INJECTABLES and IMPLANTS

The place of the injectable progestogen in family planning remains uncertain. Although some compounds have been used as injectable contraceptives for over a decade and are both popular and effective, controversy still surrounds them.

Depo-Provera® (depot medroxyprogesterone acetate), a product of the Upjohn Company, USA, is currently the only injectable progestogen in widespread use; it is available commercially for contraceptive purposes in 64 countries. Another will be available soon. Schering AG of the Federal Republic of Germany is now registering an injectable progestogen, norethindrone enanthate (also known as norethisterone enanthate) in some 70 countries. It will be marketed commercially under the brand name Norigest® and available for family planning organizations under the brand name Noristerat®.

Injectable progestogens offer many advantages that may be of special importance in developing countries. They are:

- highly effective in preventing pregnancy, on a par with oral contraceptives,
- independent of coitus,
- simple to administer,
- long-lasting, with injections required only two or four times a year,
- not lactation suppressors and thus, unlike combination oral contraceptives, can be offered to nursing mothers without danger of reducing the supply of milk,
- popular in developing countries where injections are associated with safe, effective, modern medicine.

An estimated 1 million women now depend on injectable progestogens for contraception. That number is small compared with the 50 million who use oral contraceptives and the 15 million who use intrauterine devices (IUDs), but the use of injectables appears to be gradually increasing. In recent years international donors of contraceptive supplies have received a growing number of requests for injectables and several countries have added Depo-Provera to their national family planning programs.
An injectable contraceptive is a welcome addition to family planning methods. But the present progestogen injectables, troubled as they are by menstrual side effects and unresolved questions about long-term effects, have not yet won the unqualified approval of clinicians. Nevertheless, if further research can dispel fears about carcinogenicity and disprove or define the risk of infertility after Depo-Provera use, the injectable progestogens may yet become an important component of family planning programs, especially in areas where treatment by injection is popular.

**HISTORY**

The first systemic contraceptives, developed in the mid-1950s, were short-acting progestogens administered orally (128). With the development of longer-acting progestogens shortly thereafter, injectable contraceptives also became possible. Over the past 20 years a number of compounds have been tested as injectable contraceptives, but only one—Depo-Provera—is currently being produced for international distribution and is widely used. In the USA, Depo-Provera has a checkered history of regulation and at present is not approved for contraception.

The development of progestogens (synthetic compounds with the effects of the natural hormone progesterone) grew out of the post-World War II competition among drug companies to create synthetic hormones for a variety of therapeutic purposes. These early progestogens are metabolized quickly and therefore have to be administered in frequent small doses in order to maintain their effect. As a result, when in the early 1950s Dr. Gregory Pincus and his associates set about utilizing the powerful ovulation-inhibiting properties of these progestogens for fertility control, they concentrated on developing a contraceptive which could be administered orally.

Dr. Karl Junkmann in 1953 discovered that esterifying a progestogen alcohol created a drug with long lasting effects when injected (20, 62). (Esters are formed from a free alcohol and an acid by the removal of water.) Junkmann and his associates synthesized esters of the progestogen norethindrone, including norethindrone enanthate, in 1958 (63). Medroxyprogesterone acetate was developed by the Upjohn Company at about the same time (6).

Schering AG began clinical studies of norethindrone enanthate (Noristerat) in 1957. The major field trials of this drug were conducted in Peru, but other studies have taken place in Egypt, Europe, and elsewhere. In 1967 Noristerat was first marketed in Peru, but in 1971 it was withdrawn and field trials suspended pending further analysis of toxicologic findings in rats. Some researchers have since concluded that the findings in rats are not applicable to humans, and Schering AG is now registering Noriestat in some 70 countries. The brand name Noristerat will be used when the drug is sold to international donor organizations in order to make it readily identifiable if it should be diverted from intended channels (25).

In 1958 the Upjohn Company began clinical trials of medroxyprogesterone acetate (Depo-Provera) as a treatment for threatened or habitual abortion and for endometriosis. In 1960, the USFDA approved it for these uses on the basis of its safety, but without assessing its effectiveness. In February 1974, after the agency concluded that Depo-Provera had not been proved effective for either of these uses and after steroids administered during pregnancy had been associated with congenital defects (69, 117), the USFDA withdrew its approval for use of Depo-Provera during pregnancy or to treat endometriosis (33, 34, 35).

