

Name of substance	Intake (mg/day)	Relative potency (E2 = 1)	Adjusted intake (mg/day)
DES (Estimated NOEL in men)	2.0	50	100
DES (Estimated NOEL in women)	0.1	50	5
EE (NOEL)	0.035	25	0.88
GE (Actual intake)	15	0.0018	0.027
BPA (Tolerable intake)	2.5	0.00025	0.0006
BPA (Actual intake)	<0.025	0.00025	<0.000006

DES: Diethylstilbestrol EE: Ethinyl estradiol GE: Genistein BPA: Bisphenol A

which estrogenic actions can cause any toxicity. As such, substances like bisphenol A should not be considered as endocrine disruptors.

Adverse Effects and NOEL in Humans

In considering how a substance might affect human health, it is important to examine case studies. Examples are shown in Table 3, from which it can be deduced that there are NOEL in humans.³⁾

A famous case is that of a child who was born to a mother who had taken diethylstilbestrol during pregnancy. Abnormality in genitalia and vaginal cancer occurred in the child. Regarding this matter, a very reliable epidemiological investigation was conducted,^{4,5)} which showed that there was little or no effect when the dose was small. It can also be estimated that there is no effect on the offspring if the actual intake of the mother is no more than 2 mg/day when the child is a boy and 0.1 mg/day when the child is a girl.

Ethinyl estradiol is used as a birth-control pill, and its NOEL is 0.035 mg/day. What happened in the case example of diethylstilbestrol could also happen with this pill, too, if a woman continues to take it without realizing that she is pregnant. However, it is thought that congenital abnormalities will not occur even in such cases.

The average daily intake of genistein contained in soybeans is about 15 mg in Japan. People who eat fermented soybeans, *natto*, every morning will have ingested 20 mg of genistein in breakfast alone. Of course, however, this is within NOEL, as one can expect from the fact that consumption of soy poses no adverse effects.

The TDI for bisphenol A, on the other hand, is 2.5 mg, and the actual daily intake is less than 1/100 of the tolerable daily intake.

Relative potency is shown in Table 1. Adjusted daily intake is obtained by multiplying the daily intake by relative potency.

Table 3 also shows that the TDI for bisphenol

A and the actual daily intake are small enough compared with other NOEL, suggesting that bisphenol A is very unlikely to be harmful in humans.

Low-Dose Effects

Some think that substances with hormonal activity can pose a threat to health even at a low dose. Recently, this issue has been of great interest to many.

The growing interest in this issue came about with a report by Dr. vom Saal. In this report, he reported that the weight of prostates increased by 30% in male fetuses of pregnant mice to whom bisphenol A was orally administered at 0.002 mg/kg/day or 0.02 mg/kg/day.⁶⁾

In response, an international group of bisphenol A manufacturers conducted a large-scale study using more animals and parameters, and verified that there was no such effect.⁷⁾

A three-generation reproductive toxicity study was also conducted using rats to further verify the safety of bisphenol A. A wide range of doses ranging from 0.001 mg/kg/day to 500 mg/kg/day was used to determine the effects at low doses. Also, many parameters were added so that effects related to estrogenic actions could be observed in detail. Results of this study confirmed the accuracy of the current TDI.⁸⁾

The Ministry of Health, Labour and Welfare has also conducted a two-generation reproductive toxicity study using rats to verify the effects at low doses, and confirmed that there are no effects.⁹⁾

Conclusion

In conclusion, I wish to convey the impression I have received through my involvement with issues regarding endocrine disruptors.

There is a saying, "Do not use anything suspicious." This is very reasonable, and I, as one representing a manufacturer, do not intend to sell anything that is suspicious. However, the

difficulty lies in the reality that whether or not a substance is suspicious is not determined by manufacturers such as ours or by public offices, but ultimately by consumers. This is the case because newspapers and TV programs, which have an overwhelming influence on the public, tend to take interest only in views that fuel anxiety.

If you are interested in finding out more about bisphenol A than what I have explained, as one in charge of safety at a manufacturer of bisphenol A, I would be delighted if you visited our Web site where you will find more information.^{10,11)}

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<http://www.southwave.co.jp/swave/> (in Japanese)

Potential Health Effects of Alkylphenols in Japan

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Fujio KAYAMA*, Hyogo HORIGUCHI* and Akihiko HAMAMATSU**

*Division of Environmental Immunology and Toxicology,
Department of Health Science, Jichi Medical School

**Tokyo Medical Examiner's Office

Abstract: More than twenty thousand tons of alkylphenols and alkylphenol ethoxylates are used annually in Japan in synthetic rubber industry, plastic, fabric, and metal processing industries as surfactants, cleaners, stabilizers for ethylcellulose, plasticizers, and phenol resins. Some forms of alkylphenols are reported to induce endocrine disruption especially in fish species. Data monitoring of inland aquatic environments conducted by the Ministry of Environment in 2000 reveal that the concentrations of nonylphenol in 71 monitoring sites (4.5% of all monitoring sites) exceeded the Predicted No Effect Concentration (PNEC) for fish. Even if there is no clear evidence of effects on human health by alkylphenols, the study revealed that the current environmental concentrations in these sites influence reproduction in fish species. As precautionary measures, it is recommended to curb emissions of alkylphenols and its ethoxylates into the aquatic environment.

Key words: Alkylphenol; Alkylphenol ethoxylate; Fish; Reproductive toxicity; Endocrine disruptors

Introduction

In 1991, Ana Soto *et al.* from the Tufts Medical School, Massachusetts, USA, observed an abnormal proliferation of MCF-7 breast tumor cells, grown without any stimulating agents in the culture medium. After a thorough investigation of the possible causes, they ascertained that the abnormal cell response was due to the

polystyrene plastic tubes used in cell culture experiments.

Examining plasticware from various manufacturers led Soto *et al.* to the discovery that a chemical compound extractable from plasticware of a certain manufacturer is the source of contamination. Since the manufacturer refused to disclose the chemical, adducing “trade secret” reasons, identification of the compound

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was not initially possible. Analysis of the chemical, performed in cooperation with specialists in the field, revealed that the component in the plastic was nonylphenol. Soto's group discovered that this synthetic chemical had estrogen-like activity and was responsible for proliferation of the breast tumor cells. Later, other estrogen-mimicking chemicals, including a metal can coating compound, bisphenol A, were also reported.

Sumpter *et al.* observed a high incidence of intersexuality (presence of both male and female gonadal features in the same animal) in roaches, a freshwater fish living in the River Lea in the South of Britain. To find the cause of this abnormal condition, they cultivated a number of rainbow trout in cages downstream from a number of sewage treatment plants, measured blood concentrations of vitellogenin (an egg-yolk protein) in male fish and concentrations of nonylphenol in the river water.

The results of their studies indicated that detergents containing alkylphenol ethoxylates used in wool processing factories, particularly those producing nonylphenol-group metabolites, are potentially the main cause of the intersex gonadal features observed in rainbow trout. They demonstrated a positive correlation between blood vitellogenin concentrations in male fish and nonylphenol concentration in water and reported that activated sewage sludge can degrade alkylphenol ethoxylates, resulting in the release of estrogenic alkylphenol metabolites into the water.

What are Alkylphenols?

The chemical structure of alkylphenols is based on the phenol ring with multi-carbon moieties: nonylphenol is a 9-carbon side chain alkylphenol; octylphenol has an 8-carbon alkyl chain; butylphenol has a 4-carbon side chain, and dodecylphenol is a 12-carbon side chain alkylphenol (Fig. 1). Nonylphenol and octylphenol are the most widely used alkylphenols and have the broadest range of application.

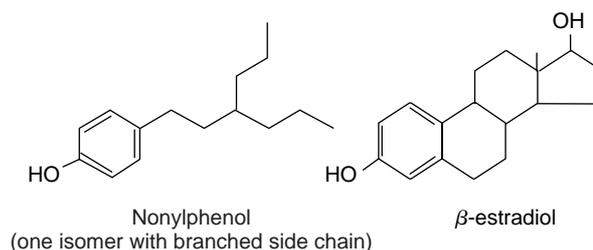


Fig. 1 Formula of alkylphenol

Alkylphenol production and consumption volumes decrease accordingly in the above mentioned order, the product with the smallest volume being dodecylphenol. Moreover, there are many alkylphenols with various chemical structures characterized by branched multi-carbon side chains.

Alkylphenols are mostly used as alkylphenol ethoxylates, that is, alkylphenols binding an ethoxy chain through their hydroxyl groups. The wide range of alkylphenol ethoxylate applications includes surfactants, ethylcellulose stabilizers, hydrophobic phenol resins, which are utilized in detergents, oil varnishes, synthetic rubber vulcanization accelerators, antioxidants of petroleum products and pesticide additives in agriculture.

Usage and Consumption Volume of Alkylphenol Ethoxylates

The annual alkylphenol ethoxylate production in Japan reached 46,850t in 1998. As shown in Table 1, the largest discharge of alkylphenol metabolites is considered to be from fabrics, metal processing, and cleaning industries, among others; however, accurate data on the volume discharged into the environment in Japan is unavailable.

It has been estimated that distribution of alkylphenol compounds after release into the environment is 58–73% for water and 27–41% for estuarine sediments. Furthermore, alkylphenol compound levels in organs of animals high in the food chain hierarchy are not neces-

Table 1 Domestic Consumption of Alkylphenol Ethoxylates (as for 1998)

Synthetic rubber and plastic industry	4,200(t)
Fabric industry	4,000
Metal processing industry	3,300
Business-use detergents	2,300
Cleaning industry	1,400
Dyes, pigments, paints, inks	1,100
Food processing industry	900
Agriculture	800
Paper and pulp industry	700
Petroleum and fuel industry	600
Civil engineering and construction industry	600
Pharmaceuticals and cosmetics industry	500
Leather auxiliaries	100
Others	3,400
Total consumption	23,900

sarily high and do not tend to get concentrated as a result of biological condensation, as demonstrated in the results of a study carried out by Tsuda *et al.* on fish species in Lake Biwa, Japan.

