Technics Guide

Capture-mark-recapture法

—インスリン依存型糖尿病発症率への応用—

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Capture-mark-recapture method ; application for IDDM incidence rate

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はじめに

ある地域で一定の期間に，心筋梗塞の患者や乳癌の患者がどのくらい発生しているのか，私たちは正確に把握しているだろうか．糖尿病についても同じである．インスリン依存型糖尿病(IDDM)の新規に発生した患者の登録制度が確立しているところは別として，その他の地域では，およその数を把握してるにすぎない．ところが，生態学者はとうの昔から，蝶の数やバッタの数を正確に把握していた．名前もなく，住所不定で，顔つきからも識別できない昆虫の数を，どのような方法によって数えたのだろうか．捕らえ所のない"昆虫"を数えることができ，住所・氏名の明らかな"糖尿病の人"を数えられない理由は何なのか．それは，生態学者はcapture-mark-recapture method(C-M-R：標識再捕法)[1~7]を知っており，私たちは知らなかったからである．

C-M-R法とは昆虫のみならず，クジラ，スイギュウ，ツルなどあらゆる動物を数えるときにひろく用いられてきた方法である．この方法は，いろいろな疾患の頻度を知るための手段としても，すでに一部で用いられていたが[8~10]，近年，IDDMなど慢性疾患の真の発症率を推定するために応用しようという考えが盛んになってきた[11~13]．

そこで本稿では，C-M-Rとはどのような方法なのか，疾患の発症率を把握するためには具体的にどうするかについて解説する．

I．個体数を推定する方法 (population estimation)

個体群の大きさをはかる最も確実な方法は，ある区域内に存在する個体すべてを数え上げる全数調査(complete census)である．しかしこの方法は，ひろい区域を対象としたときや，穴にもぐって見付けにくい動物などを対象としたときには労力的に実行不可能であり，実際的な方法ではない．したがって一般的には，これに代わるものとして，対象個体群のごく一部を標本として抽出調査し，その情報をもとに全体を推定するという方法がとられる．これをサンプリング調査(sampling census)という．

サンプリング調査の1例が区画法である．区画法では，調べようとする場所の全域を方形の小区画に分割し，そのうちの何区画かについて実測して全体を推定する．これに対して，草むらや林の中，あるいは水中などみえにくい環境にいる動きのはやい動物の個体数の推定として，もっぱら用いられてきたのがC-M-R法である．

II．Capture-mark-recapture 法

1．Petersen-Lincoln 法

ノネズミの個体数の推定を例にとって説明する(図1)．まず調べようとする場所の各所に罠を仕掛けてノネズミを捕まえる．その数(M)を数え，個体識別標識を施し元の場所に戻す．何日かあとに同じ場所に罠を仕掛け，捕らえたノネズミ(n)のうち標識のついたノネズミ(m)の割合から，そ

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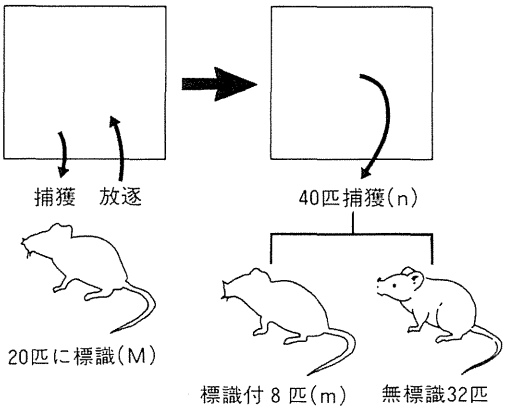


$$\frac{\text{再捕獲された標識付ノネズミ}}{\text{再捕獲されたノネズミ}} \approx \frac{\text{標識付全ノネズミ}}{\text{区域内の全ノネズミ}}$$

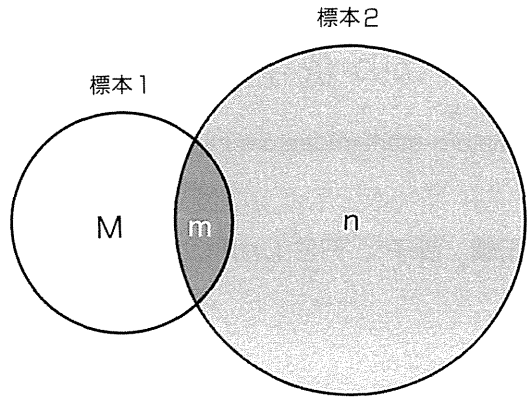
$$\frac{m}{n} \approx \frac{M}{N} \quad \cdots\cdots \text{式 1}$$

$$N = \frac{Mn}{m} = \frac{20 \times 40}{8} = 100$$

区域内に生息する推定ノネズミ数は 100 匹

$$\left.\begin{aligned} \mathrm{Var}(N) &= \frac{Mn(M-m)(n-m)}{m^3} \\ nD &= \frac{Mn(n-m)}{m(D^2Mn+n-m)} \end{aligned}\right\} \quad \cdots\cdots \text{式 2}$$

図 1　Petersen-Lincoln法



N＝推定数
M＝標本 I の数
n＝標本 2 の数
m＝標本 2 中の標識された数

$$N = \frac{(M+1)(n+1)}{(m+1)} - 1$$

$$\mathrm{Var}(N) = \frac{(M+1)(n+1)(M-m)(n-m)}{(m+1)^2(m+2)}$$

$$95\%\mathrm{CI} = \pm 1.96\sqrt{\mathrm{Var}(N)}$$

図 2　Chapman法

の場所に生息する総個体数(N)を推定する．放した個体が次の捕獲までの時間内に集団の中に無作為に混ざり，また，印をつけた個体と印をつけない(未採集)個体との間で，捕獲の効果に差がないとすれば，その地域の総個体数は，N：M＝n：mの比例関係によって求められる(**図 1 式 1**)．さらに，分散の推定値〔Var(N)〕および任意の精度(D)を確保するために必要なサンプルの大きさ(nD)を計算するためには，**図 1 式 2** を用いる．

C-M-R 法は，1896年デンマークの Petersen[1] が魚に，1930年アメリカの Lincoln[2]が鳥に，それぞれ独立に用いたもので，水産学者には Petersen 法，陸上動物学者には Lincoln 指数法と呼ばれている．