The first clinical trials of Depo-Provera as a human contraceptive began in 1963 and established a standard regimen of 150 mg every three months. Field trials began in 1965 and have since been conducted in 61 countries (48). Since the late 1960s regimens of 300 or 400 mg every six months have also been studied.

Upjohn applied to the USFDA in 1967 for permission to market Depo-Provera as a contraceptive in the USA (173), but, at first, questions about reversibility and relationship to breast cancer in beagle dogs and, more recently, questions about cervical carcinoma in situ in humans have blocked USFDA approval.

In 1972 Depo-Provera received USFDA approval as a palliative treatment of advanced endometrial cancer. Currently this is the only approved use in the USA (168). Depo-Provera has also been studied as a treatment for idiopathic precocious puberty (64, 83, 106), but its effectiveness and safety for this purpose have not been established.

Several combinations of a progestogen and an estrogen are being distributed in a few countries as monthly injectables. Promeco markets the combination of algestone acetophenide and estradiol enanthate in Mexico and Argentina under the brand name Perlutan® and in Spain under the brand name Topasel®. In Chile, Recaline Laboratories produces Aguria®, and Silesia Laboratories produces Unalmes®. Both are combinations of dihydroxyprogesterone acetophenide and estradiol enanthate.

Other steroids have also been tested as injectable contraceptives, but are not being pursued because of the expense of clinical trials needed to prove safety (130) and/or the severe disturbances of the menstrual cycle which they produced (67, 74, 109). These other injectables include Deladroxate®, developed by E. R. Squibb & Sons, USA, which was a combination of dihydroxyprogesterone acetophenone and estradiol enanthate, for monthly injection; chlorormadinone acetate, manufactured by E. Merck-Darmstadt, FRG, and hydroxyprogesterone caproate, manufactured by Schering as Prolutin Depot® and marketed by Squibb as Delalutin®. A few trials have also been con-
Combined Depo-Provera with estradiol cypionate (17, 78, 153), Norister with estradiol undecylate (66), norethisterone with estradiol benzoate (21), and utilizing the estrogen estradiol undecylate alone (28, 67).

Recent interest in progestogen-only contraceptives represents a return to the intentions of early researchers in steroidal contraception. They originally envisioned oral contraceptives as pure progestogens but then discovered that small amounts of estrogen, present as contaminants, reduced the breakthrough bleeding caused by the progestogens. As a result, manufacturers added controlled amounts of different estrogens to the pills (77). Estrogen, however, may cause annoying side effects such as nausea, dizziness, and breast tenderness (22) as well as other, more serious conditions (55). To avoid estrogens, investigators in the late 1960s turned their attention back to progestogen-only formulations—in the form of either oral "minipills" or injectables.

**MECHANISM OF ACTION**

The injectable progestogens prevent pregnancy in much the same way that combined oral contraceptives do, and with the same high degree of effectiveness, by

- inhibiting ovulation in many women
- increasing the viscosity of cervical mucus, thus forming a barrier to spermatozoa
- changing the rate of ovum transport through the oviducts
- making the endometrium less suitable for implantation.

The contraceptive effect of Depo-Provera depends primarily on its ability to stop ovulation. Norister works largely by altering cervical mucus (72, 74). After the first six to eight weeks, women using Norister often do ovulate (4, 7, 73). The two injectables differ slightly in their effects, possibly because they are derived from different sources. Norethin-dron enanthate, like most progestogens currently used in oral contraceptives, is derived from 19-nortestosterone, which is structurally similar to testosterone. Medroxypro-

gestone acetate, on the other hand, is structurally similar to progesterone.

Progestogens probably affect ovulation by acting on the hypothalamus-pituitary axis, causing suppression of the surge of luteinizing hormone (LH) normally seen at midcycle just prior to ovulation (38, 42, 74, 108, 112, 131, 139, 161). Without that surge ovulation does not take place.

