Depo-Provera – ethical issues in its testing and distribution

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Authors' abstract

Ethical issues relating to the use of the injectable contraceptive in developed and developing countries alike involve public policy decisions concerning both criteria for testing a new drug and individual choices about using a specific form of contraception approved for national distribution. Drug testing consists of an important but still evolving set of procedures. Depo-Provera is not qualitatively different from any other drug and some unpredictable risks are inevitable, even after extensive animal experiments and clinical trials. In assessing the risks and benefits of Depo-Provera use, epidemiological data from large-scale human use is now beginning to become more important than data from animal experiments and clinical trials.

The consumer's best interest is central to any ethically responsible system of drug distribution. Systems of informed choice are needed, even in societies where illiteracy remains common and medical services are weak. In the case of a contraceptive, the risks of non-use leading to unintended pregnancy, which can result in high mortality, are relevant as well as the side-effects of the method. An attempt, therefore, is made here to categorise those issues which are universal and those which are country-specific.

Introduction

The unwillingness of the US Food and Drug Administration (FDA) to widen the application of the injectable hormone, Depo-Provera, to include contraceptive purposes has sparked commentary from consumer groups (1, 2), ethical debate (3) and review in the US Congress (4). Debate in the United Kingdom (UK) has raised similar issues. Both proponents and opponents of the drug agree that testing and use of Depo-Provera include ethical as well as clinical and epidemiological issues. In the United Kingdom, use has been approved by the Committee on Safety of Medicines, but vetoed by the Minister of Health on the

grounds that doctors might use the drug irresponsibly. In Sweden, the drug is approved for use by Swedish women, but the Swedish International Development Agency does not have it included in its programme of commodities for overseas application, again on ethical rather than medical grounds.

There are two ethical perspectives at play here. One, the ethics of choice, with its individualised dimensions; the other, the ethics of decision-making, exercised by specialists, as they work to test a new contraceptive technology.

Depo-Provera (depot medroxyprogesterone acetate) is the trade name for an injectable steroid first synthesised in 1954 and subsequently used for a variety of therapies, including the treatment of uterine cancer and cancer of the kidney. In the early 1960s, it was shown to be an effective contraceptive and came to be used by many thousands of women in the United States (US). By the 1980s, it had been approved as a contraceptive by more than 80 developed and developing countries, including those as diverse as Sweden, Belgium, Thailand, New Zealand, Colombia, Indonesia and Tanzania (Table 1, overleaf). In 1974 and again in 1978, the Obstetrics and Gynecology and Biometrics and Epidemiology Methodology Committees of the US/FDA recommended registration of the drug as a contraceptive, but, on both occasions, registration was rejected by the FDA Commissioner, although it remains available in the US for cancer-related therapeutic application. In the UK, Depo-Provera is available as a contraceptive for only short-term use. At some time or another, Depo-Provera has been used by some 10 million women – approximately half in developed countries. Currently 1.25 million women around the world are thought to be using the drug as a contraceptive (5).

Depo-Provera is one of a number of long-acting contraceptive steroids now in development or use. Because of its history, it has become a symbol of a wider set of discussions, involving not merely contraceptives, but the intent and execution of family planning programmes generally, as well as the behaviour of pharmaceutical multinational organisations. It has been acclaimed as a much wanted contraceptive, the use of which will protect women from the risk of childbirth and abortion, and will

Key Words

Ethics; medical ethics; contraception; Depo-Provera; informed choice; testing; distribution; risks-benefits.

Table 1. Countries in which depot medroxyprogesterone acetate is marketed as a contraceptive

Africa	Asia and the Pacific	Europe	Latin America and Caribbean	Middle East
Cameroon	Bangladesh	Belgium	Antigua	Bahrain
Ethiopia	Burma	Denmark	Barbados	Cyprus
Ghana	Hong Kong	England & Wales	Bermuda	Iraq
Guyana	Indonesia	France	Colombia	Kuwait
Kenya	Malaysia	West Germany	Costa Rica	Lebanon
Liberia	New Zealand	Iceland	Curacao	Muscat & Oman
Libya	Pakistan	Ireland	Dominican Republic	Qatar
Malagasy	Philippines	Luxembourg	Ecuador	Saudi Arabia
Malawi	Singapore	The Netherlands	El Salvador	Syria
Morocco	Sri Lanka	Norway	Guatemala	United Arab Emirates
Nigeria	Thailand	Portugal	Haiti	
Reunion		Spain	Honduras	
Rwanda		Sweden	Jamaica	
Sierra Leone		Switzerland	Mexico	
South Africa		Yugoslavia	Nicaragua	
Sudan			Panama	
Tanzania			Peru	
Uganda			Surinam	
Zaire			Trinidad & Tobago	
Zambia				
Zimbabwe				

enhance the contraceptive choices available to assist individuals and society to meet their fertility goals. Conversely, it has been dammed as an example of Malthusian enthusiasts foisting unsolicited and questionable therapies on other people hence creating unwarranted risks especially for the poor and those least able to understand the benefit/risk considerations or to defend themselves against commercial exploitation. The debate has often been a sharp one, dividing groups who are otherwise united in their desire to try to close the hideous gap between the world's rich and poor or united in their attempts to extend reproductive choices to as many people as possible.