2．Chapman 法

さて，Petersen の式のうちで，n 個体のサンプル中での標識個体数mのみが確率変数である．このmの分布は，「赤玉M個と白玉 N－M 個が入いっている壺の中から，非復元抽出によって無作為に取り出したn個の玉の中に含まれる赤玉の個数」の確率分布と同じであり，これに誤差法則をあてはめると，Petersen の推定量は一般に正の偏りをもつことになる[7]．この偏りを補正したものが Chapman 法[3]である(**図 2**)．C-M-R 法を疾病の頻度を推定する場合には，もっぱらこの改法が用いられている[12,13]．

3．Jolly-Seber 法

C-M-R 法は以下の二つの条件を前提としている．①第 1 回目と第 2 回目の捕獲時に，各個体は独立に，かつ標識の有無にかかわりなく等しい確率で捕獲されること，②標識個体を元の場所に戻してから第 2 回目の捕獲までの間に，個体群への新規加入(出生，移入)や消失(死亡，移出)がないことである．しかし，野外で動き廻っている動物の動態を解析するとき，②の前提を満たすのはなかなか難しい．そこで，これを解除するために用

表　マドリッドにおけるIDDM発症率ーC-M-R法による推定値ー[12]

	病院から①	糖尿病協会から②	①と②の重複	①+②−③	C-M-R法による推定値	$N=\frac{(M+1)(n+1)}{m+1}-1$
症例数(例)	432(M)	138(n)	119(m)	451	501(N)	$=\frac{(432+1)(138+)}{119+1}-1$
人口10万人あたりの発症率	9.8	3.1	−	10.2	11.3	$=\frac{60,187}{120}-1\fallingdotseq501$
捕捉率(%)	86	28	−	90	100	

いられるようになったのが，Jolly-Seber法[4,5]である．この方法は，標識・放逐・再捕を間隔をおいて2回以上繰り返すことにより，各時点で存在する個体数の情報のみならず，新規加入や消失に関する情報も盛り込めるようにしたものである．したがってJolly-Seber法では，前提①は生きているが，②は無視してよい．しかし，調査期間中，出戻りはないものと仮定されている．現在，動物の個体数を推定する際に，最もよく使われている方法である．

このように動物の生態学の分野では，19世紀の終わりから個体数の推定法が考案され，時代とともに改善されてきた[14]．

III．IDDMの真の発症率推定への応用

1．方法論の解釈

さて，疾病の発症率を推定するときに，生態学で用いられてきたC-M-R法を，そのままあてはめることができるのだろうか．一定の地域にいる動物を数えることは有病率をみることと等しいが，私たちが知りたいのは発症率である．そこで「1回目の捕獲個体数＝病院調査によって見出された(第1の情報源)，1年間に発生した新規IDDM患者数」と置き換えることにする．また，「2回目の捕獲個体数＝病院以外の情報から見出された(第2の情報源)，1年間に発生した新規IDDM患者数」と解釈すればよい．ただし，ここで第1の情報源と第2の情報源の間の「独立性」が問題となる．たとえば，生態学では印をつけたことによって，その個体が捕らえやすくなったり，その逆であったりしないということが大前提である．IDDMも同様に，第1の情報源で発見された患者が，発見されなかった患者に比べて，第2の情報源でも発見されやすいということがないという条件が必要である．このように「独立性」の問題は，生態学と発症率の場合異なるようにみえるが，本質的に何ら違いはない．

生態学の個体数推定の際には，新規移入と消失なしという条件を解除するために，Jolley-Seber法がよく用いられると前述した．では，IDDMの場合はどうであろうか．この場合には，新規に発症した患者を対象にしているので移入はあり得ない．また，有病率を問題にしているわけではないので，消失(死亡)の心配をしなくてもよい．ただし，診断がつかないまま疾病の発生時に死亡した症例は問題となる．しかし，先進諸国ではこのような症例はまれと思われる．したがって，IDDMやその他慢性疾患の発症率を推定するときには，もっぱらChapman法が用いられる．

2．第1，2の情報源

わが国でIDDMの調査を行うときにしばしば使われる資料は，病院へのアンケート調査，小児特定慢性疾患公費給付申請書，小児糖尿病サマーキャンプ参加者名簿などである．しかし，これらは情報提供に同じ医師が関与している可能性が大きいので，独立した別個の情報とはなり得ない．相互依存性の高い情報は，C-M-R法の大前提を満足し得ないのである．また，それぞれの調査による症例の捕捉率が低いと予想されるときには，相互に関連している複数の情報源をまとめ，重複している症例を除外し，これを第1の情報源からの症例数(M)とする．

これに対して，学校に対するアンケート調査や健康保険請求明細書からの情報は，医療機関関係からの情報とはまったく独立していると考えてよい．したがって，これらは第2の情報源となる．学校調査では5歳以下の症例を把握することはできないが，これは大きな問題とはならない．なぜ

ならば，第2の情報源から真の症例数(N)の20～30%を把握できれば，C-M-R法を適応することができるので[17]，発症率の低い0～5歳の症例がたとえここから落ちてしまっても，全体に及ぼす影響は少ないのである．地域によっては，健康保険請求明細書からインスリンを使用している5歳以下の症例を抽出するという方法を，第2の情報源の補足とし得るだろう．しかし，時間や労力，そして経費との兼ね合いを考えて，これを用いるかどうか決めるべきであろう．また，情報源はそれぞれが独立しているのであれば，二つよりは三，四と情報源が多くなるほど発症率を正確に推定することができる[15~17]．

最近，スペイン・マドリッド行われたIDDMの発症率の調査研究では，病院の診療録からの情報と糖尿病協会会員名簿を用いて情報を得て，C-M-R法を使い真の発症率を推定している．その結果，IDDMの発症率は病院のみの調査では人口10万人あたり9.8であったが，C-M-R法を用いて検討したところ，真の推定値は11.3であることが明らかになった[12,17](表)．