The injectable progestogens make cervical mucus scant, viscous, and sticky, as it is during pregnancy and during the infertile late portion of the menstrual cycle (4, 29, 112, 131, 184). This mucus interferes with the movement of sperm into the uterus. Post-coital tests have shown that some sperm penetrate the viscous cervical mucus but rarely reach the uterine cavity or the oviducts (29, 70, 71, 181, 188). With Norister changes in cervical mucus appear during the first month after the first injection (29). With Depo-Provera, changes appear during the second month (30).

Under progestogen contraception, the endometrium becomes unable to support a fertilized ovum. With Depo-Provera, the endometrium takes on a resting or atrophic appearance which becomes more apparent as use continues (30, 112). With Norister the effects vary. In some cases the endometrium resumes normal cyclic changes during the second month after an injection (20, 74). In other cases it may remain unsuitable for implantation throughout Norister use (4, 29). Both injectables also appear to cause changes in the oviducts, interfering with ovum transport and/or sperm capacitation and transport (12, 30, 184).

**EFFECTIVENESS**

The standard regimens of Depo-Provera and Norister offer highly effective protection against pregnancy. Among
women receiving injections of 150 mg Depo-Provera at 90-day intervals or 200 mg Norigest at 84-day (12-week) intervals, fewer than one in a hundred women are likely to become pregnant during a one-year period (see Tables 1 and 2). The injectables are as effective in preventing pregnancy as combined estrogen-progestogen pills, slightly more effective than progestogen-only "minipills," and markedly more effective than IUDs.

Data on the effectiveness of the 150 mg/3 month regimen of Depo-Provera shown in Table 1 represent over 20,000 woman-years of experience with the drug. Less extensive studies using 300 or 400 mg Depo-Provera at six-month intervals have also been conducted (see Tables 1 and 2).

There are not as many published studies of Norigest as of Depo-Provera (150 mg/3 months), but the pregnancy rates reported for women using Norigest appear to be slightly higher (see Table 1). With both drugs, most accidental pregnancies occur either shortly after the first injection, before the drug has fully taken effect, or just before the end of an injection interval when its effect has begun to wear off (74, 78, 81, 136). Some failures have also been attributed to injections which were not administered deep in the deltoid or gluteal muscle as required (186).

**SHORT-TERM SIDE EFFECTS**

Though highly effective and easy to administer, the injectable progestogens are not without problems. In the short term, subjects may experience localized pain and swelling at the injection site, which usually disappears within a day or two. Some subjects may develop a red, inflamed area around the injection site which persists for several weeks. Most women experience a general feeling of fatigue and depression; these symptoms usually disappear in a few days or weeks. Occasionally, some women have severe headaches and mood swings. A very few women have developed more serious side effects, such as deep vein thrombosis or pulmonary embolism. However, these complications are rare and occur only in a small percentage of women who receive the injectable progestogens.
run, they frequently disturb menstrual patterns, sometimes severely, and Depo-Provera may also cause weight gain.

**Menstrual Cycle Disruptions**

All progestogens, but especially the injectables, disrupt menstrual patterns. Women using injectables may experience shorter or longer cycles, increased or decreased menstrual flow, and spotting. Many women tolerate these disturbances, but others do not. Menstrual disturbances cause more women to discontinue injectables than does any other side effect. Therefore, supplemental estrogens are sometimes used to regulate menstruation.

The injectables have their most unpredictable effects on menstrual patterns during the first months of use. Discernible menstrual cycles may disappear entirely, to be replaced by intermittent bleeding and spotting of unpredictable duration, interval, and rate of flow. If identifiable cycles continue, their length may vary widely from month to month and from one woman to another. In a few women, injectables immediately bring on amenorrhea. In many Depo-Provera studies fewer than half the users experienced "normal" menstrual flow following a first injection (2, 23, 81, 149, 150). Irregular bleeding often gives way to amenorrhea which may then continue as long as the drug is used. By the end of two years, 40 percent or more of Depo-Provera users may be amenorrheic (23, 81) (see Fig. 3).