Alkylphenols in the Environment

In sewage treatment plants, alkylphenol ethoxylates are degraded aerobically with sequential cleavage of ethyl moieties and release of alkylphenols. According to the fact-finding survey performed by the Japan Environment Agency and Ministry of Construction in 1998/99, the alkylphenol concentrations in water samples ranged from ND (lower than or equal to the lowest detectable limit) to $21\mu\text{g}/\text{l}$, with an average value of $0.22\mu\text{g}/\text{l}$, and $0.59\mu\text{g}/\text{l}$ (95 percentile) was tentatively set as the estimated concentration for the environment, the highest alkylphenol compound concentration for an average aquatic locality.

Feminization of Fish Species

A committee at the Ministry of Environment has temporarily established 4 testing methods to examine the impact of endocrine disruptors on fish species. They are, as follows:

1. FLF/d-rR medaka test,
2. Reproduction test,
3. Vitellogenin assay, and
4. Medaka partial life cycle test.

The items 1., 3., and 4. are described below in more detail.

Regarding the FLF/d-rR medaka test and estrogen receptor binding activity, nonylphenol binds the estrogen receptor 10-times weaker than $17\text{-}\beta\text{-estradiol}$ (E2), in concentrations ranging from 10^{-9} to 10^{-8}M . Further, based on a reporter gene assay study with estrogen receptor-introduced cells, it was demonstrated that nonylphenol elicits transcription-stimulating activity hundreds times lower than E2.

On the other hand, in regard to the vitellogenin assay and alkylphenol concentrations affecting fish species, it was reported that an alkylphenol concentration capable of inducing abnormal microscopic changes in the testicular tissue of fathead minnow (a North-American cyprinid freshwater fish) was $1.6\mu\text{g}/\text{l}$; in juvenile trout, the effective concentration that produced elevated liver vitellogenin levels was $10\mu\text{g}/\text{l}$ and in mature male trout, the concentration sufficient to induce elevated serum vitellogenin levels was $20\mu\text{g}/\text{l}$.

Concerning medaka partial life cycle test, secondary sex characteristics changes (male fish feminization) were observed in male fish at alkylphenol water concentration of $23.5\mu\text{g}/\text{l}$, with ovotestis and vitellogenesis at an alkylphenol water concentration of $11.6\mu\text{g}/\text{l}$.

The medaka full life cycle test was performed in order to make a detailed examination of the alkylphenol effects on subsequent fish generations, revealed abnormal sex differentiation and lower fertilization rates among parental male fish at alkylphenol water concen-

tration of $17.7\mu\text{g}/\text{l}$. In the second generation, the ovotestis condition was found to be present at the concentration of $8.2\mu\text{g}/\text{l}$, a level not observed in the first generation males.

Ministry of Environment Survey —A Summary

The results of the survey on alkylphenols performed by the Ministry of Environment revealed that fish develop an ovotestis condition after exposure to low concentrations of octylphenol; which brings the endocrine disrupting activity of this alkylphenol compound into question. On the other hand, nonylphenol was considered a strong endocrine disruptor in fish, backed by results of *in vitro* studies on its nonylphenol ability to bind estrogen receptor and transcription-stimulating activity.

Based on the medaka partial life cycle test and alkylphenol concentration in water, the Lowest Observed Effect Concentration (LOEC) that affected fish sexual behavior was demonstrated to be $11.6\mu\text{g}/\text{l}$, and the No Observed Effect Concentration (NOEC) to be $6.08\mu\text{g}/\text{l}$. The Predicted No Effect Concentration (PNEC), the estimated concentration of alkylphenols in water that does not affect wild-life species, was calculated as 1/10 of NOEC value, that is $0.608\mu\text{g}/\text{l}$.

Thus, with the PNEC being $0.608\mu\text{g}/\text{l}$, water concentrations ranging from ND to $21\mu\text{g}/\text{l}$ in the domestic aquatic environment (data obtained from the environment fact-finding survey), and alkylphenol concentrations detected in 71 sampling locations (4.5%) exceeded the PNEC value. It was therefore considered that nonylphenol, in concentrations detectable in our country's aquatic environment, impacts on the endocrine system functions in fish species and possibly affects their reproductive system, as well.

Risk Reduction Measures

The advanced measures undertaken in many

foreign countries to reduce alkylphenol ethoxylate applications, which target a number of industries, include various initiatives such as legislative regulations and usage limitations. In Japan, such actions include the ban on alkylphenol ethoxylate applications in domestic-use detergents and efforts to find alkylphenol substitutes for business- and industrial-use detergents. Hence, in implementing the Pollutant Release and Transfer Register system, it would be necessary to promote the automatic administration policy and cooperation between industry, the government, and academia.

Toxicity in Mammals

Although even very low alkylphenol concentrations produce harmful effects in fish species, alkylphenol toxicity in mammals has been demonstrated by acute oral toxicity test results in rats, the lethal dose being 50% (LD_{50}) of 1,200–2,400 mg/kg. Moreover, a repeated dosing study in rats revealed that pathological changes initially appear in the liver and kidneys. The no observable adverse effect (NOAEL) dose was found to be 100 mg/kg/day for non-branched nonylphenol and 50 mg/kg/day for branched nonylphenol.

Regarding the toxicity of alkylphenols on the reproductive system, on the second and third generation tests, endocrine disrupting activities such as weight increase of the uterus, weight decrease of the ovaries, decrease of sperm density in epididymides, elongation of the maturation period and other abnormalities were demonstrated with alkylphenols in doses of several 10 mg/kg/day. It has been considered that mammals are less sensitive to nonylphenol than fish. Similarly, *in vitro* studies have also demonstrated that both binding to the human estrogen receptor and transcription-stimulating activity in mammals are extremely weak in comparison with binding to the medaka estrogen receptor and transcription-stimulating activity in fish.

Estrogenic Activity of Alkylphenols

The effects of endocrine disruption by alkylphenols may be summarized as follows: 1. Added to the culture medium, alkylphenols stimulate *in vitro* proliferation of the MCF-7 breast tumor cells. 2. They bind to the estrogen receptor and elicit transcription-stimulating activity. 3. At the water concentration of 10 ppb, alkylphenols induce an increase of serum vitellogenin levels in male rainbow trout. 4. In mammalian species, they cause mammary gland cell proliferation and elongation of the sexual cycle, applied in 0.01 mg/kg dose in rat chronic oral toxicity test. 5. Moreover, male rats fed with 1 mg/l alkylphenol in drinking water in the prenatal period and from the 22nd day after birth, have lower-weight testis and lower sperm counts.

Thus, compared with fish species, mammals tend to be less sensitive to alkylphenolic compounds. One source of concern, however, is the low dose effect problem of endocrine disruptors.

Low Dose Effect of Endocrine Disruptors

Fred von Saal *et al.* from the University of Louisiana reported that treatment of pregnant rats with very low quantities of bisphenol A resulted in delivery of male offspring with lower prostate weights. The dose-response curve drawn in their experiment was not sigmoid-shaped, as is generally observed, but had an inverted U-shape. Furthermore, von Saal *et al.* also reported the early sexual maturity of female offspring born to rats treated with ethynyl estradiol during pregnancy. Their findings, known as the “low dose effects,” have attracted considerable attention.

The reason for the special interest aroused by the “low dose effect” hypothesis is that until the publication of von Saal’s results, toxic dose evaluation of a given pharmaceutical or chemical agent was based on the NOAEL calculation

from the oscillating dose-response curve. Using the NOAEL value, a safety factor, $\text{NOAEL} \times 0.1$, was established with the specific difference between laboratory animals and humans defined as 0.1, and then taking into account the diverse patterns of human sensitivity to chemicals further multiplied by 0.1. The allowance dose was determined from the estimation that the safe dose equals $\text{NOAEL} \times 100$ -fold as the safety factor value.

If endocrine disruptors produce low dose effects, then this necessitates the redesigning of safety assessments for a whole range of chemicals, including subjects treated with even lower concentrations of a chemical or pharmaceutical agent into experimental groups, redoubling the cost burden as a result. The “low dose effect” hypothesis has already been openly and aggressively challenged by the chemical industry.

A similar phenomenon to low dose effects has been known to exist in biology; however, since the two arguments are at loggerheads, a conclusion has yet to be reached. However, the concept of reassessing safety doses for all chemical compounds taking the “low dose effect” into consideration does not appear to be the opinion of the majority.

Studies on Changes in Male Reproductive Functions

In 1987, Carlsen and Skakkebaek *et al.* issued a report based on a meta-analysis of papers published in various countries and related to semen qualities. Their findings indicated a significant decrease in sperm counts—by 50% over the past 50 years. The researchers proposed that the cause of such a condition was the prenatal disruption of reproductive organs development due to exposure to sex hormone-mimicking chemicals. Though their study drew some criticism concerning the differences between the subjects examined in the included papers, the inability to control the quality of data in some countries and the inappropriate statistical methods applied by some authors,

the work of Carlsen and Skakkebaek *et al.* made a major contribution to the research on male reproductive functions, which, since publication, has become more vigorous worldwide. Subsequently, reports on reproductive system abnormalities observed in wildlife species and the decline of semen quality in men have garnered widespread interest, leading to the establishment of fair-sized-budget research projects in Europe and America since the mid 1990s.

Likewise, in 1998, using what little basic data are available, we conducted research on the quality of semen among healthy Japanese men, in collaboration with the Department of Urology, School of Medicine, Sapporo University. In fact, the department mentioned above conducted research on healthy men from Sapporo some 20 years previously, and a comparison with the 1998 survey data revealed no marked changes in sperm count or sperm density. Since semen quality is influenced by periods of abstinence, sperm collection methods and daily fluctuations among individuals, the importance of a standardized system had been raised. An international quality control program led by Skakkebaek from Denmark, related to the research on male reproductive function has been highly promoted.

Additionally, we collected fat tissue from human autopsies to measure endocrine disruptor concentrations and to analyze sperm formation; an estimation of exposure to and impact from given endocrine disruptors was simultaneously conducted on the histopathological samples. During the study, our attention was drawn to lifelong changes in testes' weights. We discovered that, unlike general growth acceleration changes observed among young men from 1945 (the time of administrative autopsy program implementation), testes' weights did not follow the growth acceleration pattern of gradual increases in body height and weight, but entered a plateau phase or even decreased among men in their 20s born in and after 1970 (Fig. 2).