CHOICES

Contraceptives are instruments that allow individuals to make choices about their own fertility. As such, the individual has a right of access to knowledge about the risks/benefits of any contraceptive method, as well as to information about alternative methods. The existence of a choice of methods enhances the ethical position. Contraceptive use offers the possibility of choice as well as meeting a health need. Ethical judgments about use need to be made against two distinct but partially overlapping frameworks: need and choice. The element of *need* is congruent with other medical therapies; however, the element of *choice* brings in considerations of individual risks and benefits. These are similar to those an

individual assesses before he or she dives into a swimming pool, smokes cigarettes or skis down a mountain. There is reason to believe individuals make private decisions about choice in relation to a personalised risk and benefit equation (6, 7).

Depo-Provera is a specific example of a generic problem: defining the risks and benefits of any therapy and conveying such information to potential users and decision-makers. We believe the use of drugs, devices or procedures should always offer the patient seeking therapy, or the consumer using contraceptives, the choice which places them at less risk of morbidity and mortality than if they did not use the product in question. The ethic delineated in this paper is that the consumer's best interest must be paramount. Those providing contraceptives must combine distribution with appropriate product information and the decision to use or not to use the method must be made by the user and, except in extreme cases, not by the medical personnel dispensing the product or service.

In choosing a contraceptive method, an individual must be free of any trace of explicit or implicit coercion. But if these ethical ideals are to become a reality, then appropriate questions must be posed in a logical order and the structure of decision-making understood. We will review the criteria for arriving at risk/benefit decisions, the philosophy of choice in making decisions concerning safety and the problem of whose choice – the providers' or the users', the government's or the individual's?

Criteria for assessing risks and benefits

PRE-MARKET TESTING

Before a new drug can be widely used, it must undergo a series of tests in animals and carefully controlled trials in human volunteers (8). In the US and a number of European countries, such as Sweden and Great Britain, the process is complex and can cost the manufacturer millions of dollars and require many years to complete (9). In some developing countries, drug regulation is a simpler process, a fact that has made some observers wary. However, most countries now have the clinical expertise to evaluate the published information available on any drug product and to arrive at a judgment about the risks and benefits it may pose to individuals in that country.

In the case of testing potential contraceptives, the US/FDA requires studies to evaluate carcinogenesis in animals: two years in rats, seven years in dogs, and 10 years in monkeys. There are, of course, important ethical questions about the experimental use of animals, particularly primates, in gynaecological research (10), although this issue will not be dealt with here.

The step from animal testing to human application involves many unknowns. Initial (Phase I) testing on small groups of human volunteers (short-term use by 10–20 people) requires careful supervision and a corresponding degree of informed judgment. Phase II trials may involve 100 or more individuals to determine if the drug has the required effect. Phase III clinical trials on several hundred, or perhaps thousands, of volunteers are necessary to establish efficacy and to determine short-term side-effects. Phase I and II clinical trials are best conducted in developed countries where volunteers can be most readily informed of any hazards and where back-up medical services are readily available. However, the ethics of where to conduct Phase III trials can be argued two ways: if conducted exclusively in developed countries then products or techniques which are applied in developing countries may be culturally inappropriate, or overlook important differences in genetics or disease patterns among potential users. If conducted in developing countries, then charges are made that the Third World poor may become 'the guinea pigs or beagle dogs for the world's contraceptive testing' (11). Warwick has contended that early oral contraceptive trials in Puerto Rico involved 'lower-income groups' because they were 'more available for . . . mass experimentation' and 'if all did not go well, they were less likely than well-heeled mainlanders to mount political pressure and initiate lawsuits' (11). In fact, the history of the situation is somewhat different and evolved around the fact that John Rock and Gregory G Pincus, who were primarily responsible for developing the oral contraceptive, happened to be working in Massachusetts where contraception, under the nineteenth-century Comstock laws, was still illegal (12). In reality, as Sai has pointed out, ethics and the

common sense of clinical investigation indicate a need to conduct Phase III trials in developing as well as developed countries (13).

Tests in developing countries can be justified provided they are primarily aimed at acceptability, and the identification of any possible interaction with different host and environmental factors which cannot be undertaken in the country of development or manufacture. It must be emphasised that tests in the country of development or manufacture, regardless of how extensive they are, should always be supplemented with studies in developing countries. Large distributors of contraceptives have an obligation to monitor products in use, irrespective of how extensively they have been employed (13). In the case of oral contraceptives, the first several million pill users were nearly all in developed countries. In the case of Depo-Provera, studies have been more equally divided between developed and developing countries.