おわりに

先進諸国では，多大な労力と時間をかけて医療機関およびその関連の情報を最大限に駆使すれば，IDDMの新規症例の大多数を把握することは可能であろう．これによって算出した発症率もほぼ正確と考えてよいであろう．しかし，科学的にその数値の確かさを証明するためには，客観的な評価方法が必要である．また，同じ方法論を用いなければ，地域間であるいは国際間で発症率の比較をすることはできない．しかし，C-M-R法を応用すれば，たとえ患者の捕捉率が90%に満たなくても真の発症率を推定できるし，他のデータと比較することも可能である．とくに調査方法として診断の標準化を明確にし，地域人口動態別にその推移年次的に追跡することができる．また，疫学調査として比較的経済的に実施できる．これらの点でC-M-R法は臨床疫学調査方法として非常に優れた方法である．今後，慢性疾患とくに疾病の病態変化のはやいIDDMやその他の代謝疾患，あるいは心筋梗塞などの疫学調査として有用であると考えている．

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Counting Diabetes in the Next Millennium

Application of capture-recapture technology

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Monitoring diabetes is critical for our understanding of the etiology and natural history of disease and for public health actions. However, traditional methods for monitoring are either too expensive (e.g., IDDM registries, NIDDM-OGTT prevalence surveys) or too inaccurate (routinely collected data or passive surveillance) for broad, accurate, national programs for monitoring the incidence and prevalence of disease. We suggest that one technology called capture-recapture would considerably increase our ability to "count" diabetes, both nationally and globally. Implementation of this approach could lead to accurate inter- and intracountry data on rates of disease. Moreover, such tracking of diabetes could serve as the model for the monitoring of all diseases in the 21st century and beyond.

"Counting" the frequency of diabetes both across geographic area and over time has taken on a prominent role in the study of the disease. The place where an individual lives is one of the most important—if not the most important—determinants of risk for both IDDM and NIDDM (1,2). Moreover, it appears that worldwide diabetes is rapidly increasing, in epidemic proportions in some cases (3,4). Effective monitoring is needed not only for the prevention of disease, but for the allocation of limited health-care resources.

Since 1980, an important epidemiological development for monitoring IDDM began with the establishment of standardized incidence registries (5). For the first time, the registries permit the direct comparison of IDDM around the world. For NIDDM, the standardization of the OGTT, a consistent method for defining NIDDM, and standardized approaches towards population studies have evolved so that it is now possible to compare the prevalence of disease across populations and time (6,7). As we will explain, these developments, although extremely important, are still inadequate for broad-based counting of diabetes.

We believe that a revolution in the technology of monitoring the frequency of diabetes is about to take place. This paradigm shift will permit individual areas and countries to broadly evaluate the patterns of diabetes.

In the history of science, major paradigm shifts have frequently occurred as the result of improvements in our ability to measure (8). For example, microscopes, X-ray machines, and telescopes have led to vast increases in our knowledge, as we could see better, and the information in nature could be brought into the limited domain of man's senses and cognition. Once improvements in the technology of measurement are developed, scientists can better understand nature.

In laboratory science, technological advances typically have meant new instruments or techniques. However, in diabetes epidemiology, the population is our laboratory. Can there be a revolution in diabetes epidemiology based on new techniques to facilitate measurement? Can this directly lead to a revolution in how we view and quantitate health? We believe so.

The fundamental building block of chemistry is the atom; of genetics, DNA; and of archaeology, fossils. The foundation of epidemiology is the rate of disease occurrence (incidence and prevalence) (9). We believe that a technology is available that can sharpen our measurement ability to count diabetes and produce accurate rates of disease. This will transform how we approach diabetes, because we will be better able to see diabetes across place and time.

Rose and Barker (10) noted that, "Rates are the hallmark of epidemiology, for they form the bases of comparisons between population groups." The better we are able to measure diabetes rates, the

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; OGTT, ORAL GLUCOSE TOLERANCE TEST; CI, CONFIDENCE INTERVAL; WHO, WORLD HEALTH ORGANIZATION.

better we are able to understand diabetes.

The core to both incidence and prevalence rates of diabetes is the identification and counting of cases of the disease. For incidence, this would be the identification of newly occurring cases, for prevalence, this would represent existing cases. Traditional methods of case identification fit into three broad categories, the first of which is registries. As will be presented, the traditional approaches are inadequate.

IDDM INCIDENCE REGISTRIES — IDDM epidemiology now has a well-established system of standardized registries for identifying new cases. In 1983, a group met in Philadelphia to begin to establish the standards of incidence registries. A simple set of criteria was set forth. These consisted of the definition of a case and the description of the population at risk. The group also called out the need for a secondary source of case ascertainment that would provide a check on the degree of ascertainment. It was agreed that all registries should strive for at least a 90% ascertainment for the primary source of ascertainment (1), thus 90% of the cases in a population should be counted.

The simple criteria have served us well for the past 9 years. One of the largest global health projects in existence, the WHO DiaMond effort, has evolved, with more than 100 centers in 65 countries, monitoring the incidence of disease for more than 200 million children (5).

Despite the enormity of the effort and the remarkable findings as the registries evolved, their limitations also became evident (11–13). The major difficulty is that registries have proven to be too little and too late for the identification of rapidly changing patterns of disease epidemics. Registries are ill suited for epidemic identification and prevention, as they do not monitor sufficiently large populations, and the latency between changing patterns of incidence and the identification of the changing patterns of incidence is too long to serve well in any hot pursuit of causative factors for epidemics. Moreover, the cost to identify all cases is quite high. Thus, approaches are needed that rapidly obtain accurate IDDM incidence data across large areas to complement current registry approaches (13).

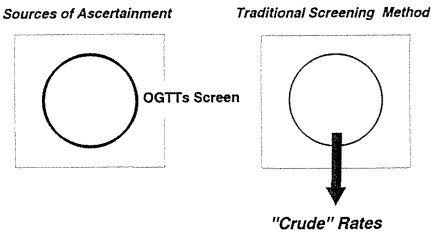


Figure 1—*Traditional NIDDM prevalence screening.*

The fundamental principle of IDDM registries is one of active surveillance systems in which the research is led by a small group of interested investigators who actively go to hospitals, pharmacies, and the like to identify new cases. The goal is to identify and count as close to 100% of cases as possible. As the participants in the WHO DiaMond project have found, a high degree of ascertainment has been extremely important, but also expensive, because without constant vigilance, the case identification rate can easily slip below 90%.