From the aforementioned observations and

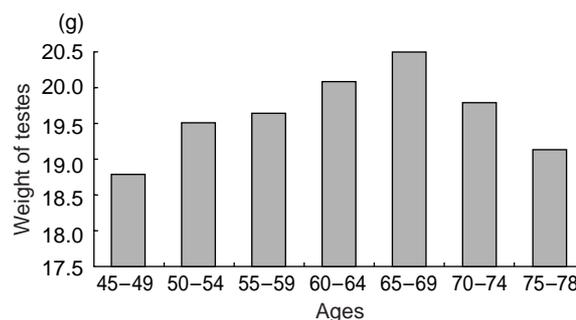


Fig. 2 Changes in weights of testes among men in their 20s

regarding risk assessment of the alkylphenol compounds, we concluded that since exposure to these endocrine disruptors in prenatal and neonatal period causes suppression of testis development, alkylphenols cannot continue to be considered safe for a mammalian organism. A more detailed and prospective survey is necessary.

Changes in Environmental Policies

In our country, the main objective and starting point for many environmental policies is to protect human health from any environmental pollution. The Environment Agency has adopted specific measures to act sensibly in compensation cases for victims suffering from Minamata disease, Itai-itai disease, Yokkaichi asthma, and similar diseases. It is no exaggeration to say that to date, the environmental standards have predominantly been based on prevention of environmental harm to human health.

On the other hand, the US Environmental Protection Agency (US EPA), which aims to protect the survival of wildlife species, was established after the findings that exposure to DDT causes abnormal reproduction in birds. In fact, approval of a new pesticide in Europe and America requires reproductive toxicity testing in birds; this is not a preventive measure towards potentially harmful effects on the human reproductive system.

Regarding the effects of nonylphenol, the

Ministry of Environment has recognized the harmful effects of this alkylphenolic compound on reproduction in wildlife species and has established an environmental protection

policy. Protection of wildlife species, which are more sensitive to environmental harm than humans, is an epoch-making decision.

Participation of the Japan Pediatric Association —A training project for consultants in children's mental health—

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Kiyoshi HOSHINA

Chairman of Pediatrics, Tokyo Teishin Hospital

Abstract: Not only normal physical development and growth, but also normal mental development is important for the health of children. The pediatrician occupies a unique position that allows him to see children and their parents from the earliest years of life. The Japan Pediatric Association (JPA) has planned a training course for pediatricians so that they can obtain a deep understanding of the child's mind and provide better care that promotes favorable mental development. The subjects covered by the 4-day training program include the mental problems of 2-year-old infants, problematic behavior of children older than 2, the basis and practice of psychotherapy, psychiatric illnesses, and school problems.

Key words: Child; Mental health; Mental health of children; Pediatricians

Introduction

Sound mental development is essential to the health of growing children, as well as sound physical development and growth.

It is a privilege for pediatricians that they can see individual children and their parents from the earliest years of life as family advisers. Pediatricians who have been following the growth of children from soon after birth have also been observing their families and living

environment, as well as their growth and their physical and mental development.

Consequently, pediatricians should also take actions to cope with the mental problems of children, which have become a serious social problem.

Objectives and Outline of the Training Course

From the viewpoint described above, a train-

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ing course was held so that pediatricians could gain a deeper insight into the child's mind and could make a greater contribution to the mental development of children.

The subjects of the training course were as follows:

- First period
 1. Mental problems of 2-year-old children, which are the most difficult to handle.
 2. Mind of the child up to age 3.
 3. Mental development of children.
 4. Psychology of the parent-child relationship.
 5. Problematic behavior in infancy and early childhood.
 6. Problematic behavior at school age.
 7. Problematic behavior in adolescence.
 8. Development of the ability to participate in social relationships.
 9. Psychotherapy: An introduction to counseling.
- Latter period
 1. Psychiatric illnesses in children.
 2. Psychosomatic illnesses in children.
 3. Children who cannot cope with school and countermeasures.

The training course has been held twice already. Because different lecturers have different views on the same subject, more than half of the lecturers who participated in the first session were changed for the second session.

The training course was divided into two 2-day periods. The subjects covered by the first 2-day period were basic, whereas the latter 2-day period covered clinical subjects.

The lectures given during the training course, particularly those from the first period are reproduced in the following.

Lectures from the First Period

1. Mind of the child up to the age of 3

At the beginning of this training, the participants were taught about the importance of mental development during the first 3 years of life, together with the high possibility that men-

tal development in this period has a substantial impact on future development and growth.

The emeritus president of the Japan Pediatric Association, Dr. Jushichiro Naito, stated that knowledge about the mind of children from this age group would help pediatricians to improve their practice.

In many instances, parents (especially the mother) deal with children in the wrong way. Knowledge of a child's mind will help pediatricians to give pertinent advice.

Every child has a spirit of independence. This is expressed when the parents deny or neglect his/her ego, which he/she wants to keep intact. It was emphasized in the lecture that children become more eager to do something themselves if their parents encourage them by saying, "Let's do it," or "You can do it, can't you."

Next, various data were presented to show the association between mental development and brain development during the first three years of life. With respect to the mental development in children, the superego, formed before around 3, is very important. I think that pediatricians know this very well.

In the 1998 Health and Welfare White Book, the collapse of the myth about 3-year-old children is described. From an adult viewpoint, even this myth has been exploded, the superego is still in full force when mental development during childhood is considered (although this is my personal view).

2. Mental development of children

With respect to personal relationships, in the course of mental development, children realize the importance of being able to trust and to be trusted and while they are playing with friends, become aware of self-assertion and self-control. Thus, children learn social rules. In modern society, however, many children cannot play with friends. The nuclear family has deprived children of the chance to live with grandparents, and hence they have become unable to cultivate consideration for others.

To ensure a child's future, it is desirable that

children should; 1) have a dream, 2) establish high self-esteem through experiencing a feeling of accomplishment, 3) develop curiosity, 4) have the ability to gain the confidence of friends, and 5) recognize that they are loved. Both society and the family must make efforts to accomplish these goals.

Products of creation are not important for mental development of children. Development of creative imagination through repeated use is a prerequisite of mental development. Consequently, adults who are caregivers should have a fertile imagination.

3. Psychology of the parent-child relationship

Victims of domestic violence by children, which seems relatively major in Japan, are believed to be mothers in many cases. Among children who attack their mothers violently, not a few have been gentle and rather obedient until the attack, and have grown under the domination of their mothers. Attention should be paid to this fact.

4. Problematic behavior of children

The participants received a lecture about problematic behavior in relation to the stage of development (e.g., infancy, school age, and adolescence).

In infancy and early childhood, problems originating in the basic living habits were mentioned. Turmoil in the classroom that makes lessons impossible has been related to egocentric children. The ability to participate in acceptable social relationships used to be established during infancy to early childhood. Today, however, children in these age groups cannot develop good social relationships because of the education system. In addition, children are not adequately disciplined at home. Both school education and home discipline are problematic. In this stage of development, children should be able to recognize that they are loved.

Problematic behavior at school age can be considered an expression of poor social relationships. Typical problems include school refusal,

bullying, and attention deficit hyperactivity disorder (ADHD). These problems share some background factors. The common factors mentioned in the lecture included a society that values efficiency and hence undervalues the mental state and morals, both of which are difficult to visualize, the decreased number of children per family, and adults who are incapable of caring for children in the community.

It should be understood that there is the lack of learning, experience, or maturity appropriate for their age in the background of children who cause such problems. To cope with these problems, the children should be respected and their inappropriateness should be accepted.

With respect to problematic behavior in adolescence, modern Japanese children grow early, but are psychologically immature because they reach adolescence without having experienced the life events that children should have experienced or without having been trained to develop personal relationships due to the social environment characterized by urbanization and the decreased number of children per family. This gap between physical and psychological of development results in increased stress on children when it is combined with the current social conditions. Because parents are facing their own midlife problems, children have become unable to find a calm coexistence between father and mother.

The role of pediatricians is to detect problems of adolescence at an early stage and prevent transformation into psychosis. It was emphasized that in order to perform this role, pediatricians and children must always have confidence in each other.

5. Development of the ability to participate in social relationships

In the lecture, the term "acceptable social relationships" was defined as a state of consciousness in which children are able to understand anything if an adequate explanation is given.

The level of socialization varies with the age or

stage of development. The adults around a child should give him/her adequate advice, so that the child grows and develops to become an adult who can understand anything by explanation.

6. Psychotherapy

In the practice of psychotherapy, the wishes of the child should be respected as in the case of obtaining informed consent for medical procedures. In addition, therapy should proceed in collaboration with the child. These two considerations are fundamental.

During the therapeutic process, the disease may appear to become temporarily worse for those around the patient. This apparent aggravation is often a reflection of the process of demolishing the self before its reconstruction.

Explanations about various forms of psychotherapy, including play therapy, family therapy, sand play therapy, art therapy, and behavior therapy were given.

7. Basis and practice of counseling

Counseling in a narrow sense is highly specialized. In a broad sense, however, it includes consultation and giving advice.

Counseling is a time-consuming process and the optimal timing of intervention is often missed. Consultation that provides information on present problems, on the other hand, can work as an intervention in immediate crisis. When the immediate crisis is managed, the patient should be treated in cooperation with a counselor. At a pediatric outpatient department, even consultation or mere provision of information can be useful.

Counselors should be ready to listen to the child and to carefully tell him/her what they feel and think. Because children cannot express complicated ideas that or internal sensations, non-verbal approaches are also necessary in some instances.

It is meaningless to ask a child with problematic behavior the reason why he/she has done something. Instead of asking the reason, you should ask him/her what was done so that he/

she can become aware of personal feelings or those of other persons. Through this process, the ego is cultivated and the experience gained through past personal relationships can be corrected.

Training during the Latter Period

1. Psychiatric disease

According to DSM-IV, disorders of conduct and oppositional defiance included in Category 1 "Diseases of which diagnoses are made for the first time usually in childhood, early adolescence, or late adolescence," as well as anti-social personality disorder and borderline personality disorder from Category 16 "Personality disorder," were explained.