The US/FDA regulates clinical testing by granting a licence to investigate a new drug (IND) and by giving, or withholding a new drug approval (NDA) on the basis of animal testing and Phase I–III clinical trials. Unfortunately, animal tests and Phases I–III clinical trials only determine whether it is *responsible* to have the drug used by a larger number of people; they do not prove the absence or presence of rare, but possibly serious, side-effects, neither do they prove absolute safety. As a drug moves from clinical trials to wider application, unpredictable risks could surface because it is impossible to know all the risks and benefits of the drug; an unpredictable risk is an *unpredictable* risk. In the last analysis, every new drug is an experiment on our own species. A genuine assessment of safety only emerges *after* prolonged and extensive human application. If, for example, there is a 1 in 2000 chance of a serious effect while using the new drug, then it may require 100,000 users or more before such a risk becomes apparent to researchers. If a drug causes one death in a 100,000, it will most likely require over a million users before the epidemiological facts concerning mortality can be elicited. There are important ethical and practical consequences of the fact that information concerning the risks/benefits of use is often gleaned after a drug has been approved for marketing, as has been the case with oral contraceptives.

Drug surveillance is still an evolving discipline and those who work in the field can do no more than their sincere best at any one time. It was not unethical to use antiseptics in surgery before aseptic techniques developed and neither should it be judged wrong that some of the observations carried out on steroidal contraceptives 10 to 20 years ago did not necessarily meet current standards of excellence. The emotional nature of some of the contemporary criticisms of contraceptive development has a long pedigree. In 1921, a Scottish doctor, Halliday G Sutherland, criticised Marie Stopes's efforts among the poor, warning that 'owing to their poverty, lack of learning,

and helplessness, the poor are the natural victims of those who seek to make experiments on their fellows' (14). The nature and language of the criticism are similar to those made against Depo-Provera, even though Stopes was using mechanical methods that are now accepted as safe throughout the world.

Ethics may deal with ideals; however, ethical decisions can only be made on factual information, perhaps with a modicum of allowance for some speculation. An ethical approach to drug regulation and testing requires acceptance of the reality of unknowns and humility in the face of uncertainty. Risks and uncertainties are intrinsic in the development of any new drug – and a great many other novel chemical agents, from detergents to artificial sweeteners. It would, of course, be wrong or unethical knowingly to expose an individual to, say, an unacceptable risk of cancer or heart disease, as the result of drug use, once such an association had been established. But blame should not be assigned retrospectively, or previous actions be considered *a priori* unethical if an adverse effect is discovered after all prudent and practical steps have been taken and if users were informed about the potentially inescapable unknowns surrounding the introduction of any new drug.

Turning specifically to possible life-threatening risks, Depo-Provera is not qualitatively different from any other drug, although the assessment of possible risks and benefits is influenced by the unusual historical situation in which it was developed. Firstly, as a result of its long history of use, including application for non-contraceptive purposes, a large volume of data based on human utilisation, now exists. Secondly, some of the animal tests conducted on the

drug only became a routine and required part of drug testing after Depo-Provera was already on the market.

Briefly, with regard to potentially lethal effects, Depo-Provera has performed somewhat better than oral contraceptives had at a similar stage of human use, but has given rise to more questions during animal experiments. When given up to 50 times the human dose, it produces breast and uterine malignancies in dogs and monkeys. Species differences can be important and, for example, if research on penicillin had been limited to guinea pigs, that antibiotic might never have been introduced as a human therapeutic agent because the animal model is unusually sensitive to the drug; or if periodic sexual abstinence (Billings Method, cervical mucus or sympto-thermal) were to be judged by animal models, it would be condemned as predisposing to congenital abnormalities, should failures occur (15,16). Having said this, if the animal data accumulated in recent years on Depo-Provera were the *only* information available, use of the drug might be unlikely. However, ongoing studies conducted by the World Health Organisation (WHO) in Southeast Asia have failed to show a statistically significant increase in the risk of human breast cancer among users (17). The numbers available for the study of ovarian and uterine cancer are less, although again there is no suggestion of increased risk among users (18). On biological grounds, it may be speculated (and in our present incomplete state of knowledge, responsible speculation about benefits, as well as about risks, must still take place) that long-acting injectables, such as Depo-Provera, could have the same effect as oral contraceptives do in preventing cancer in these two organs (19, 20). In high doses, Depo-Provera is used to treat human uterine cancer (21). It is also

Table 2. Advantages and disadvantages of Depo-Provera use

Advantages	Disadvantages
Highly effective	Slow return of fertility
Convenient to use	Cannot discontinue use in less than 3–4 months
No adverse effect on quality or quantity of lactation	DMPA presence in milk at same level as in serum
Probably helps reduce iron deficiency anaemia	Often associated with weight gain
No known mortalities among users or evidence of association with congenital abnormalities in offspring at 150 mg dose every three months	Non-contraceptive use in high doses associated with congenital abnormalities
Used as a non-contraceptive therapeutic agent (up to 1000 mg/week) without ill effect	Causes cancer of two organs in animals
No significant effect on blood clotting and fewer metabolic changes than the pill	Produces very irregular patterns of uterine bleeding, often with long intervals of amenorrhea
More thoroughly studied than contraceptive implants, rings or spermicides	Not as well studied as combined oral contraceptives

important to note that no adverse effects, such as cardiovascular changes, occur when very high, non-contraceptive doses are given to treat cancer.