NIDDM PREVALENCE SCREENING — A second type of monitoring is that typically used in research on NIDDM—that of population-based screening using a 75-g OGTT (Fig. 1). With this approach, a small community is identified (as represented by the square in Figure 1) and invited to take an OGTT. Typically, participation is not perfect, with ranges from 60–75% (14–16) (as represented by those that would fall inside the circle in Fig. 1, who received an OGTT). Conclusions drawn from the 60–75% from the small community are then interpolated to an entire country—should information be needed about the number of diabetic individuals in Japan, Italy, or the U.S., for example.

COMMUNICABLE DISEASE SURVEILLANCE — Registries and population screens for counting diabetes can be contrasted with the third approach for identifying cases of disease—passive disease surveillance systems typically used in the area of communicable diseases (17). As seen in Table 1, these counting systems usually are situated in public-health agencies and are voluntary, in that the cases are reported into a central source or are part of routinely collected lists rather than the result of investigators having actively sought them out. These systems typically evaluate multiple communicable diseases, cases are rapidly identified, and the cost for the identification of cases is small. Using the U.S., Italy, and Japan as examples, currently <5% of these countries' populations is being monitored for diabetes, but 100% is being monitored for measles, mumps, rheumatic fever, and other infectious diseases. The communicable dis-

Table 1—*Comparison of disease counting approaches*

	IDDM REGISTRIES	NIDDM SCREENING	COMMUNICABLE DISEASE SURVEILLANCE
SOURCE	ACADEMIA	ACADEMIA	HEALTH DEPARTMENTS
SPEED OF IDENTIFICATION	SLOW	SLOW	FAST
COST PER CASE	HIGH	HIGH	LOW
GEOGRAPHIC COVERAGE	LOW	LOW	HIGH
ASCERTAINMENT	PRESUMED HIGH	PRESUMED HIGH	LOW AND VARIABLE

ease system has certain advantages compared with registry and screening-based systems in that it permits broad, inexpensive, timely coverage of disease occurrence.

However, the communicable disease model has a fundamental drawback in that the rates of ascertainment are low and variable, and thus are extremely inaccurate. Evaluation of passive systems reveal that typically <20% of the cases are identified and counted. But the imprecision of the rates generated from these counts is not a major problem in communicable disease research where a spiking incidence may represent a 10-fold increase in the number of cases. Thus, even imprecise measures of rates can identify an explosion of the number of cases. With diabetes, however, the monthly or yearly change in incidence is of a much lower magnitude, therefore, to identify changes, one needs far more precise measurement tools. Hence, the methods of registries and diabetes screening developed and evolved with the primary concept that the only way to achieve precise rates is to approach a 100% count of the cases.

Even with registries, 100% ascertainment frequently is not achieved. We are confronted with the same problem with registries in diabetes, although important information has been generated, they are just too costly for long-term, broad, rapid geographic coverage to monitor disease (11). Moreover, even with the population screening for NIDDM, a high degree of undercount or bias occurs, as 25–40% of the population at risk typically is not tested and only small communities can be evaluated; questions are bound to arise about the representativeness of these communities for entire countries. We are confronted with a major problem in diabetes research as we face a trade-off between striving to achieve a high degree of ascertainment and the cost of monitoring diabetes in a broad and timely manner.

To monitor diabetes and transform diabetes epidemiology in the next millennium, our approaches will need to be modernized towards determining rates of disease, because the current methods are neither efficient nor cost effective. It is time to move to the next paradigm of counting technology to complement existing systems.

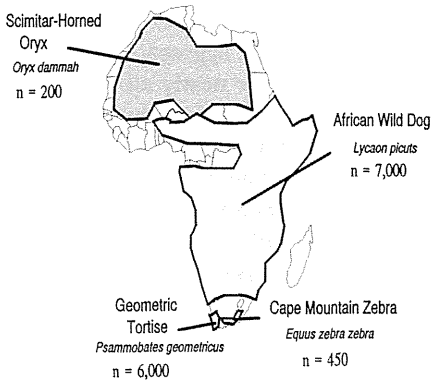


Figure 2—*Threatened animals in Africa.*

CAPTURE-RECAPTURE TO COUNT DIABETES — Recently, we argued that such a technology is available, in an article entitled "Counting Birds, Bees, and NCDs" (18) and in several other papers describing the methodology (17–24). Why do we know that there are 110,000 California seals and 90,000 sea lions off California (*USA Today*, 6/23/92)? How can we know the numbers of threatened species and their ranges in Africa (Fig. 2)? It is rather amazing that we know more about "hot spots" for animals, particularly threatened animals—with high concentrations in Africa and around the world—than we know about the global and temporal patterns of diabetes. The reason that we know much more about the number, geographic spread, and changes over time of animals than we know about diabetes is that we are better able to count animals. We believe that the methods of animal ecologists show us the way to revolutionize our approaches towards counting diabetes. It is from this animal literature that the next generation of diabetes monitoring systems will evolve.

To illustrate an approach from animal ecologists, suppose the objective was to count the number of mice in a field. Naturalists would not go out to count all the mice—as we try to count all cases of diabetes. The wildlife ecologists realize that it would be virtually impossible to identify all cases. Instead, they count mice through a simple capture-recapture procedure. First, they go to the field and capture mice, which are then tagged and released, and recaptured the following day: the proportion of cases in common then is used to estimate the number of mice in the field with 95% CI (Fig. 3). Animal population scientists rarely catch >20% of the cases in each sample, yet they obtain very accurate estimates of the number of cases. In contrast, we constantly strive for >90% ascertainment in our primary sources for IDDM and for a 75% participation rate for screening for NIDDM. However, such high rates of ascertainment are not truly needed for accurate rates. Using a simple formula (see Appendix), we can estimate the total number of mice in a field, sea otters in the ocean, bald eagles in the world, or diabetes in the U.S., Italy, or Japan (23).