Children with oppositional defiance assume a hostile attitude, but are not aggressive. The major symptoms become manifest within the home. Consequently, this should be discriminated from periods of transient insubordination during adolescence.

The patient with conduct disorder is aggressive and has neither empathy nor consideration for others. Conduct disorder with the onset in childhood is liable to undergo transformation into anti-social personality disorder.

Personality disorder is usually diagnosed during adolescence or later, while patients with anti-social personality disorder usually have symptoms of conduct disorder before the age of 15. With borderline personality disorder, it was mentioned that because it is an intermediate disorder between neurosis and psychosis, the personal relationships, self-image, and emotions are unstable and the person is impulsive.

To cope with the mental problems of children, it should be recognized that the negative aspects of TV and other factors have become predominant because the current Japanese society is a mass media society.

2. School refusal

When children cannot adapt to school, inadequate socialization, insufficient play experi-

ence, and poorly developed tolerance are considered to be the causes. In particular, the lack of tolerance is important.

Tolerance is usually established before the end of early childhood. Consequently, it depends on the parental attitude during childcare. Overprotection of children, although not recognized by parents themselves, is an important problem that needs to be addressed. Intolerance of children can only be prevented by taking good care of them during their infancy and early childhood. Caregivers should let children learn social relationships and tolerance. Society will not change soon, but improvement should be started by pediatricians.

To solve the problem of school refusal, it is important to provide opportunities for adults listen to children. If an adult and a child can spend time together, there is a chance that the child will spontaneously cease school refusal.

The psychology lecturer gave the lecture from the standpoint that children do not need to attend school, while the pediatrician took the standpoint that attendance is a prerequisite for mental development. It is not important which standpoint is right, so the physician who treats a child should select one depending on the findings at interview.

Why does an adolescent develop school refusal in the course of formation of self? School is a large barrier to children and there are many problems to be discussed.

3. Measures to be taken during the practice of pediatrics

A pediatrician who aims at pediatric care for both the mind and the body gave a lecture on this subject. The present state of childcare and the social environment, the actual measures taken in community pediatric care, and services offered in cooperation with various occupational specialists were explained.

In addition, when the relation between children and their caretakers appears to be dysfunctional, the following four items should be checked:

- (1) Does the caretaker have his/her own dream? Has he/she made efforts to realize that dream?
- (2) Is the caretaker aware of his/her role in childcare? Does he/she focus on pride and ambition?
- (3) Does he/she have an excellent adviser?
- (4) Does he/she have an affectionate relationship with the child?

This lecture was given by a pediatrician who is practicing these points.

Finally, a pediatrician who has continued to have contact with women from before childbirth gave a lecture.

In order to assess the symptoms of children accurately, the pediatrician classified a "physical pain" as "mental trouble" while considering the pathology related to the symptoms. Even if complaints appear trivial, they are serious problems for the parents. Consequently, the pediatrician should accept the complaints and cope with them.

During health checks and pediatric practice, or as a school doctor, pediatricians should handle the patient with a sympathetic attitude for the parents and talk dialogues with them about the wisdom of life. Such behavior by pediatricians may alleviate the uneasiness of parents and help them care for their children, while such childcare is effective in protecting children from mental problems.

Because pediatricians have comprehensive knowledge about the mental development of the children, they should make efforts so that all children can develop their individual mental faculties smoothly in their own way.

Although living happily with children and equal opportunity for men and women are hallmarks of this age, the mother still has the central parent-child relationship. Other people should thus cooperate with and support the mother.

Because the wife and husband have grown up under different circumstances, they should exchange views with each other and react against each other. This is the natural way of

living together. Seeing their parents living in such ways, children can grow up.

This lecture concluded with the following statement: When children quarrel, leave them until they cry. Children who are crying should then be treated gently.

Conclusion

Exploration of the mental troubles of children and seeking for the causes is an endless process. Pediatricians can solve such problems in quite a few cases. They should start making efforts now, so that such problems can be solved one by one.

It is no exaggeration to say that only pediatricians deal with parents and their children from infancy and early childhood. Frequently, mental problems have been brought to the attention of a pediatrician before they surface, which suggests the importance of the role that pediatricians could play.

We who are operating this program have a desire that the participants of this training course can contribute to the better mental development of children through acting in a network with psychologists, schools, nursery schools, day nurseries, and child consultation centers.

The Activities of Regional Medical Associations —Committee on Mental Health Countermeasures of the Tokushima Medical Association—

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Tsuneo NINOMIYA

Professor, School of Health Sciences, University of Tokushima School of Medicine

Abstract: The psychosomatic problems of children that occur during the developmental stages stem from complex parent-child relationships or interpersonal relationships that exist in group activities, the personality of the child or the child's tolerance to stress. The problems are developmental distortions or disorders of interpersonal relationships. Early detection and active assistance by physicians involved in infant care and school health are desirable. In tandem with the task of dealing with the psychosomatic problems of children, it is important to take note of factors such as the mental health of the parent, the parent-child relationship and to moderate the interpersonal relationships between family members, while seeking the cooperation of health clinics, kindergartens, schools, and other sources of group activities. Healing the psychosomatic problems of children is dependent on the concerted exchange of information and coordinated assistance between the physicians, teachers, and school counsellors within their respective fields of expertise.

Key words: Psychosomatic problems; Mental health countermeasures; Coordination; Family support

Introduction

The number of children with psychosomatic problems is on the rise. The majority of these problems are intricately linked to the personality traits of the child during the developmental stages, the child's tolerance to stress, and the

interpersonal relationships that exist in their educational and social environment.¹⁾ The psychosomatic problems of children are developmental distortions or disorders that stem from interpersonal relationships. Therefore, assistance should focus on measures to adjust parent-child relationships and relationships between family

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members, in conjunction with cooperation from group activity centers such as the child's pre-school, kindergarten, and primary school.

Infant care and school physicians are responsible for the early detection, help, and active coordination of family support. In addition to reviewing the developmental environment of a child with psychosomatic problems, the physician must pinpoint dangerous or critical factors and to take preventive measures.

The Tokushima Medical Association has operated a Committee on Mental Health Countermeasures aimed at addressing the psychosomatic problems encountered in school health. Initially, the committee was engaged in providing advice regarding primary school children with psychosomatic problems, but lately, consultations regarding infants have increased. Therefore, this paper will review the mental health countermeasures that target this latter group with regard to the role of the physician and family support in coordination with pre-schools and kindergartens.

Activities of the Committee on Mental Health Countermeasures

The Committee on Mental Health Countermeasures was established in February 1997 in accordance with the school physicians sectional meeting of the Tokushima Medical Association. The past activities of the committee have been presented annually at the National Conference on School Health and School Physicians,²⁻⁵⁾ therefore, the details have been summarized in this report. Measures to strengthen the linkage between the school and school physician, the school physician and specialized institutions, and between specialized institutions were pursued. Furthermore, a Help Line to actively address the psychosomatic problems of children was established within the Tokushima Medical Association headquarters to provide a more comprehensive counselling system. Telephone counselling services were provided for schools and families and intro-

ductions to specialized institutions were given as needed.⁶⁾ In August 1999, the patient case review meetings were expanded, and the first biannual Tokushima conference on mental health research was held.

Current Conditions and Telephone Counselling Related Issues

Telephone counselling services for pediatric psychosomatic problems are currently provided by pediatric counselling centers, the Police Department, prefectural educational committees, educational colleges, the Regional Legal Affairs Bureau, and other institutions. To provide a more unique counselling service, the medical association focused mainly on cases that required medical assistance. As of December 2000 when the pediatric psychosomatic help-line services began, a total of 207 cases were handled. This is not a modest statistic in view of the large number of institutions that presently provide help-line counselling services.

Due to referrals from school educational committees, the majority of the callers were initially parents of primary and secondary school children. But with the advent of newspaper articles that introduced the medical association's help-line services, calls from pre-schools and kindergartens increased. In June 1998, counselling was provided for an infant suffering from night-terrors. Subsequently, counselling for 37 cases of infants and preschoolers suffering from the same ailment have been provided since that time. In addition, counselling has been provided for other ailments such as tics, stammering, genital fondling, frequent urination, nocturnal enuresis, convulsions, temper tantrums, reluctance to attend preschool, autism, thumb-sucking, eating problem, gait disturbance, and nearly all other health related problems.

In one case, a mother of a four-month old infant sought help because her infant would not smile. She had solicited the assistance of many other counselling services, but the prob-

lem remained unresolved and she was continuously apprehensive.

One of the foremost disadvantages of helpline counselling is that the caller remains anonymous. In serious cases where abuse is suspected, information must be collected and continuous support is needed. The caller or patient must visit the counselling center or receive visits from social workers to ensure that uninterrupted support or assistance is provided. Although telephone counselling provides the security of anonymity, the greatest challenge faced by the counsellor is his or her ability to link the caller to an assistance team that will provide the patient with continuous support.

Assisting the Children and Family

1. Basic attitude

It is important that the child and family members have close access to assistance. To accomplish this, the physician must have knowledge about the child's psychogenic reaction or psychosomatic disorder, as well as counselling capabilities to alleviate the stress of the parent that stems from parent-child interaction. The outward physiological symptoms must be treated by therapy; the internal and emotional symptoms must be addressed through psychology, psychiatry, and human development studies; and problems stemming from interpersonal relationships must be redressed through family therapy and human studies. The collective knowledge of these various fields of study must be utilized to treat the physical symptoms, without arousing feelings of self-condemnation and lowering the self-esteem of the child. In addition, it is important that the physician help family members to adopt an attitude of patience and acceptance.

2. Focusing on the mental health problems of the mother

The ratio of support and assistance for the mother should be increased in addition to focusing on efforts to resolve the child's problem

with family members. In discussions with the mother about her child's psychosomatic problem, the mother will frequently confess to feelings such as "I don't think I'm qualified to be a parent", "My child won't smile. I'm tired of raising the child", "I don't think I love my child", "I spanked the child", or "I'm afraid that I'm going to hit the child". In very serious cases, she will confess to feelings of physical abuse toward the child. In actuality, the counselling serves to help the mother release her pent-up feelings of emotional fatigue stemming from child-rearing activities rather than problems that are directly related to the child. Mothers in self-denial reluctantly discuss concealed problems or their innermost feelings because of their desire to regain their confidence as mothers, i.e., she has internalized the problems related to her child.