Like all other systemically active contraceptives, Depo-Provera has a series of important but non-lethal side-effects that the user should understand (Table 2, page 12). In the great majority of users, Depo-Provera causes serious alterations in uterine bleeding and most women, after prolonged use, have long intervals of amenorrhea. The return of fertility after discontinued use can be slow (22). But follow-up over 48 months since discontinuing the drug, shows no overall reduction in fertility. Weight-gain can also be associated with use.

Combining all the medical evidence on risks and benefits, we believe a reasonable medical case can be made for offering Depo-Provera as a contraceptive in developed and developing countries (5,23). We also accept the fact that the evidence is by no means one way. Some commentators argue that any drug which has caused cancer in mammals, and especially primates, is too dangerous to use. Experimental animals, it is maintained, are *deliberately* given unusually high doses of drugs in order to determine risks that may occur when the same agent is administered in smaller amounts to large numbers of people. However, the counter-argument is that this logic may apply to antibiotics or tranquillisers, but not to hormones where the natural actions are only mimicked by natural dose levels.

Whatever the outcome of the purely medical discussion of risks and benefits, it is only the first of a series of questions with ethical overtones, relating to risks and benefits that need review. How is a modest benefit distributed among many people to be weighed against the death of a few? Are there non-medical risks and benefits? Do methods of distribution influence risk and benefits? Is it ethical to recommend Depo-Provera in one country but not in another, or put another way, are medical standards to be universal.

Depo-Provera has important non-medical risks and benefits. As a long-acting preparation, it is convenient to use, perhaps especially by those whose daily lives are burdened by the harsh realities of poverty and concern for survival. But as a long-acting contraceptive, it is more likely that both the user and provider of Depo-Provera will misapply it than the oral contraceptive: a woman who is distressed by a side-effect or changes her mind about fertility control may be condemned to suffer the effects of an injection for many weeks.

It is essential for those who provide the product to combine distribution with appropriate product information and the decision to use or not to use the product should be that of the user not the medical personnel providing the service. The fact that there is no visible evidence when Depo-Provera is used as a contraceptive, unlike, say, intra-uterine devices (IUDs) which have a string that protrudes through the cervix, can be an advantage to women whose natural autonomy is threatened by their male partners, or their

mothers-in-law, or who are subject to other social injustices. Conversely, the long-acting drug could be attractive to a government or institutional health worker attempting to subvert the woman's own decision-making about fertility. These opposite points of view have been well expressed by Christopher (24) and Savage (25).

DISTRIBUTION

The hazard of a contraceptive (or any other drug) is a matter of probability in which every individual user may have an exceedingly small hypothetical risk of death, but that risk is immediately translated into 100 per cent certainty for the one who dies. If a drug carries lethal risk, then use of that drug is a form of Russian roulette. That does not help the individual who is the victim, but it helps shape the ethical context. Put another way, the convenience and benefits of many may be counterbalanced by the suffering and death of a few. This type of problem is common in modern society. A driver or passenger of a car not only risks his or her life in order to benefit from this type of transport but may kill a pedestrian who does not own a car and never benefits from one. In the case of therapeutic drugs or contraceptives, the situation is simpler because, generally, only the user runs the risk. We believe such a balancing of risks and benefits is most likely to be ethically acceptable if those who enter into it are appropriately informed and do so of their own free will. Unfortunately, society still finds it difficult, both ethically and administratively, to deal with informed consent and risk assessment (27). It is often necessary to balance non-comparable data from conflicting sources. How does one weigh a research finding that monkeys given fifty times the comparable human dose of Depo-Provera for 10 years have developed malignancies, while after 15 years on the market in developed and developing countries, there is no evidence that the same drug induces cancer in people – especially when people do not live in cages and cannot always be followed methodically? Yet, nearly every activity in life has measurable risks of mortality and morbidity. Such risks can be expressed in several ways: as a rate per 1000 of the population or as an expectation of life, supposing all causes of death except the one under consideration were removed (Table 3, overleaf) (28). An appreciation of the fact that practically every choice in life has a quantifiable risk of death associated with it is ethically helpful and the risk and benefits of using a drug, such as Depo-Provera, can be fitted into some type of perspective, however limited.

A universal and coherent philosophy of health care would assert that all useful medical therapies should be as widely available as possible. Ethically, if health is a basic human right, then it is reasonable to assume that any drug should be available without prescription *unless* there are clinical reasons for restricting access. Such reasons can be assessed by asking eight questions, each of which will be addressed with regard to Depo-Provera. These help to resolve the question of whether

Table 3. How long would an individual live if he or she were immortal except for the specified risk of death? (US and UK data)

Risk	Life expectancy (years)
Smoking 40 cigarettes per day	100
Riding a motorcycle 10 h per week	300
Driving a car 10 h per week	3,500
Powerboating once a month	6,000
Giving birth every year	10,000
Playing football twice a week	25,000
Person (age 16–68) viewing television 200 h year	50,000
Travelling by train 100 h per year	200,000
Being struck by lightning	10,000,000

If the cardiovascular risks of oral contraceptives are considered, then a non-smoking user would live 63,000 years. If the protective action against certain cancers is considered, she might be immortal – as, on the available evidence, would a Depo-Provera user (!).

it should be distributed:

Can the patient diagnose the disease requiring the therapy? All contraceptive use is the exercise of a private choice by an individual not the treatment of a disease diagnosed by a second party.