The primary assumption of the sample case of capture-recapture is one of independence of sources. In health, this is a difficult assumption to achieve. For example, pediatricians will refer to specific hospitals, and insulin prescriptions may come from a certain set of

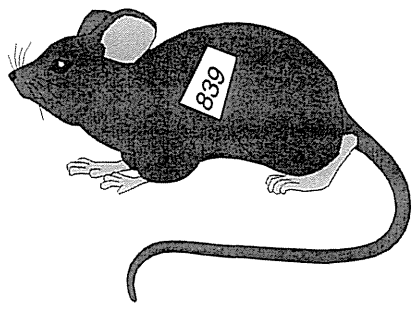


Figure 3—*Tagged animal.*

physicians. However, in an elegant method, Bishop and Feinberg (21) showed that if we use more than two sources for the identification of cases, then source dependencies can be modeled and taken into consideration when estimating the number of cases. In diabetes epidemiology, there are many possible incomplete sources of ascertainment, including hospitals, physicians, diabetes associations, laboratories, death certificates, etc. What is critical is not the exact nature of the log linear modeling, but rather what this means for estimating the counts of disease. These models allow us to use data that are readily available, but have been neglected, to adjust for dependencies between sources to correct for ascertainment. Moreover, if more than two sources of identification of cases are used, then the assumption of independence need not be made. It typically is much less costly to use multiple incomplete sources of ascertainment than to count all cases from a single source. This approach to counting has become the standard for estimating many elusive species. It is just beginning to be used in diabetes research.

To understand how these approaches towards counting animals can be used to count cases of diabetes, it is best to contrast these with the traditional approaches of IDDM registries, NIDDM prevalence screening, and passive surveillance.

INCIDENCE RATES OF IDDM: APPLICATION OF CAPTURE-RECAPTURE — When we attempt to identify new cases of IDDM, we frequently use multiple sources (Fig. 4). For example, people with diabetes are identified from hospitals, pediatricians, schools, and laboratories. To determine the numerator (e.g., the number of new cases), the researcher(s) typically aggregates the sources, culling out duplicates. It is this total that is used for determining the incidence rates, as we have pointed out in several papers (17–20,24). However, this incidence rate should be considered the crude rate, because it assumes that the aggregate of the lists represents all (or nearly all) of the cases in the population. It assumes that the number of missing cases is zero, and undercount is ignored.

The traditional method can be contrasted with the capture-recapture approach. In capture-recapture, instead of eliminating the duplicates, attention is paid to the them because they provide important information about the degree to which cases may have been missed. These duplicates represent "recaptured" people who have diabetes. Thus, the degree of undercount is estimated, and the rates of disease are corrected for undercount, which yields an ascertainment corrected rate. This method potentially can revolutionize our approach to counting IDDM, which is best illustrated with an example—one from Madrid with a registry established by Prof. Serrano Rios and Dr. Moy (25).

The registry began with the review of the three major referral hospitals in Madrid. A secondary source of validation was established through the review of the Madrid Diabetes Association. In the initial few weeks, >50% of the cases were identified from the three hospitals. It took an additional 4 mo to achieve an additional 40% of the cases. Thus, as with any registry system, it took a short amount of time to count ~50% of the cases, but an enormous amount of time to approach 100% ascertainment.

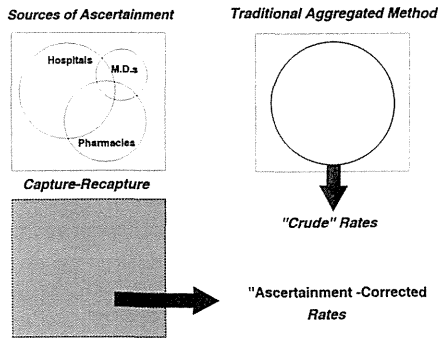


Figure 4—*Ascertainment-corrected incidences rates.*

Figure 5 represents the samples collected from the total population (the open squares). Once ascertainment correction is done, the estimate of the incidence rises closer to the truth, as represented in the dark boxes. What will occur is that the precision of the estimate as presented with the 95% CI in Table 2 is reduced, but not markedly. What is important is that attempting to achieve complete ascertainment is extremely costly. The loss of a small degree of accuracy produces enormous potential gains in the feasibility of conducting the work. As Table 2 shows, the precision of the estimates is reduced but still is quite acceptable. The 95% CIs are widened, but still are not large. The central point is that it is extremely difficult and time consuming to attempt to count all cases. We can obtain almost the same degree of precision for much less cost through the use of multiple incomplete sources of case ascertainment.

This methodology is currently being tested by Prof. Baba in Kakogawa City, Hyogo prefecture, Japan. Multiple independent sources of case ascertainment are available, and IDDM is the first noncommunicable disease to be monitored. Subsequently, other noncommunicable diseases will be added to the system, based on the experiences with IDDM.

Diabetes researchers have been progressive in part, in that capture-recapture frequently has been used to check and correct for undercount with registries. We still, however, have the goal of trying to find all new cases of IDDM. This goal is expensive and thus cannot be used across broad areas or over time. It is not yet widely recognized that we can break away from having to "count" everyone in order to obtain accurate incidence rates. But, if accurate estimates of wildlife can be produced with <20% ascertainment per sample by using capture-recapture, then the same can apply to IDDM. We thus can con-

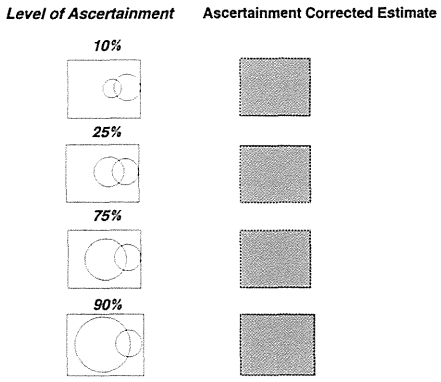


Figure 5—*Point estimates, precision, and capture-recapture.*

sider that multiple sources of ascertainment, each of which identify a fraction of cases, can yield precise, standardized estimates of cases. Thus in Table 1, we would have all the advantages of the communicable disease monitoring system with none of the disadvantages. This would truly be a paradigm shift in IDDM epidemiology, as we would have accurate incidence data in countries, across the world and over time.

PREVALENCE RATES OF NIDDM: APPLICATION OF CAPTURE-RECAPTURE

— To estimate the prevalence of diabetes, epidemiologists have used OGTTS in small population samples in isolated communities. Because of costs, rarely are tens of thousands of people evaluated. The total number of individuals screened in population-based cohorts for the past decade is <80,000 people; most of the community-based epidemiological studies are in the range of 500 to 4000 people. But 80,000 represents only 0.002% of the world's population. In contrast, for many endangered species, we have accurate estimates of the total number in the whole world. It would be a major advancement if we could estimate the number of people who have diabetes as readily as we can estimate the number of sperm whales.