In treating the psychosomatic problems of children, it is important for the physician to listen to the parents and other family members and not solely the child. The physician's attitude must be one of unhurried attention and must never give the impression of being judgmental when guidance or supervision is provided. Most importantly, the physician must show an attitude of faith that the family will be able to resolve the problems. If the physician is required to provide guidance or supervision, it must be given tactfully. The physician is also responsible for evaluating the outcome of his treatment, and therefore, must see the patient through continuous counselling sessions.

3. Assisting the family

The husband's emotional support of his wife has a major impact on her perspective as a mother. Comments from mothers such as, "When I felt like hitting my child, my husband told me to hit myself first, take a deep breath and count to ten. I felt so relieved when he understood how I felt".

In addressing psychosomatic problems in counselling sessions, the physician will often ask the mother if she has the cooperation and

support of her husband. In many cases, there is the lack of encouragement and understanding from a spouse or the mother is isolated and blamed for the emotional problems of the child within the family, which has made it difficult to resolve the problem. There are also cases where stress stemming from the relationship between the wife and her mother-in-law is directed at the child by the mother. In such cases, the mother is encouraged to assert herself or to seek the cooperation of her spouse. However, the husband will often keep silent to prevent aggravating the problems between the wife and mother-in-law further. Or the mother will reconcile herself and suppress her feelings due to the close relationship between her spouse and his mother. Consequently, the mother's feelings of isolation are reinforced. When the psychosomatic problems of the child surface, the mother (wife) becomes agitated in her need to resolve the problem quickly, in order to avoid criticism by her mother-in-law. In her haste to resolve the problem, the child inevitably becomes the target of her frustration and a vicious cycle is established. Therefore, to resolve the problems of the child, the mental health of the mother within the family must be improved.

Following telephone counselling sessions, the attendance of both the wife and husband at the face-to-face counselling sessions is desirable. Family and interpersonal relationships can be learned from the family.

4. Linkage and cooperation

When the psychosomatic problems of the child begin to surface with matriculation to school or the participation in group activities, a linkage of cooperation and support for both the parent and child is required. There are three means of cooperation: (1) the physician who provides the initial treatment introduces the parents to an appropriate specialized institution, (2) a circle of information exchange is established between the relevant physician, preschool teacher, and clinical psychologist

who provide their respective support for the child and family, (3) the former two methods are utilized according to the symptoms and the progressive stages of the symptoms exhibited by the child. The permission of the child and family members to establish this type of linkage and cooperation is obtained prior to its start.

All of the approaches described above have their benefits and disadvantages, but the approach described in (2) is the optimum plan that actively enables each party to utilize and to learn from the other's expertise. In pursuing this approach, a supervisor will be required. Ideally, the physician who is able to accurately diagnose the child's symptoms should fulfil this role.

5. Coordinating with the preschool or kindergarten teacher

When the psychosomatic problems of the child are manifested at the preschool or kindergarten, the teacher usually advises the mother "to get reliable advice on how to handle the child". Information about the characteristics of the physical symptoms that are seen, the hidden internalized problems that exist, and advice on how to cope with the child, that is relayed to the preschool or kindergarten teacher from the physician through the mother, is generally inadequately communicated. In addition, the observations of the preschool teacher about the child's behavior are also an invaluable source of information for the physician. Therefore, the preschool or kindergarten teacher must be included as a member of the group of specialists and family members who are involved in treating the child, and the physician and teacher must meet to exchange information on a regular basis. The physician is responsible for relaying to the teacher the diagnostic name and the various psychological conditions that are manifested.

Advice such as "you're being too nervous and that's why these symptoms are surfacing" or "there appears to be a lack of affection that's being shown, perhaps you should show the child more affection" will only serve to worsen

the condition of the emotionally nervous and psychologically fatigued mother. Comments to the mother such as “you’d better hurry up and get him toilet trained or he’ll be the target of bullying in the future” by the preschool teacher about a child that wets his pants during the day will only heighten the mother’s agitation.

The factors underlying the psychosomatic problems of an infant are the irritation and frustration of the parent, the mother’s overly methodical attitude about child-rearing, the lack of affection, neglect, strictness, an overly protective parent, sibling rivalry and jealousy, and other problems stemming from interpersonal relationships between family members. However, condemning the mother will not resolve the psychosomatic problems of the child. Hence, it is essential to alleviate her stress. The preschool teacher must be informed of the importance of providing support that is focused on the interaction between mother and child and the relationships between family members, in order to resolve the psychosomatic problems of the child.

Sharing information through group cooperation helps to increase the amount of information needed to assist the child and family and enables changes to occur in the assistance that has been provided separately by each specialist.

6. Establishing cooperation and support in the community

Other parents indirectly condemn the mother for the behavioral problem of her child with backbiting gossip such as, “That child creates problems for other children at the kindergarten. I wish that child wasn’t there. What kind of discipline is the mother giving at home?”. Mothers who are the target of such gossip become socially isolated and subsequently do their grocery shopping in distantly located communities. Therefore, in addition to resolving the psychosomatic problems of the child at an early stage or providing encouragement for the mother, it is important to cultivate understanding and support in the community. The preschool and

kindergarten can become an initial source of support for the mother in the community. They can fulfil an important role in improving the community environment and the difficult human relationships that prevail. The number of communities that tend to isolate mothers of children with psychosomatic problems is probably larger than anticipated.

Conclusion

The psychosomatic problems of infants are generally closely intertwined with the child’s personality and the interpersonal relationships between family members. Therefore, collaboration is important between the physician and preschool teacher in their respective areas of expertise to help improve the relationships between family members and the mental health of the child’s mother, while treating the outward behavioral and emotional problems exhibited by the infant.

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Background of the Tuberculosis Emergency Declaration

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Toru MORI

Director, The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association

Abstract: Following the long-lasting smooth decline after the war, the improvement of tuberculosis situation in Japan has been slowed since the 1980's and the trend has become reversed after 1996. Basically it is related to the rapid ageing of the population with the growing of the heavily infected population segment born during early decades of the last century. As a result, Japan's tuberculosis case rate remains at a quite high level, i.e., about 6 times that of USA, or the level of USA's late 1950. At the same time, there is a remarkable concentration of TB patients on more susceptible populations such as medically compromised people or socio-economically deprived people. This has changed the clinical and managerial aspects of TB greatly, requiring more intensive care for each patient including care for underlying illnesses, drug side-effects, and social and psychological support for completing treatment, such as DOTS. Enhancing social and professional concern to this problem is urgently needed in order to respond to the Declaration of TB Emergency most properly.

Key words: Tuberculosis control; Risk factor; Socio-economic factor; Patient management; DOTS

Why TB Emergency Now?

The decrease in the TB case rate in Japan had been slower since around 1980, and finally in 1996 the case rate began to go upwards. From 1997 through 1999, there has been an increase in the rate for three consecutive years for the first time after World War II. (Fig. 1)

This could be seen as a temporary tumult in a long lasting and steady downward tide of

tuberculosis epidemiology, although there is a substantial influence of rapid ageing of the population after the war. However, depending on how we deal with that in the coming few years, this trend might give a birth to a new problem. We have a lot to learn from the example of the United States, where TB had been on the increase from the late 80's to the early 90's due to the neglect in TB control services. In fact, it can be said that the same signs

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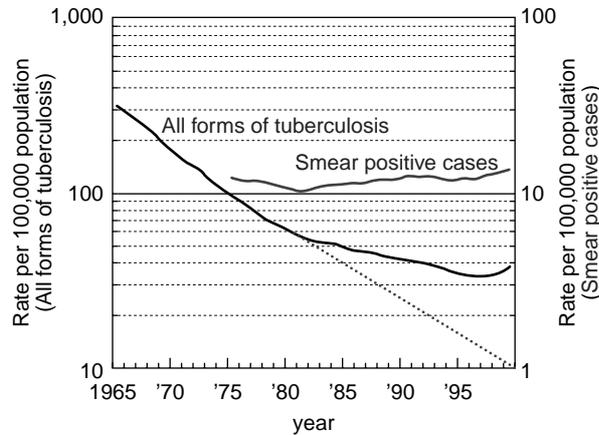


Fig. 1 Trend of TB case rate in Japan (1965 through 1999)

have begun to appear partly in Japan. Moreover, it seems that the response from various quarters to the problem has been somewhat unconcerned in effect. The tuberculosis emergency announced by the Minister of Health and Welfare in July 1999 has been regarded as drawing serious attentions to such a situation. Following this announcement, this paper examines the current situation of TB control and discusses how it should be in the future.

Increase in Cases with More Serious and Difficult Disease

The proportion of bacteriologically confirmed cases among newly registered cases, which is used to measure the seriousness of the condition of new TB patients, shows a significant increase from 19% in 1975 to 55% in 1999. Although, of course, it has to be taken into account that bacteriological examinations had become widespread and bacteriological findings had come to be considered more important during this period, this still seems to indicate that more patients have serious disease at the time of onset, and/or that tuberculosis is more likely to be detected only after it becomes very serious.

As a result, the prognosis of patients in terms

of their fatality has also worsened. The case fatality rate of the patients, which is estimated by dividing the number of patients who died within 1 year after they were registered by the number newly registered cases, has increased from 1.8% in 1989 to 2.9% in 1999. According to some source, 12% of the smear positive patients who have never been treated for tuberculosis before have died within 9 months after the treatment began.

Another issue to be warned for beside the above tendency is that the drug resistance is also on the increase. According to a nationwide survey on drug resistant tuberculosis conducted in 1997, 10.2% of patients who had never received TB treatment before had resistance to one or more major drugs at the start of their treatment, and among them 4.2% had resistance to isoniazid (INH), which has a particularly important role in tuberculosis treatment. Also, regarding those who had previously received treatment, more than 40% had some resistance and in particular, over 20% were resistant to both INH and rifampicin (RFP), i.e., the nucleus of drug regimen in the current treatment (multi-drug resistance).