Researchers who have studied both injectables suggest that Noriest distorts menstrual patterns less than Depo-Provera (29, 74, 185). But comparing separate studies of the two injectables is difficult because of differing definitions of normal menstrual patterns and differing methods of aggregating data. While more and more Depo-Provera users experience amenorrhea as usage continues, Noriest users appear to experience an increasing proportion of normal cycles as time passes (29, 144) (see Fig. 4). This observation may be biased, however, by the fact that women with disrupted menstrual patterns are more likely to abandon the method than are women with normal cycles.

**Management of Bleeding**

Orally administered estrogens are often used to treat menstrual disturbances caused by injectable progestogens. At first the estrogens suppress menstrual bleeding. Then, when they are withdrawn and estrogen levels drop, withdrawal bleeding, which may be similar to normal menses, usually occurs. Thus, cyclic administration of estrogens can be used to treat excessive bleeding, irregular bleeding, or amenorrhea.

Various estrogens have been used in different regimens, ranging from a full cycle of oral contraceptives (23) to a single 10 mg injection of long lasting (depot) estrogen (93, 136) to 1 mg or less of oral estrogen daily for several days each month (9, 24, 29, 67, 84, 91, 101, 122, 129, 136, 154, 184). Supplemental estrogens have been adminis-
tered either routinely, in response to a patient's request or complaint, or when indicated by objective criteria such as heavy bleeding. McDaniel has suggested the following indications for the use of supplemental estrogens with Depo-Provera:

- prolonged spotting (more than 7 days in 28)
- heavy bleeding (more than was usual before injections began)
- more than 7 days bleeding
- any bleeding which is or could become a source of progressive anemia
- three or more months of amenorrhea, if it is disturbing to the woman (91).

Other conditions, such as pelvic infection, cervicitis, malignancies, menilasis, or trichomoniiasis, may also produce menstrual disruption. Clinicians should therefore ensure that these conditions are absent before blaming the injectable (8).

Although he has suggested specific indications for the use of supplemental estrogens, McDaniel himself administers them routinely to all his patients in the McCormick Hospital Family Planning Program in Chiang Mai Province, Thailand. He does so in an attempt to provide women with the reassurance of at least one withdrawal bleeding between injections and to prevent the rare occurrences of heavy bleeding which would require immediate medical care difficult to obtain in rural areas (52).

If oral estrogens are used in conjunction with injectable progestogens, some women may consider the method not much more convenient than taking standard oral contraceptives (24, 67). This objection may be largely overcome by the administration of a single dose of long acting oral estrogen, such as quinestrol, given monthly or at the time of injection, as is currently done in the McCormick Hospital program (94). Despite the fact that estrogens sometimes cause side effects such as nausea and dizziness, the advantages of a regular menstrual pattern outweigh the disadvantages of estrogenic side effects for some women (155). Also, the advantages of complete protection for a three-month interval may outweigh the apparent inconvenience of using both oral medication and injections. Furthermore, the woman who fails to take her oral estrogen supplement does not increase the risk of pregnancy as does the woman who fails to take an oral contraceptive tablet (24, 91).

Several researchers have studied either Depo-Provera or Norigest combined with a long-lasting injectable (depot) estrogen—for example, 25 mg medroxyprogesterone acetate with 5 mg estradiol cypionate (17, 78) or 50 mg norethindrone enanthate with 5 mg estradiol undecylate (68). These combination injectables, administered monthly, produce fewer menstrual pattern disturbances than the higher-dose, longer-lasting progestogens alone. No pregnancies have been reported with these combinations, but experience is still very limited.

**Weight Gain**

Weight gain, which may be an advantage to some and a disadvantage to others, occurs in a majority of Depo-Provera users (2, 46, 87, 122, 141, 155). In clinical studies mean weight gain has ranged from 1.4 pounds (141) to 9 pounds (155) in the first year of Depo-Provera use. Some researchers find that weight gain levels off after the first year (15, 46, 190). Others report a slow and continuing increase (141, 150). McDaniel et al., studying 800 Thai women who used Depo-Provera for 30 months, found that mean weight gain at the end of 12 months was 2.8 pounds; at 24 months, 5.1 pounds; and at 30 months, 5.4 pounds (103). Which women will be affected is not predictable, although obese women may gain less than others (87).