Does the dose need to be adjusted to an individual? As opposed to treating diabetics with insulin, for example, a standard dose of Depo-Provera is given to all women.

Does the therapy require a trained person to administer it? Injections require simple sterile precautions and a syringe and needle. (In the case of Depo-Provera, refrigeration is not required.) Over most of the Third World, pharmacists, ‘injection doctors,’ or traditional healers dispense a wide variety of potent injectable drugs and there seems no reason why Depo-Provera should not be added to the list.

Is overdose dangerous? Unlike many drugs, overdose with Depo-Provera is not a lethal risk. While accidental overdose should be avoided, it would have no clinically adverse effect on the woman, although high non-contraceptive doses could be dangerous and have been associated with fetal damage.

Is the drug addictive? Depo-Provera is not addictive.
Is there a possibility of side-effects related to predisposing conditions that only a physician can diagnose? It is necessary to know if the woman might be pregnant but if doubt exists, she can be asked to return in two or four weeks, or, if available and appropriate, a urinary pregnancy test can be carried out. Unlike oral contraceptives, there are no absolute contraindications other than possible pregnancy to Depo-Provera use. Product information, to include any known side-effects, can be conveyed by someone other than a physician. (When Depo-Provera was first used, only older women with several children were given the drug, but even then conservative criteria could be implemented by non-physicians.) A possible source of confusion related to the perceived need for close medical supervision of contraceptives may be the

tradition of performing certain preventative screening tests at the time of prescription – such as a gynaecological pelvic examination or a smear for cervical cancer. Such tests are good medical practice when facilities are available, but they should never be an absolute prerequisite to contraceptive distribution. *Can the user determine the level of risk to which she would be exposed?* In the case of Depo-Provera, this is a key question and will be dealt with later under the heading ‘informed choice’.

Are medical skills necessary for long-term surveillance? Clinical and ethical responsibilities for the management of a systemically active contraceptive do not cease when it reaches the user. Successful, *prospective* cohort studies, where many thousands of oral contraceptive users and non-users are kept under close medical supervision for several years, to date, have been limited to a few developed countries, such as Great Britain. Almost without exception, the first insights epidemiologists gain into the rare adverse or beneficial effects of long-term contraceptive use come from case-control *retrospective* studies, where examination begins with the condition under suspicion (for example, breast cancer) and asks how many women with that condition and how many women in a control group are using, or have used, the contraceptive in the past. In this case, the degree of original medical supervision is less important than the woman’s own history and a responsible and effective level of surveillance can be achieved when contraceptives are distributed without close medical supervision.

In 1973, the International Planned Parenthood Federation concluded:

‘The limitation of oral contraceptive distribution to doctor’s prescription makes the method

geographically, economically and sometimes culturally inaccessible to many women. As a consequence, deaths and sickness of women and children, which might otherwise be avoided by voluntary limitation of fertility, continue' (29).

These same arguments apply to the use of Depo-Provera. They are not an invitation to set up two standards of medicine for rich and poor countries, as doctors in developed countries have also put forward arguments why it should be unnecessary for every woman who receives oral contraceptives to go through the hurdle of a doctor's prescription (30, 31, 32). Dr Mahler, Director General of the WHO has observed, it is 'nonsensical to insist upon using only doctors or other categories of professionally qualified personnel, if you can standardise or simplify your technology to make it safe and applicable' (33). The constraints limiting the availability of a medicine are often specific to a particular locality and the regulations controlling the distribution of drugs by an individual government need not be universal.

In making a country-specific decision on a contraceptive, a number of questions need to be asked to create a functional backdrop to any assessment of risk and benefit in both medical and non-medical terms. Again, generic questions will be answered by reference to Depo-Provera.

1) *What is the pattern of disease and genetic predisposition to drug side-effects in a particular community?* Geographical and genetic variations interact with contraceptive use. For example, the same contraceptive steroid can be metabolised and excreted differently in different populations (34) and Depo-Provera, specifically, appears to have a beneficial effect on the course of sickle-cell anaemia, quite apart from, and additional to, its contraceptive effectiveness among women who have a particular need to control pregnancy (35).

2) *How dangerous is childbirth?* The risk of death associated with pregnancy varies from 1 in 10,000 in some Western countries to close to 1 in 100 in some developing countries, such as Papua New Guinea. For many parts of the developing world, contraceptives, such as Depo-Provera, are an immediate, realistic alternative to the dangers of unwanted pregnancy. And those most likely to use modern contraceptives are commonly older, high-parity women who are more at risk for death in childbirth (31) or more likely to suffer the waste of the perinatal loss of a child.

3) *Is abortion legal?* Induced abortion is a prime variable in human fertility, with key ethical dimensions of its own. But from a purely public health point of view, laws controlling abortion alter the equation of risks affecting other fertility control options (36, 37). Where abortion is illegal, the pressure to provide new and available methods of contraception is even greater than where abortion is legal (38). The ethical demands, likewise, may be greater.