Typically, in screening programs, only 60–75% of the population at risk in a community is tested, as presented in the dark circle in the upper left hand of Fig. 6. In prevalence studies of NIDDM, no additional sources are employed to identify cases other than the OGTT. Typically the communities in which the OGTTs are completed already have diagnosed cases of diabetes, as represented by the other circles in Fig. 6. One suspects that these cases would have a differential response rate to participation. One could obtain lists of diagnosed cases relatively easily from the community—such as from physicians, pharmacies, and hospitals—and compare the rates of diagnosis of diabetes for the screened and nonscreened populations. In addition, these sources could provide information about a much broader population in the community. Moreover, instead of crude extrapolation from the prevalence of diabetes identified by OGTTs in the small community to the country as a whole, we can use readily available lists on even a country-wide basis in conjunction with the OGTT results to much more precisely determine the number of people who have diabetes.

The OGTT would be used for two reasons: first, it serves as an additional source of ascertainment of cases; second, it would accurately estimate the degree to which people in the population fulfilled the criteria for diabetes. Thus, for people who have been "labeled" as having diabetes, the OGTT can then accurately estimate how many truly have diabetes by WHO criteria. For those who have not been labeled, it can estimate the numbers of undiagnosed cases. Thus the ascertainment-corrected prevalence rates would also be adjusted for the sensitivity and specificity of the diagnosis.

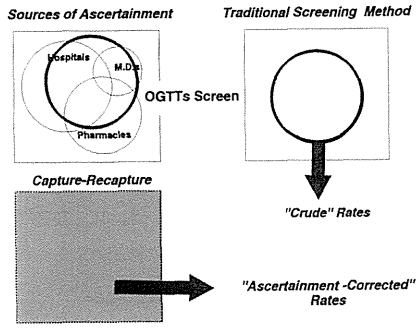


Figure 6—*Capture-recapture and ascertainment-corrected prevalence rates.*

Perhaps the greatest contribution of capture-recapture to NIDDM estimates is that, potentially, estimates of the prevalence of diabetes can become much broader than for 0.002% of the world's population. The reason is that even though country-wide efforts using OGTTs is extremely expensive, lists of cases are available from multiple sources, as presented in Fig. 7 (lower left). The OGTT screen can be done on only a small sample of the population. With the incorporation of readily available lists, broad, precise estimates of rates and numbers of people who have diabetes can be attained.

Inclusion of the readily obtainable information into the NIDDM prevalence surveys would have several important advantages. First, the representativeness of the tested population with regard to the prevalence of diabetes could truly be determined. Second, the precision of the estimates of the numbers and rates of individuals who have diabetes in a country and the world would increase dramatically. The incorporation of information from the readily obtainable lists with that of the OGTTs would potentially lead to much more cost-effective monitoring,

Table 2—*95% CIs in Madrid, Spain at various levels of ascertainment per 100,000*

Level of ascertainment (%)	Ascertainment-corrected incidence	± 95% CI
10	10.9	8.0
25	10.9	2.1
75	10.9	0.7
90 (actual)	10.9	0.3

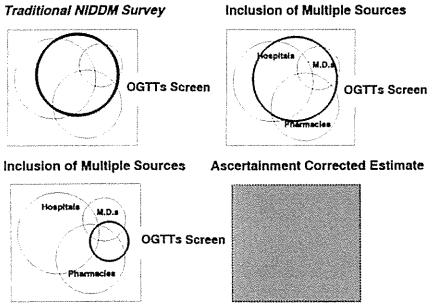


Figure 7—*Capture-recapture, ascertainment-corrected prevalence rates, and broad screening.*

covering much broader areas. Accurate country-wide monitoring, which currently is not feasible with the existing approaches, could be accomplished over time.

IMPLICATIONS FOR HEALTH AND WELFARE FOR PEOPLE WHO DEVELOP DIABETES IN THE 21ST CENTURY AND BEYOND

— The essence of prevention of diabetes and its complications is to reduce the incidence and prevalence of diabetes and its complications. Many national and international prevention programs are implemented without valid information as to how frequently diabetes and its complications occurs. Any local or national program of diabetes prevention must have accurate data concerning the rate of disease. Until now, this has not been feasible as accurate registries and broad monitoring of diabetes through population-based OGTTs are too expensive and slow. However, implementation of natural monitoring systems such as with capture-recapture may be able to provide much broader and more timely monitoring.

Monitoring of diabetes should be under the purview of government health agencies. Academic centers do not have the network nor the resources for national monitoring of diseases. Perhaps agencies such as the Ministries of Health in Japan and Italy and the Centers for Disease Control in the U.S. should begin discussions about approaches toward monitoring the rates and numbers of cases of diabetes in current and future generations.

During the last few years, governments have been starting to establish programs for the prevention and control of noncommunicable diseases, one of which is diabetes (26). It is impossible to prevent and control diabetes and its complications unless we know the frequency at which diabetes and its complications occur. Therefore, as part of all national programs for diabetes and other noncommunicable diseases, there needs to be monitoring. We believe that the use of a system such as capture-recapture will bring accurate yet cost-effective monitoring to a national level.

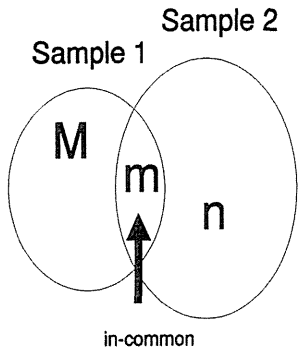
CONCLUSIONS — We cannot prevent diabetes unless we know how frequently it occurs, yet we know surprising little about the rates of diabetes within our own countries and throughout the world. The existing paradigms for measuring diabetes are simply not cost effective for broad and timely monitoring of diabetes mellitus in the 21st century and beyond. We must begin to evaluate alternative means of counting that have been established and proven effective in other disciplines, such as animal-population science and quality control in industry. One of these methods is capture-recapture.