This may seem relatively better in comparison with the US data showing the initial drug resistance between 1992 and 1996; 13% to some drugs, 8% to INH and 2% to both INH and RFP. Nevertheless, it is necessary to carefully consider this matter, since the number of patients with difficulties in receiving treatment will increase for medical and social reasons as discussed below.

The current problems in TB incidence and its treatment are summarized in the points that I raise as following. First, the development of TB is concentrated on medically compromised subjects including the aged and others, and thus their conditions tend to get severe. In 1999, 58% of newly recorded patients were over 60 years old, and 40% were over 70 years old. In addition, the population over 80 and 90 years old has been experiencing a remarkable increase in the case rate.

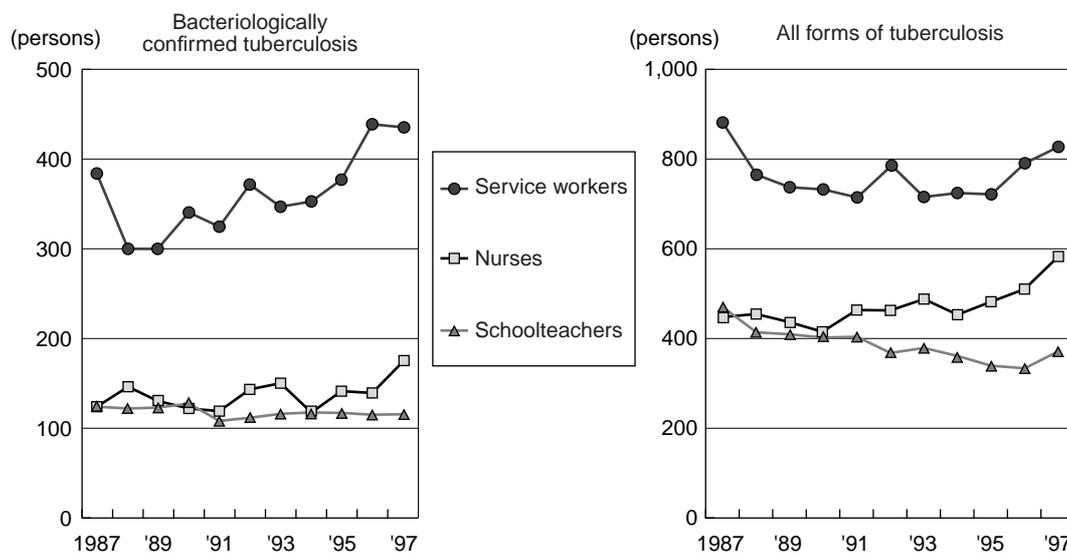


Fig. 2 Changes in the number of newly registered patients in different occupations

According to a survey conducted in Yamagata Prefecture, 14% of newly registered patients had diabetes. Similarly, 14% had a history of gastrectomy or under treatment for stomach ulcer, 6% under treatment for malignancies, 4% under treatment with corticosteroids, 3% with renal failure (under hemodialysis), etc. It is not difficult to imagine that once individuals with such medical risks present TB symptoms, they would easily develop them into severe conditions.

Drifting of TB to Socioeconomically Fragile Population

Another factor for the increase of TB patients that readily get into severe conditions is that the TB occurrence is concentrated on socioeconomically fragile people. The case rate of Nishinari Public Health Center, Osaka City that has "Airin Area" within its jurisdiction is 535 per 100,000 population, i.e., 14 times as high as the national average. The case rate estimated specifically for the homeless and the slum inhabitants is as much as 1,500–2,000. The concentration of TB incidence has also been observed in poor families and those engaged in

service businesses or working in small companies. As shown in Fig. 2 the number of the newly registered cases with positive bacteriology in service businesses has also been clearly increasing. It would be fair to say that one of the factors for this is inadequate health care in everyday life. However, it has been known that regarding newly recorded patients there is a strong correlation between the proportion of patients detected by health examinations and the proportion of those with smear positive cases among all new cases according to the type of occupation: in occupations such as nurses and teachers, the proportion of patients detected in health examinations is high and the proportion of smear positive cases is low; on the contrary, for the unemployed and the self-employed that have less chances to have health examinations, the proportion of patients detected in health examinations is low and proportion of smear positive cases is high. Thus, we should take it into consideration that administrative failure in extending such services to the socioeconomically weaker people may have contributed to the increase of TB among these occupations.

Improving Hospital Treatment

Next, I would like to summarize how tuberculosis medical services have been affected by the ever-continuing qualitative changes of patients in the midst of the TB upsurge.

First, it is becoming more important to detect TB patients in general consultations. It is commonly observed that the aged who have medical consultations for various medical problems are often found to have TB, or those who have less chances to have health examinations belatedly visit medical facilities due to the symptoms and are diagnosed as TB. As a result of this, 80% of patients in all age groups, and 90% in the age of 60 or over, have been detected in consultations at medical facilities due to the symptoms. Thus, patient detection in earlier stages of clinical setting rather than in health examination is becoming increasingly important. The result of inadequate functioning of this process has been the increase of patients with serious conditions and poorer prognosis as well as problems such as outbreak of small epidemics and nosocomial infections of tuberculosis. It is particularly necessary to implant and maintain the awareness of 'TB is still around!' both under- and post-graduate training of physicians.

Next, TB treatment is becoming more necessary in general consultations. As discussed above, TB patients with medical complications or underlying conditions are on the increase. Also, treatment for side effects of anti-tuberculosis medications is difficult. For TB treatment, these patients are often moved to TB beds, i.e., TB ward under the current legislation of medical facilities; nevertheless, that leads to the problem that treatment for underlying illnesses tends to be neglected. It is hoped that in the future a certain number of TB beds will be placed in general wards and both underlying illnesses and TB will be treated there. The Ministry of Health and Welfare has already been promoting the provision of such hospital room under the subsidiary program named "Model

TB Beds Program" since 1992. Although this program is aimed at providing subsidies for reforming a general hospital bedroom for the infection control so that TB patients can be accommodated safely, it seems that that has not been working quite well in practice.

Issues of Patient Support

Also, the importance of patient education is being reconsidered. The increase of socio-economically deprived patients indicates that completion of the treatment on a regular base will be difficult. The problems are caused by their maladaptation to hospital treatment and economic problems, etc. The best strategy for this is DOT, directly observed therapy. This is a strong patient management system where patients with difficulties in continuing hospital treatment and are discharged come to the hospital everyday and take drugs under the observation of the staff like nurses, combined with human communication between the patients and the staff, support as required, and visits the patients' houses when they do not attend the hospital. This program has been successful in New York as well as in developing nations. Also in Japan, although on a small scale, the program has been implemented in San-ya Area of Tokyo, Kotobuki Area of Yokohama City, Airin Area of Osaka City, and been successful. However, since hospital treatment is more readily available in Japan, it is hoped to establish a more flexible system where hospitals have a well working appointment system for OPD to check patients' regular attendance and a public health center in cooperation conducts education and support patients that are defaulting from regular drug taking and hospital attendance, rather than rigorous patient management like DOT that may not be practicable everywhere. We should also consider that there would be a time in the future when treatment under detention that has been conducted in many states of the USA will be considered for more uncooperative patients.

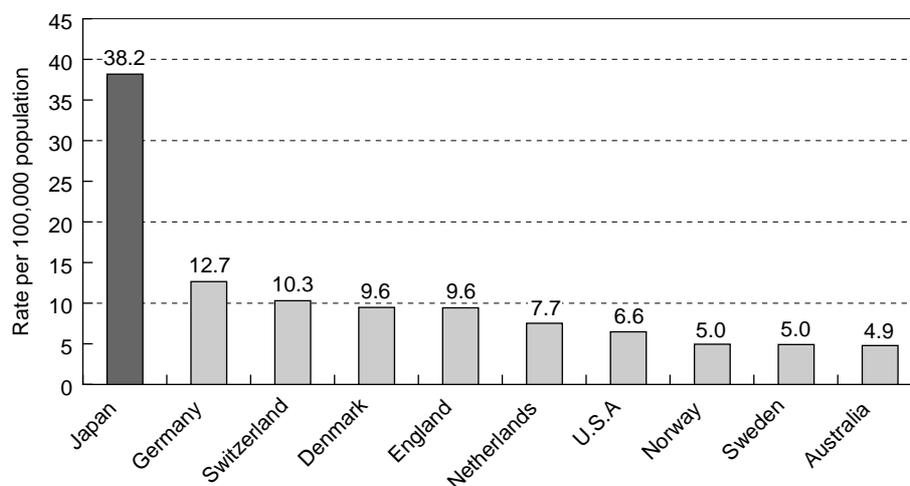


Fig. 3 Comparison of TB case rates between Japan and some other developed nations (1998, for Japan 1999)

Urgent Problems in Provision of TB Treatment Service

Apart from these general matters, however, there are several problems that have to be urgently dealt with. First, it is feared that TB patients might not be able to be hospitalized. Currently there are about 13,000 of TB beds that are specifically designated to accommodate infectious TB patients, and actually 60% of them have been occupied. However, their distribution is uneven, varying from place to place. It has been increasingly observed in some areas, especially in large cities that over 90% of them have been occupied. In those areas, patients currently discharging TB bacilli are unable to be hospitalized and thus have to wait, or be hospitalized in inconvenient, distant facilities. It is worried that the motivation for managing the hospital may be lowered due to the unprofitability and laboriousness of TB treatment, and the situation has been worsened by the abolition and conversion national and other public hospitals.

The next problem is that anti-TB drugs may be unavailable. Capreomycin became uncovered by the health insurance and the TB control law in 1997. It has been alleged that this

is because of the unprofitability resulting from the too low drug cost. Some other drugs such as ethionamide, cycloserine, and PAS have in the past faced the supply crisis for similar reasons. As we cannot have the pharmaceutical industry continue to sell products at their cost, it is needed to consider the revision of price list of drugs to a reasonable level.

Also, the authorization of new drugs that are to be used for TB treatment has been delayed. In many foreign countries, drugs such as quinolones are widely prescribed for patients with drug-resistance. However, in Japan these have not been approved by insurance nor TB Control law due to the difficulties in conducting clinical trials that are required for the formal approval procedure. In many other nations, the use of these drugs has been permitted due to the urgent demands. Adaptable administrative actions are urgently needed for exceptional approvals of these drugs.