In some parts of the world weight gain is actually an asset (3, 16). Apelo et al. report from the Philippines that:

> Weight gain did not prove to be a problem because this was usually welcomed by most women, especially those who belonged to the lower socioeconomic group. A gain in weight, to them, connoted tolerance to the drug and they felt happy about it (3).

**Carbohydrate Metabolism**

Depo-Provera may have some effect on carbohydrate metabolism, although this relationship has not been definitely established. Some researchers find that Depo-Provera raises glucose levels in the blood (13, 39, 114, 160); others report that it does not (30, 150, 165, 167, 171).

The clinical issue at stake in the debate over carbohydrate metabolism is whether diabetics and pre-diabetics should use Depo-Provera. If Depo-Provera does raise blood glucose levels, diabetics and pre-diabetics may not be able to produce the additional insulin necessary to metabolize the extra glucose (39). Since diabetics and pre-diabetics face higher risks during pregnancy, their need for effective contraception is great. Close medical supervision during their use of contraception is necessary.

Progestogen-only minipills do not seem to interfere with carbohydrate metabolism (133). No changes in carbohydrate metabolism have been reported in women using Norigest (29, 40, 184).

**Other Side Effects**

Other complaints reported by users of injectables include nausea, dizziness, headache, nervousness, chills, change in skin pigmentation, galactorrhea, painful menstruation, lessening of libido, diminished orgasm, and acne. How
often nonmenstrual side effects occur and what proportion of users experience these often highly subjective symptoms vary from one study to the next. In the Upjohn Company's cooperative studies of Depo-Provera, Schwalie and Assenzo reported that nonmenstrual side effects other than weight gain were similar in type and frequency to those reported by users of oral contraceptives (149, 150). On the other hand, Scutchfield and his associates found that, in a Georgia (USA) family planning clinic, the side effects among Depo-Provera users paralleled those of IUD users rather than those of oral users (154). Larranaga and Kesseru have commented that there are fewer nonmenstrual side effects with Norigest than with orals (86). Injectables might be expected to cause fewer nonmenstrual side effects because they do not contain estrogen, which has been blamed for nausea, dizziness, and headache associated with combination oral contraceptives (22).

With the possible exception of weight gain in Depo-Provera users, clinicians have not observed symptoms of metabolic or endocrine changes among users of injectables. Most field trials have yielded no clinical evidence that the injectables adversely affect blood clotting, adrenal or liver function, blood pressure, or lactation, all of which are affected to some degree by estrogen-progestogen contraceptives. Nor have laboratory studies produced any conclusive evidence of adverse metabolic or endocrine effects.

CONTINUATION

Despite the side effects of injectables, 60 percent or more of all users can be expected to continue with the method for at least one year (see Table 3). Continuation rates are influenced not only by the characteristics of the contraceptive method but also by the age and parity of the user, social and cultural attitudes, accessibility of services, availability of alternate methods, and other factors. Therefore, comparisons among studies are difficult to make. Researchers who have compared continuation rates for different contraceptive methods in similar patient populations have found that the continuation rate for Depo-Provera was higher than that for orals but lower than that for IUDs (3, 95, 154) (see Fig. 5). Doctors at a clinic in Egypt report that the continuation rate for Norigest was higher than rates both for IUDs and for orals (29).

Among side effects of Depo-Provera, excessive and irregular menstrual bleeding or spotting can be blamed for the largest proportion of discontinuations—between one-quarter and one-half of all first-year drop outs. Amenorrhea is responsible for about 10 percent of discontinuations (see Table 4). Menstrual disturbances caused by Norigest, because they are less severe than those due to Depo-Provera, apparently cause fewer discontinuations, though reports are few. In the Peruvian field trials of Norigest, by the end of two years 5.5 percent had dropped out because of menstrual disturbances, most of that in the first year. Some 87 women discontinued Norigest because of amenorrhea; 15, because of spotting or breakthrough bleeding (74).