Approaches toward monitoring are meant to complement, not replace, registries and in-depth population screening, because for many preventive actions, case-control studies, or health services studies, it is necessary to be near perfect in case ascertainment. However, if the goal is to determine the number or rate of diabetes, capture-recapture offers a viable contrast to the other traditional methods.

It is important to recognize that these methods need to be evaluated for use in diabetes. Our existing methods are inadequate and nowhere near delivering the truth for broad monitoring of disease. Methods such as capture-recapture are not perfect—they do not give an estimate of incidence and prevalence where the point estimate is the absolute truth. However, these types of methods help bring us closer to the truth than inadequate existing systems.

Approaches like these and others can produce a major paradigm shift concerning our knowledge of diabetes across the world. It seems rather ironic that we know more about the numbers of many

Capture-Recapture



$$N = \frac{(M+1)(n+1)}{(m+1)} - 1$$

N=Estimate of Number
M=Number in First Sample (those Marked)
n=Number in Second Sample
m=Number of "marked" items in Second Sample

$$Var(N) = \frac{(M+1)(n+1)(M-m)(n-m)}{(m+1)^2 (m+2)}$$

$$95\%\ CI = \pm 1.96\sqrt{Var(N)}$$

Appendix—*Formula for capture-recapture technology.*

animals in the world then we know about the numbers of people afflicted with diabetes.

We believe that diabetes counting can take the lead not only for diabetes but all diseases in the next millennium. Population-counting technologies such as capture-recapture bring this into the realm of feasibility.

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平成 27 年 3 月　　日

先生御机下

拝啓

早春の候、ますます御健勝のこととお喜び申し上げます。

貴院の先生方には、以前より小児期発症１型糖尿病に関する調査研究に関してご協力賜りまして深く感謝申し上げます。お忙しいところ大変恐縮ですが、該当する患者さんにつきましてご協力をお願い申し上げます。

本研究は、成人に達した小児期発症１型糖尿病患者の生活の実態を調べるため、以前に小児インスリン治療研究会コホートに登録していただいた患者さんを中心に、

発症年齢 16 歳未満、かつ平成 26 年 4 月 1 日現在 20 歳以上の 1 型糖尿病患者さん

について調査させて頂きたいと考えております。

＜ご回答頂きたい内容＞

・同封のはがきに、**本研究の対象に該当する患者さんの人数**をご記入の上、ご投函下さい。

・大変お手数ですが、**すでに転院されている場合は、転院先**につきましてもご記入いただけると大変ありがたく存じます。

＜今後の流れ＞

事務局より、ご教示頂きました貴院通院中の患者さんの人数分のアンケート調査用紙一式をお送りします。（すでに転院されている患者さんにつきましては、以降は事務局で調査を継続させていただきます。）

書類が届きましたら、患者さんへ同意説明書を用いて本研究の趣旨をご説明いただき、アンケート調査票への記入をご依頼いただきますようお願いいたします。その後、患者さんには自由意思に基づきご自宅にてアンケート調査へ協力するか否かを決定して頂きます。

患者さんの個人情報は厳重に管理し、研究目的以外に利用することはありません。本研究は東京慈恵会医科大学倫理委員会の承認を得ております。ご教示頂きました患者さんの数に応じて誠に些少ですが謝礼のクオカードを先生方にお送りいたします。また、ご協力いただきました患者さんにも、500 円相当のクオカードをお送りいたします。

先生のますますのご発展をお祈りいたします。

敬具

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「1型糖尿病の疫学と生活実態に関する調査研究」
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貴院名：＿＿＿＿＿＿＿＿＿＿＿＿病院・ｸﾘﾆｯｸ・医院