Thus, it has to be said that the situation surrounding TB treatment in Japan is rather inactive. The medical expenditure for TB amounts merely 0.4% of the whole medical expenses in 1998. It was 27% in 1955. The wise utilization of this small amount of money would protect patients and surrounding people, and in turn

bring about the security to the national population for the decade to come. In order to achieve this, the awareness “TB is still around!” has to be raised still higher.

Comments

The case rate of TB in Japan is 38 per 100,00 population, which is 6 times as high as the US figure. USA passed this standard already in the 1950's (Fig. 3). As this is currently on the increase, the entire medical community of Japan should reconsider TB with new perspectives and take necessary actions. I believe that

that is the responsibility for medicine as a response to the TB Emergency Declaration.

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Treatment of Snoring

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Tadao NISHIMURA

Professor, ENT Department of Fujita Health University Second Hospital

Abstract: For proper treatment of snoring, it is important to perform inquiry, inspect the nasal cavity, pharynx and larynx, and hear the snoring sound by using a tape recorder. If sleep apnea syndrome (SAS) is suspected, overnight monitoring is performed. Dynamic MRI during sleep and upper airway endoscopy are very useful in the determination of sites responsible for snoring and SAS for the selection of an appropriate therapeutic method. Treatment of snoring is broadly classified into two major methods, conservative treatment and surgical treatment. Conservative treatment is indicated for the following cases: (1) high-degree obesity, (2) elderly patients or patients with heart diseases, (3) when improvement is not expected, and (4) when the patient is unwilling to undergo surgery. Conservative treatment includes (1) guidance of living, (2) medication, (3) nasal CPAP, and (4) use of dental appliances. Surgical treatment includes (1) intranasal operation, (2) UPPP (uvulo-palato-pharyngoplasty), (3) LAUP (laser-assisted uvulo-palatoplasty), (4) LMG (laser midline glossectomy), (5) tonsillectomy/adenoidectomy (especially for children) and (6) tracheotomy. It is important to select the proper method strictly based on the outcome of diagnosis.

Key words: Snoring; Surgical treatment; Sleep apnea syndrome (SAS); Nasal CPAP (continuous positive airway pressure); Dynamic MRI

Introduction

In times bygone, snoring was regarded as a symbol of a great man and large snoring sound was considered to reflect deep sleep. However, snoring, as matter of fact, is associated with two problems.

The first problem is that loud snoring produces noise during night when it should be

naturally quiet. The person himself is usually unaware of his snoring, but his snoring disturbs the sleep of his/her bed partner or family. In addition, when a snorer goes traveling with his/her friends or coworkers, he/she may be secretly worried whether his snoring would be hated or ridiculed.

The second problem is that loud every night snoring is suspected to be associated with sleep

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apnea syndrome (SAS). In other words, snoring is an inevitable symptom of SAS. In the presence of SAS, sleep is divided into fractions. This results at times in daytime somnolence and also affects the circulatory disorders including hypertension and heart disease.¹⁻³⁾

Diagnosis and Examinations for Treatment of Snoring

Investigation for the causes of snoring requires inquiry, inspection (nasal cavity, oral cavity and pharynx), hearing of snoring sound, and monitoring of nocturnal sleep. Moreover, upper airway endoscopy and dynamic MRI under drug-induced sleep have to be performed.

1. Inquiry

Presence or absence of nasal obstruction, midnight awakening, early morning headache, daytime sleepiness, and fatigability are inquired.

2. Inspection

It is important to observe the condition of the nasal cavity, oral cavity, and pharynx to examine for the presence of any abnormality. Severe nasal obstruction is observed in some cases, and the cause is repletion of bilateral nasal cavities with polyps that induce mouth breathing and obstruction at the root of tongue in inspiration during nocturnal sleep. In these cases, snoring and/or SAS are expected to improve following polypectomy. If inspection reveals severe hypertrophy of tonsils, snoring and SAS are attributable to the hypertrophy of tonsil in both children and adults, and dramatic elimination of snoring and SAS is, therefore, frequently experienced after tonsillectomy.

3. Hearing of snoring sound

To determine the severity of snoring and the type of snoring, 'vibratory type' or 'stenotic type,' it is therapeutically useful to ask the patient to record his snoring sound during sleep at home using a tape recorder and to bring the tape to the clinic for reference during

Table 1 Conservative Treatment of Snoring

• Treatment of obesity:
Nutrition education, exercise therapy
Mazindol (Sanorex)
Chinese medicine (<i>Bofu-tsu-sei-san</i> , <i>Dai-saiko-to</i> , <i>Boui-ou-shi-to</i>)
• Treatment of nasal allergy:
Local remedy
Tramazoline hydrochloride (Towk)
Oxymetazoline hydrochloride (Nasivin)
Naphazoline nitrate (Privina)
Tetrahydrozoline hydrochloride (Cor-Tyzine)
Nasal topical thermotherapy
• Other pharmacotherapy:
Acetazolamide (Diamox)
Progesterone preparations
Tricyclic antidepressants
• Other conservative treatment
Life guidance
Sleeping posture education
Dental appliances
Nasal CPAP (nasal continuous positive airway pressure) therapy

treatment.

4. Examinations

At the author's clinic, patients are hospitalized for 1 to 2 nights to perform overnight monitoring by polysomnography to examine the presence or absence of SAS and the severity of snoring.

In addition, dynamic MRI and upper airway endoscopy are performed under drug-induced sleep to determine the site responsible for snoring and SAS.⁴⁾ Dynamic MRI examination requires an expensive instrument and is available only at limited facilities, while the upper airway endoscopy is relatively easy to perform and is very useful in the determination of the therapeutic method.

Actual Treatment of Snoring

Treatment of snoring is broadly classified into two types, namely conservative and surgical treatments.

1. Conservative treatment

Conservative treatment is classified into pharmacotherapy and treatment without medication. (Table 1)

(1) Pharmacotherapy

Pharmacotherapy is indicated in the following cases: (1) Patients with high-degree obesity, (2) elderly patients or patients with heart disease in whom operation is contraindicated, (3) when it is not known whether any surgical treatment is available, (4) when the patient is unwilling to undergo operation.

As a pharmacotherapy of snoring associated with obesity, mazindol (Sanorex) is covered by national health insurance for patients with a high-degree of obesity index of 70%, or BMI (body mass index) of 35 or higher after 1992. In other words, pharmacotherapy is applicable to clinical treatment as an auxiliary therapy for diet therapy and exercise therapy.⁵⁾ In addition, Chinese medicines including *Bofu-tsu-sei-san*, *Dai-saiko-to*, and *Boui-ou-shi-to* are used to achieve weight reduction.⁶⁾

For snoring associated with nasal allergy, nasal drops of a vasoconstrictor agent before bedtime are effective for the treatment of nasal obstruction. In addition, a number of anti-allergic agents are available for internal use and most of the recently developed drugs effectively improve nasal obstruction with little sleepiness. Moreover, their concomitant use with local remedies improves nasal symptoms and is effective against snoring.

Besides these, acetazolamide (Diamox), progesterone preparations, and tricyclic antidepressants are also used in pharmacotherapy against SAS or snoring though they are not so common.

(2) Conservative treatment other than pharmacotherapy

(i) Life guidance, (ii) instruction of sleeping posture, (iii) dental appliance, and (iv) nasal continuous positive airway pressure (CPAP) are also used.⁷⁾

(i) Life guidance is considered as an important therapy because guidance to living

and exercise therapy against obesity may be successful in reducing body weight and thereby improve snoring or SAS. Some patients living an irregular life and consuming excessive alcohol may try to remove sleepiness by drinking canned coffee (canned-coffee syndrome). Life guidance is extremely important in such patients. Furthermore, in order to make these patients realize their obesity, it is very effective to make them record their body weight every day to graphically show the body weight change and to write a body weight diary. Furthermore, at the authors' clinic, some patients are given instructions about meals by a nutritionist.

- (ii) Regarding the guidance of sleeping posture, improvement or even elimination of snoring and/or SAS is achieved in many patients who have snoring or SAS in a supine position by making them sleep in a lateral position. However, some patients have a habit of lying in a supine position and we advise them to attach a baseball on the back to keep a lateral position all the time.
- (iii) Concerning the use of dental appliances, it is necessary to make the appliance at the dentist. The appliance is a kind of a big denture which when attached causes the lower jaw to project forward and the pharyngeal cavity to enlarge, thereby producing easy respiration and reduced snoring and/or SAS. It is effective for mild SAS but is not indicated for complicated cases with nasal diseases.
- (iv) Nasal CPAP is generally not used for patients suffering only from snoring. However, it may be indicated for cases of loud snoring associated with SAS. Nasal CPAP involves the application of positive pressure through the nose by a device during sleep and is often used in SAS patients in the United States. Also in Japan, it is the most popular medical therapy. The demerits of the method are that the patients need

Table 2 Surgical Treatments of Snoring

(i) Intranasal operations (turbinectomy, intranasal septal correction, nasal polypectomy)
(ii) UPPP (uvulo-palato-pharyngoplasty)
(iii) LAUP (laser-assisted uvulo-palato-plasty)
(iv) LMG (laser midline glossectomy)
(v) Adenotonsillectomy
(vi) Tracheotomy