4) *What resources are available for medical care?* The demand for medical care far exceeds the resources of even the richest nations. One of the central ethical issues in medicine is the obligation to use finite medical resources as cost-effectively as possible. Problems of ethics and effectiveness are not always in conflict; neither are they limited to the developing world. The use of medical resources is a complex, but ever-present problem, involving such decisions as whether to provide open-heart surgery for the few who need it or infant welfare clinics to meet a near-universal need among the urban and rural poor; or whether specified tasks, such as Depo-Provera injections, are to be performed by physicians or delegated to paramedical workers.

In rural areas of the Third World the ratio of doctors to potential patients is often as disparate as 1:100,000 (in the United Kingdom it is 1:900), and these inequalities will persist for decades. Additionally, among the new doctors graduating in many developing countries, up to half emigrate to developed countries and of those who remain, many practise in the big cities. There are, for example, more medical graduates from India practising in developed countries than there are available for the whole rural citizenry of that populous country!

One stark way of stating the problem is to note that any contraceptive method requiring supervision by a physician (a common Western standard) simply cannot be made available to rural areas in the developing world where 70 per cent or more of the people still live. Such a fact cannot justify the use of a method where, without supervision by a physician, risks might outweigh benefits, but it should encourage an urgent ethical review of possible alternative methods of distribution wherever possible (39). As Rosenfield states, this often results in the use of 'fewer physicians' but the delivery of 'more care' (40). The solutions being sought are innovative and positive, not retrograde and negative. If, for example, Depo-Provera distribution is limited to a physician's prescription, then *de facto* scarce skilled medical resources will have to be taken from other areas of health care. To put it another way, what are the relative merits of insisting that doctors examine women prior to receiving Depo-Provera or that doctors administer the injection, if, in the same community, medical resources are insufficient to care for women in labour or to treat the husband's tuberculosis? Rigorous adherence to so-called Western standards may only exacerbate already formidable problems.

Safety versus choice

The problem of balancing an individual's liberty against the possibility of self-harm becomes increasingly difficult in a modern technological society. An extreme example is the US proposition that the 'right' to bear arms outweighs the associated mortality and morbidity: between 1963 and 1973 46,121 Americans were killed while fighting in-

Vietnam and 84,646 were killed in the US from hand guns. Clearly, societies differ in how much freedom of decision-making they allow even to the extent of permitting bad decisions to be made. For example, a new UK law requires motorists to use a car seat belt, while the US leaves this life-saving choice to the individual. In a way it is a paradox that the US, which promotes freedom at the expense of safety in some areas, has the most cautious drug regulatory authority.

Contraception is an individual choice, where personal judgments arise and where perceptions of convenience may alter the arithmetic of risk and benefit. In the case of the pill, an older woman might make a personal decision to use the method rather than, say, choose a barrier method backed up by abortion, even if the medical risks somewhat outweigh the benefits. Similarly, an individual may choose to use Depo-Provera which has many fewer proven risks than the pill does for older women, but which has not been studied in so much detail. We do not suggest that the argument is taken to absurd lengths, like that of gun control where it is argued that the person, not the weapon, is dangerous. But we do believe individual liberty can be a legitimate part of a decision relating to contraceptive distribution. The key question then becomes, how dangerous must a drug be to curtail use? In everyday life, we often make decisions where convenience is deemed more important than risk when mortalities are in the range of one death in 10,000 to one death in 100,000 per year.

With the evolution of contraceptive devices an ethically intriguing problem is arising: once a method is as widely used and as well understood as the pill, on what grounds should a new method be introduced? As pointed out above, no current or future method can ever be proven safe prior to widespread use. Do we, then, fix our contraceptive technology for all time in the mid-1980s because there is no logical way of proving that any new method will be as good or better than the pill? Or do we live with the same unknowns as we did when oral contraceptives were first introduced and continue to offer society new choices, ones which may carry with them, at least during the first 20 years of use, some inescapable risks?

Informed choice

The individual is the most important focus of any discussion on drug use and distribution and, in the case of Depo-Provera, those problems that have arisen during distribution have sometimes been as much a failure to inform the potential user and respect her choice, as they have been due to side-effects of the drug (25).

How much information is necessary for an 'informed' choice? And how feasible, in practice, is informed choice? In the case of contraceptives, we suggest an informed choice should include consideration of information about the risk of the drug or device (Table 2), as well as realistic information

about the risk of pregnancy and childbirth or abortion consequent on non-use, and about the use of other methods of contraception. In the specific case of Depo-Provera, a user would need to know that the drug frequently causes gross menstrual irregularities and that the return of fertility, after discontinuing use, can be slow. Where possible, an informed choice should include the possibility of withdrawing from any path of action at any time and, as noted, Depo-Provera is at a disadvantage in relation to the pill as its effects, by design, are more long term.