Women may find menstrual disturbances upsetting because they think that irregular or excessive bleeding is a symptom of sickness or that amenorrhea is a sign of pregnancy. Religious practices, folk beliefs, and rumors may also contribute to a woman's concern. For example, in Egypt, investigators have reported that:

Table 3—Percentage of Women Continuing Use of Depo-Provera or Norigest by Months of Use in Selected Studies, 1970-1974

<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Reference Number</th>
<th>Country</th>
<th>Number of Women</th>
<th>Dose Interval in Months</th>
<th>Percentage of Women Receiving Next Injection by Months of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td><strong>DEPO-PROVERA:</strong></td>
<td></td>
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<tr>
<td>Apelo et al. 1974</td>
<td>3</td>
<td>Philippines</td>
<td>226</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>Dodds 1971</td>
<td>23</td>
<td>Hong Kong</td>
<td>1,883</td>
<td>3</td>
<td>61</td>
</tr>
<tr>
<td>Khan et al. 1973</td>
<td>76</td>
<td>Pakistan</td>
<td>145</td>
<td>6</td>
<td>54</td>
</tr>
<tr>
<td>Koetsawang et al. 1974</td>
<td>81</td>
<td>Thailand</td>
<td>886</td>
<td>3</td>
<td>98</td>
</tr>
<tr>
<td>McDaniel et al. 1974</td>
<td>103</td>
<td>Thailand</td>
<td>9,284</td>
<td>3</td>
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<tr>
<td>McDaniel &amp; Pardthaisong 1974</td>
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<td>McDaniel &amp; Pardthaisong 1973</td>
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<td>Thailand</td>
<td>217</td>
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<td>McDaniel &amp; Pardthaisong 1972</td>
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<td>2,967</td>
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<td>92</td>
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<td>SchwaUie &amp; Assenzo 1972</td>
<td>149</td>
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<td>991</td>
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<td>USA</td>
<td>723</td>
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<td>92</td>
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<tr>
<td>Sin et al. 1973</td>
<td>156</td>
<td>Malaysia</td>
<td>550</td>
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<tr>
<td>Zartman 1970</td>
<td>190</td>
<td>USA</td>
<td>478</td>
<td>3</td>
<td>92</td>
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<tr>
<td><strong>NORIGEST:</strong></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Kesseru-Koos et al. 1973</td>
<td>74</td>
<td>Peru</td>
<td>1,844</td>
<td>84 days</td>
<td>86</td>
</tr>
</tbody>
</table>
For many women this unpredictable menstrual behavior was disturbing as they feared that amenorrhea may indicate pregnancy or they believe that retention of menstrual blood has a serious toxic effect on the body. Spotting is troublesome as it compels our cases to prohibit intercourse due to religious habits; mild or excessive bleeding is most alarming (67).

Bantu women believe that amenorrhea means blood will collect in the head, causing headaches (68). In Chiang Mai Province, Thailand, the rumor once circulated that amenorrhea leads to insanity (95).

If such fears can be eliminated, many women will tolerate amenorrhea. That a woman's psychological well-being depends on regular menstruation may be, as Molitor puts it, "a somewhat masculine idea" ("une idee un peu masculine") (113). Poor nutrition and short birth intervals in developing countries may make regular menstrual patterns the exception rather than the rule. Clinicians from various areas report that many women actually are pleased by the absence of menstruation (81, 84, 113).

Educating and reassuring women about menstrual disturbances can promote continuation of the method. In Mexico, Rice-Wray and her associates have found that the continuation rate depends largely on the confidence the patient has in the doctor and the explanation she received (136).

Zanartu, in Chile, has recommended group instruction about menstrual disturbances (186), and Chinnatamby, from Sri Lanka, has stressed the importance of repeated assurances (16).

Among nonmenstrual side effects of Depo-Provera, weight gain is sometimes a reason for discontinuation, but, because the gain usually is moderate, it is not a major cause of dropouts. For example, in the Upjohn Company's cooperative studies, involving mainly US women, it caused only 1.7 percent of the participants to discontinue (149).

Various other nonmenstrual symptoms, including those subjectively determined, are responsible for a small proportion of discontinuations among users of injectables. Only 1.1 percent of the women in the Peruvian field trials abandoned Norigest because of nonmenstrual side effects (74). In most large studies of Depo-Provera, less than six percent discontinued because of nonmenstrual complaints other than weight gain (16, 81, 104, 149, 150).