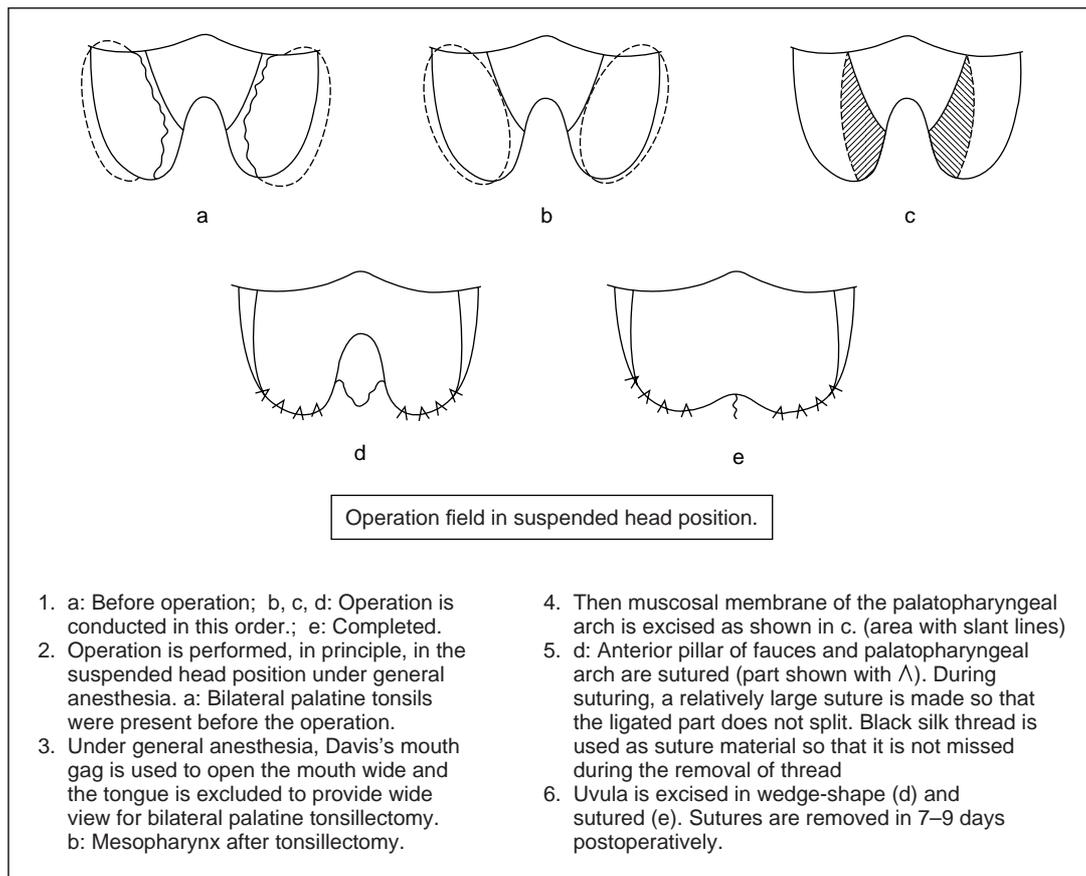


Fig. 1 UPPP (uvulo-palato-pharyngoplasty) technique
(Quoted from Reference 8)

to wear a mask in bed every night and the device produces some sound. Therefore, it is not indicated for all patients (applicable to 60–80% of patients). Also, it is not indicated for patients with severe nasal obstruction associated with nasal polyp, septonasal flexure, hypertrophic rhinitis, and nasal allergy.

2. Surgical treatment

Surgical treatment is considered extremely effective against snoring and SAS. Surgical treatment includes (i) intranasal operation, (ii) UPPP (uvulo-palato-pharyngoplasty), (iii) laser-assisted uvulo-palato-plasty (LAUP), (iv) laser midline glossectomy (LMG), (v) adenotonsillectomy, and (vi) tracheotomy. (Table 2)

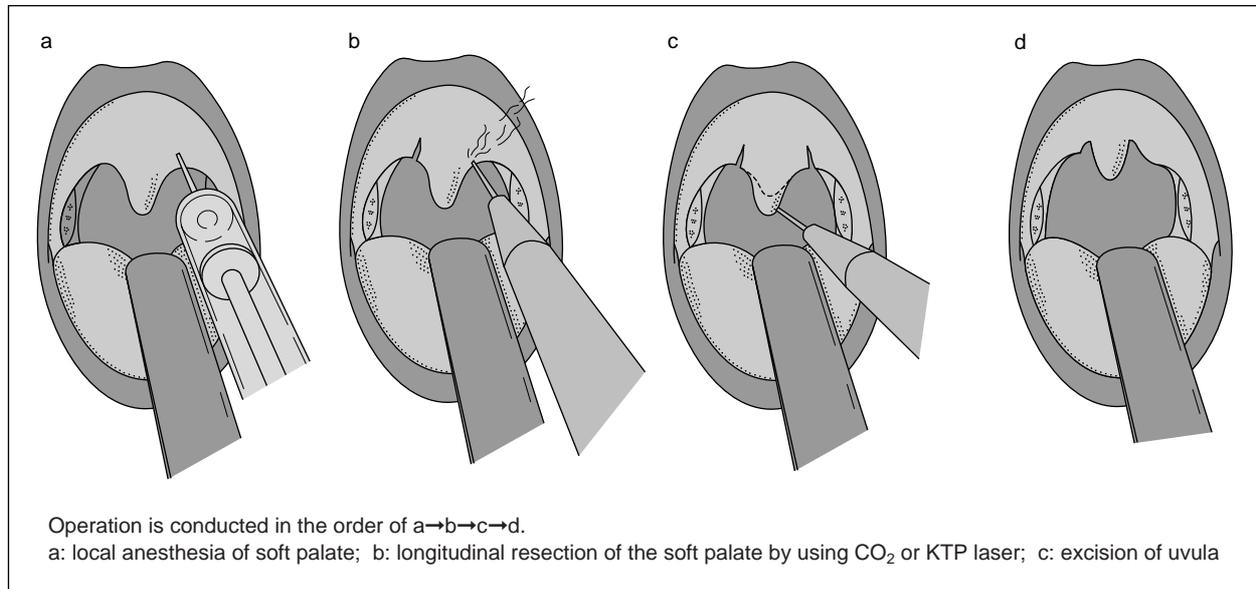


Fig. 2 LAUP (laser assisted uvulo-palatoplasty) technique
(Quoted from Reference 9)

- (i) Intranasal operation is a radical treatment of snoring caused by nasal diseases including bilateral nasal polyp, deflected nasal septum, and swelling of inferior turbinate due to nasal allergy and of snoring associated with SAS.
- (ii) UPPP operation (Fig. 1) is the most common operation for snoring and SAS. This operation is usually combined with tonsillectomy to enlarge the pharynx.⁴⁾
- (iii) LAUP (Fig. 2) involves upward excision of the bilateral soft palate by using CO₂ laser followed by excising the uvula short.⁹⁾ This operation is widely used as an operation for snoring in Western countries. However, UPPP and LMG are required more than LAUP for the treatment of more severe stenotic snoring.
- (iv) LMG (Fig. 3) is indicated for patients with a big tongue and for cases in which the tongue is forcefully drawn posteriorly downwards during inspiration to cause obstruction at the pharynx.¹⁰⁾
- (v) Adenotonsillectomy has a dramatic effect against snoring and SAS, especially in chil-

dren. This technique is, also, very useful against severe hypertrophy of tonsils in adults.

- (vi) Tracheotomy is used in rare cases with a high-degree of SAS for which improvement is not expected with any other treatment.

Conclusion

According to an epidemiological survey in Japan, SAS has a prevalence of about 2–4% and is always accompanied by snoring. In addition, SAS has significant effects on hypertension and respiratory/circulatory organs. Thus attention should be paid to loud nocturnal snoring and it is advisable to consult a physician for diagnosis and treatment at a special medical institution as early as possible.

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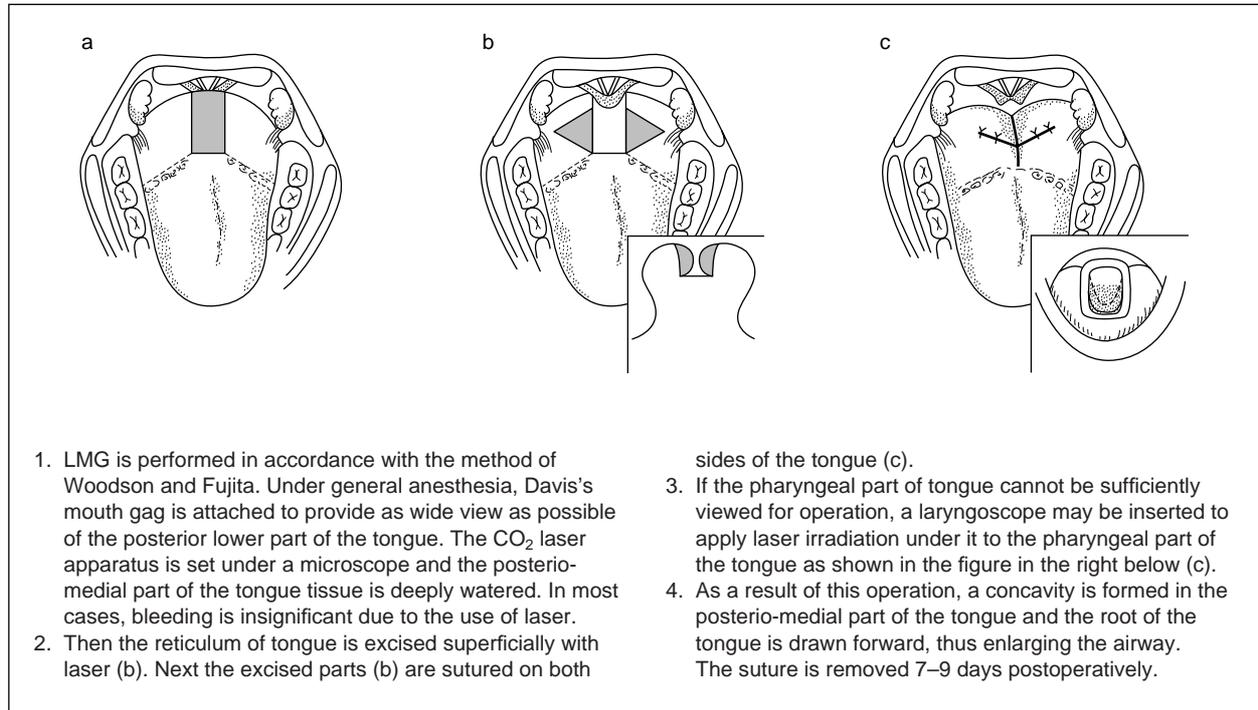


Fig. 3 LMG (laser midline glossectomy) technique
(Quoted from Reference 10)

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