Of special concern, from an ethical point of view, are societies where many people are illiterate. The problems arising when these individuals are exposed to information and make judgments about competing risks could be worse, or could remain the same as in a developed country. Analysis has shown that as a practical matter, literate individuals tend to underestimate the risk of common but non-dramatic diseases, such as tuberculosis, and to over-estimate the risk of rare but well publicised events, such as death from tornadoes or botulism (6). Clearly, contraceptives, because of their association with sex and reproduction and because of the publicity they provoke, are likely to have their risks overestimated. This should not make us shrink from the ethical responsibility to provide potential users, of all sorts, with accurate, clear information designed to enhance their ability to make informed individual choices.

The Program for the Introduction and Adaptation of Contraceptive Technology (PIACT) is developing a series of illustrated booklets to provide product information on contraceptive choices to illiterate couples. These and other methods that convey information in a way that the user can understand should be promoted to improve the degree of informed choice (41).

Weighing risks and benefits at an individual level is always a difficult task, but the first step is always to obtain the best information available and the second is to handle that information with a sense of proportion. Warwick, writing on the ethics of introducing drugs, conjures up the kind of statement research workers might present to women in the Third World: 'There is a 5 per cent chance that you will have a blood clot as a result of the pill' (11). He argues that such a statement would not be understood and he may be right, especially as the fictional figure Warwick chooses is one hundred times higher (!) than that observed in practice. Nevertheless, the sincere attempt to communicate genuine information must go on.

The special case of a mentally incompetent woman being given Depo-Provera is important, but ethically it is only one of several significant issues regarding therapy for mentally incompetent individuals. Society must always scrutinise the care of individuals incapable of giving informed consent as strictly as possible. However, there should be no conflict in philosophy or practice between respect for the individual, even if mentally retarded, and concern for her total health care

and the prevention of possible abuses. It would be wrong or unethical to set aside one aspect of a patient's care, namely fertility regulation, and treat it as if it required a separate philosophy and pattern of drug regulation. Doctors and other health professionals have a responsibility to ensure the well-being and happiness of mentally handicapped patients. Such individuals must be given the maximum opportunity for an independent life and permitted to make their own decisions as far as is consistent with their limitations. The handicapped have sexual needs and are entitled to have as much liberty as possible, while being protected from exploitation and emotional hurt. As far as such as the mentally handicapped are concerned, no perfect solutions exist. However, daily needs must be met. A long-acting reversible method of contraception may have advantages over surgical sterilisation.

Leavesley and Porter (26) have published a comprehensive review of sexuality and contraception for the disabled. They point out that Depo-Provera can be an effective choice for fertility regulation among the intellectually disabled, 'because of its high effectiveness and ease of administration. However, the need for regular injections may not always be readily acceptable to all clients. This fact should be adequately stressed in preliminary counselling as should the altered menstrual patterns likely to be encountered'.

But, returning to the mentally competent users, who should decide about the use of a new contraceptive? Since there is an intrinsic risk with every new drug and device then, although 'experts' may be called upon to offer their judgments, society as a whole and users in particular, must understand the nature of the problem, and if individuals choose to use the method, they must accept the risks associated with the unknown.

Who decides?

Decisions about drug testing and distribution are necessarily in the hands of specialists who must make judgments based upon data which of necessity is incomplete and cannot be individualised. The process is ethically significant because it determines how a new technology is tested and whether, and under what conditions, it can be made available to a wider audience. Unfortunately, there are no quantitative guidelines concerning the degree to which the risk-benefit ratio should favour the consumer (and any future children). However, in the case of contraceptives, the potential scale and duration of use, largely by healthy individuals who are, by definition at risk of pregnancy, invites more stringent criteria in relation to the testing and distribution than might be appropriate, for example, for a hypotensive agent.

Medical specialists, political leaders and even consumer groups are all subject to biases. All should have a say, however, in the process of decision-making.

Daniel Callahan (42) sets out one possible conflict when he writes:

'A major impetus for the development of national family planning programs, and of broader national

population policies, has been the contention that couples have the right to plan both the size and spacing of their family. At the same time, however, the nations of the world have also claimed a right to national sovereignty, and in the name of that right have sometimes felt entitled to establish population policy that can conflict with the putative rights of couples'.

However, the World Fertility Survey (WFS) as well as numerous Knowledge, Attitude and Practice (KAP) surveys, demonstrate a strong demand for family planning, and the evidence from many countries of a significant decline in desired family size is consistent and impressive (Table 4, overleaf). Support for a demand for Depo-Provera, in particular, comes from existing sales (often at relatively high prices) and the judgement and analysis of evidence by those who have firsthand experience of meeting contraception needs in various countries (43). The choice of Depo-Provera could be one important element in what Sir Dougald Baird many years ago called the Fifth Freedom (44): the freedom of individuals to determine their own fertility.

Today, in most of the world, there is a happy convergence between the desires of individuals to control their fertility and the perceived needs of many of the world's most populous sovereign states to bring about a fall in the national birth rate. In much of the Third World, the social marketing of injectable contraceptives (ie, subsidising the price, but still asking the consumer to pay a token amount) would create an effective distribution system and preserve the ethical ideal of proven freedom from coercion.