記載者：＿＿＿＿＿＿科＿＿＿＿＿＿先生

貴院通院中の該当患者さんの総数：＿＿＿＿名

転院された患者さんの総数：＿＿＿＿＿＿名

転院先（お分かりになる範囲でご記入ください）

①名称：＿＿＿＿＿＿＿＿＿＿＿＿病院・ｸﾘﾆｯｸ・医院

所在地：＿＿＿＿＿都道府県＿＿＿＿＿＿市区町村

主治医：＿＿＿＿＿＿科＿＿＿＿＿＿先生

②名称：＿＿＿＿＿＿＿＿＿＿＿＿病院・ｸﾘﾆｯｸ・医院

所在地：＿＿＿＿＿都道府県＿＿＿＿＿市区町村

主治医：＿＿＿＿＿＿科＿＿＿＿＿＿先生

③名称：＿＿＿＿＿＿＿＿＿＿＿＿病院・ｸﾘﾆｯｸ・医院

所在地：＿＿＿＿＿都道府県＿＿＿＿＿市区町村

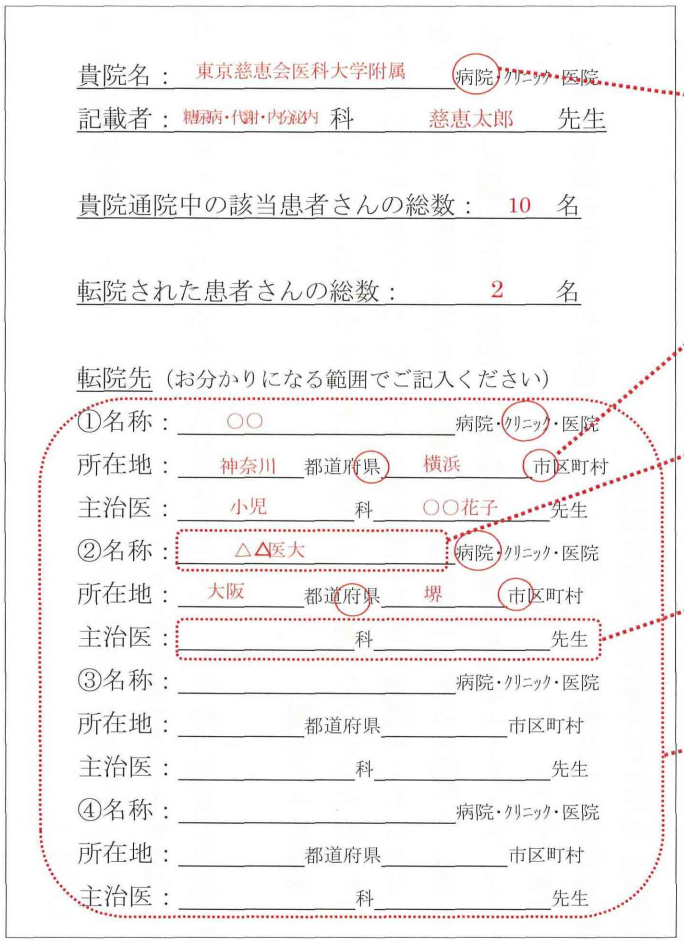
主治医：＿＿＿＿＿＿科＿＿＿＿＿＿先生

④名称：＿＿＿＿＿＿＿＿＿＿＿＿病院・ｸﾘﾆｯｸ・医院

所在地：＿＿＿＿＿都道府県＿＿＿＿＿市区町村

主治医：＿＿＿＿＿＿科＿＿＿＿＿＿先生

記入例


貴院名：東京慈恵会医科大学附属　病院・クリニック・医院
記載者：糖尿病・代謝・内分泌内 科　慈恵太郎　先生

貴院通院中の該当患者さんの総数：10 名

転院された患者さんの総数：2 名

転院先（お分かりになる範囲でご記入ください）
①名称：○○　病院・クリニック・医院
所在地：神奈川 都道府県　横浜 市区町村
主治医：小児 科　○○花子 先生
②名称：△△医大　病院・クリニック・医院
所在地：大阪 都道府県　堺 市区町村
主治医：　科　先生
③名称：　病院・クリニック・医院
所在地：　都道府県　市区町村
主治医：　科　先生
④名称：　病院・クリニック・医院
所在地：　都道府県　市区町村
主治医：　科　先生

病院名・所在地は、
該当する箇所に「○」をつけて、選択してください。

病院名は略称でも構いません。

不明の箇所がある場合は、空欄のままお送りください。

転院された患者さんが 4 名を超える場合は、
お手数ですが事務局までお問い合わせ下さい。
《問い合わせ先》
〒105-8461　東京都港区西新橋 3-25-47　愛宕マークビル 5 階
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平成 27 年 3 月　　日

先生御机下

拝啓

春陽の候、ますます御健勝のこととお喜び申し上げます。

先生には、平成 26 年度厚生労働省科学研究補助金　循環器疾患・糖尿病等生活習慣病対策総合研究事業「１型糖尿病の疫学と生活実態に関する調査研究」（田嶼班）に関してご協力賜りまして深く感謝申し上げます。

生活実態に関する調査研究として、先日ご教示頂きました患者さんの人数分のアンケート調査票一式を同封させていただきます。

同封書類

＜患者さんにお渡しいただきたい書類＞

①同意説明書

②同意書

③アンケート調査票

＜先生にお渡しするもの＞

④はがき（アンケート調査票と同一番号）

⑤謝礼のクオカード

＜お願いしたいこと～調査の流れ＞

□　発症年齢 16 歳未満、かつ平成 26 年 4 月 1 日現在 20 歳以上の 1 型糖尿病患者さんに、

□　**『①同意説明書』を用いて本研究の趣旨を説明**

□　**①～③の書類を患者さんに渡す**（②、③への記入は、患者さんの自由意思に基づき、ご自宅にて行って頂きます。）

□　**『④はがき』へ、アンケート調査票を渡した患者さんの性別、年代を記入。**この際、**『④はがき』裏面上の No. と『③アンケート調査票』の表紙右上の No. が同一**であることを確認（このはがきは、本アンケート調査の精度を評価する一環として、性別・年代ごとのアンケート回収率を算出するためのもので、患者さんの個人を特定することにはつながりません。）

□　**『④はがき』をポストへ投函**

患者さんの個人情報は厳重に管理し、研究目的以外に利用することはありません。本研究は東京慈恵会医科大学倫理委員会の承認を得ております。

末筆ながら、先生のますますのご発展をお祈りいたします。今後ともご指導ご鞭撻のほどよろしくお願い申し上げます。

敬具

「１型糖尿病の疫学と生活実態に関する調査研究」

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研究分担者

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「1 型糖尿病の疫学と生活実態に関する調査研究」

同意説明書

1 型糖尿病は、インスリンを補充すれば、就職、結婚、出産など、健康な人と何一つ変わらない生活を送ることができる病気です。

しかしながら、実際に 1 型糖尿病と付き合いながら生活をしていくうえで、不便に感じること、不安に思うこと、1 型糖尿病が生活の支障になっていると感じることがあるかもしれません。

1 型糖尿病の皆さんが、具体的にどのようなことに困っているのかを明らかにし、国に現状を知ってもらうことで、医療費の軽減や福祉の充実など 1 型糖尿病患者さんの負担を減らすお手伝いをしたいという思いからこの研究を始めました。

1. 研究の目的　＜何のために行うのか？＞

世界の小児 1 型糖尿病の有病者数は約50万人で、年間8万人が新規発症しています。生涯インスリン治療が必須な 1 型糖尿病の治療・管理は容易ではなく、合併症の発症と進展を阻止するためには、医療や福祉体制のさらなる整備が必要で、就業や就学に支障がないよう社会啓発活動も求められています。一方で、患者さんが背負っている社会的・経済的

負担や生活実態の詳細は分かっていません。

そこで本研究は、１型糖尿病を16歳未満で発症し、20歳以上に達した患者さんの治療状況、合併症、生活の実態等に関する正確な情報をアンケート調査によって集計・解析し、行政に対する具体的な疾病対策の構築、医療体制の改善、費用対効果等の提言につなげることを目的として立案しました。

本研究は平成26年度厚生労働科学研究補助金　循環器疾患・糖尿病等生活習慣病対策総合研究事業「１型糖尿病の疫学と生活実態に関する調査研究」（田嶼班）の一部として実施されます。

2. 研究の方法　＜ご協力頂きたいこと＞

主治医からアンケート用紙を渡されますので、記入後、東京慈恵会医科大学「１型糖尿病の疫学と生活実態に関する調査研究」（田嶼班）事務局まで返送してください。

3. 予想される副作用について

この研究はアンケートの回答のみであり、医療行為は伴いません。このため、副作用などの心配はありません。