A particular problem arises when foreign aid is directed from rich countries to poor. Whose standards shall prevail in relation to the supply of donated drugs? Currently, it is the Western standard that is applied, therefore, Depo-Provera is not, for example, distributed for contraceptive use by the US agency for International Development (USAID) programme. Yet, if USAID supplied Depo-Provera in the same way it supplies oral contraceptives its use in developing countries would rise rapidly. Is it ethically acceptable to deny potentially beneficial contraceptive drugs to the countries of the Third World simply because these countries do not duplicate the conditions that govern testing and distribution standards in the donor country? To be sure, the answers are not simple: we suggest that while the present situation may be comfortable for developed-world decision-makers, it is by no means self-evidently the choice with the least known risks for some Third World women.

Where standards in the donor country are the product of contemporary political and medicolegal perceptions, there is reason to believe it ethical to have developing countries use locally devised standards and methods for testing and distribution. We must accept, not side-step, the difference in pressures relating to contraceptive testing and distribution in the Western countries and those in the developing world. A simple but acceptable role for the aid agencies of rich countries

Table 4. Desired and achieved family size in selected developing countries (US and UK data)

Country	Total Fertility rate* (1974)	Desired family size
South Korea	3.6	3.2
Malaysia	4.7	4.4
Thailand	4.9	3.7
Pakistan	6.3	4.3

*Total fertility rate: the number of children an average woman is likely to have in her lifetime at current rates – an estimate of likely achieved family size (Modified from Potts M and Bhiwandiwalla P (1979) *Birth Control: an International Assessment*. University Park Press, Baltimore).

might be to respond to requests from developing countries when the recipient country has arrived at a country-specific solution to its problems.

Conclusions

Patterns of contraceptive testing and distribution involve decisions with ethical dimensions. But ethics, if they are to be meaningful, should represent a formalisation of the desire to extend justice to individuals and societies. Contraceptives have health benefits and, therefore, decisions about use overlap with the ethical framework relating to therapeutic drugs. While it may be said that contraceptors are not ill, the fact that 70 per cent of the births in the world today are unattended by a trained person is a serious health hazard as well as an obscene social injustice. To deny individuals access to contraceptives, such as Depo-Provera, and thereby eliminate the possibility of choosing not to give birth is to compound, not to relieve, that injustice and frustrate the right to reproductive freedom.

Often there are gaps in the information, but decisions still have to be made and the nature of those judgments understood. Levine has pointed out ‘Whatever ethical assessment can be made at this time of Depo-Provera use depends on admittedly incomplete factual information’ (3). The illusory search for evidence of long-term safety, which cannot be complete until long-term use has occurred, does not further the resolution of difficult short-term problems. Both specialist decision-makers and users can find it very difficult to jump from the numerous imperfections of medical data collected in the real world to the problem of a ‘yes’ or ‘no’ licensing decision, or to the problem of use or non-use.

It is easy to fall into the oft-victimised trap of believing that the medical ‘standards’ of the Western world are necessarily correct and, therefore, should be universal. While they may be relevant comparatively, such an absolutist position is misleading, as is the assumption that international agencies in the field of family planning conspire to foist untested contraceptives on the peoples of the Third World. At the time of writing

the US/FDA is considering an appeal by the manufacturers to overturn the FDA’s rejection of Depo-Provera as a contraceptive for the US. If non-approval is overturned, it may encourage wider use in developing countries. But even if it stands, the FDA has made it clear that its decisions are country-specific. To argue that the criteria used by the FDA must apply to the developing world (at the risk of indulging in hyperbole) would be for a committee to design a mousetrap while the village is being attacked by a tiger. Risk/benefit ratios differ, medical resources are unequally distributed, and, in the case of contraception, access or lack of access to particular fertility control options, such as safe abortion and voluntary sterilisation, inevitably affect decisions over the availability and supervision of other methods, such as Depo-Provera. The problem is not one of giving priority to ‘population control’ programmes, but of attempting to extend socially and clinically responsible choices to people of all backgrounds. Many aspects of the process differ quantitatively between rich and poor countries, but remain qualitatively similar. The ethical calculus is composed, then, of two interrelated factors – one involves public policy-making, the other individual choice. A weighing of relative risks and benefits is an exercise common to both. In our judgement, it is reasonable to make Depo-Provera available as a contraceptive in both developed and developing countries. We recognise the strength and sincerity of possible counter arguments and hope that by dissecting the problem into its component ethical parts it will be easier to move from conflicting policies to consensus.

It is, of course, true that the health, demographic and socio-economic problems that the family planning programme set up in the 1960s and 1970s attempted to ameliorate have not gone away. For hundreds of millions of people, both now and in future generations, the preservation of the human freedom to choose their family size depends in large part on the vigour and realism of the voluntary family planning programmes that can be mounted and sustained in this decade. We

believe Depo-Provera has a circumscribed, but essential, contribution to make to human welfare. In dealing with an issue of such importance, it is essential to define the ethical framework in which questions are both asked and answered. The individual's right to exercise fertility choices and to have access to the best information possible is critical to any discussion in a developed or developing country.

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