## FERTILITY-RELATED EFFECTS

Return of fertility may be delayed for several months or longer after discontinuing use of an injectable. This effect is more frequent and longer lasting with Depo-Provera than with Norigest. In addition, various progestogens may be associated with virilization and an increase in congenital defects among the offspring of women who receive the drugs during early pregnancy.

### Return of Fertility

A study of 114 women who discontinued Depo-Provera in order to become pregnant showed that median time to

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**Table 4—Percentage of Women Discontinuing Use of Depo-Provera for Menstrual Disturbances by Years of Use in Selected Studies, 1970-1973**

<table>
<thead>
<tr>
<th>Author &amp; Date of Publication</th>
<th>Reference Number</th>
<th>Country</th>
<th>Number of Women Starting Depo-Provera</th>
<th>Percentage Discontinuing For Amenorrhea 1 year 2 years For Excess or Irregular Bleeding 1 year 2 years For All Reasons 1 year 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dodds 1971</td>
<td>23</td>
<td>Hong Kong</td>
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<td>6 9 13 17 39 52</td>
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<td>Pakistan</td>
<td>145</td>
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<tr>
<td>McDaniel &amp; Pardthaisong 1973</td>
<td>102</td>
<td>Thailand</td>
<td></td>
<td>117 137 221 241</td>
</tr>
<tr>
<td>Scutchfield et al. 1971</td>
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<td>Sin et al. 1973</td>
<td>156</td>
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<td>Zartman 1970</td>
<td>190</td>
<td>USA</td>
<td>478</td>
<td>1 4 23</td>
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</tbody>
</table>

*Postpartum women. Routine estrogen supplement administered after weaning of the infant—usually at 9-12 months.*
conception was 13 months from the date of the last 150 mg injection, or 10 months from the assumed end of contraceptive protection. By comparison, median time to conception after discontinuing IUD or diaphragm contraception is two months. However, by 18 months after discontinuation cumulative conception rates become similar regardless of the method previously used (151) (see Fig. 6). McDaniel, using 15 weeks after the last injection as the discontinuation point, reported that 76.8 percent of 135 women were pregnant within one year (97). He compared this to one year cumulative conception rates of 84 percent for oral contraceptives (142) and 88 percent for IUDs (162). By 14 months, 82 percent of the former users of Depo-Provera were pregnant.

Fertility returns more quickly after Norigest use. Zanartu has estimated that conception is likely to occur three to six months after the last Norigest injection (182, 183). A study of 48 women who discontinued Norigest found that 15, or 31.3 percent, became pregnant within six months after the last injection (74). While a quicker return of fertility may make Norigest more acceptable than Depo-Provera for a woman who wants more children, it may also mean an unplanned pregnancy for a woman who is even a few days late receiving her next injection.

The duration of infertility after discontinuation of Depo-Provera apparently bears no relationship to the length of time the injectable is used (23, 95, 150, 151), but rather may reflect individual differences in the rate of drug absorption and excretion (151, 174). Women with lower body weights tend to conceive sooner after discontinuing Depo-Provera (151).

Suspicion that Depo-Provera may cause permanent infertility has been a major impediment to its wider use. But, despite the importance of the issue, little research has been conducted on it, possibly because of the difficulty of confirming infertility or determining its causes. Thus, it is not possible to estimate what percentage of women may be affected or even to state firmly that Depo-Provera does cause infertility. Ovulation-stimulating drugs have been used successfully to return fertility after Depo-Provera injections (140), implying that no damage to the reproductive system had occurred.

**Fetal Effects**

In the late 1950s and early 1960s researchers discovered that some progestogens, when given in early pregnancy, occasionally cause masculinization of the external genitalia of female fetuses (1, 127, 179). In most of these cases, progestogens were given in large doses to prevent threatened or habitual abortion. In large doses medroxyprogesterone acetate (the active ingredient in Depo-Provera) virilizes rat and rabbit fetuses (107, 127), but no such effect on human fetuses has been reported, either with doses of Depo-Provera as high as 400 mg (41) or with Norigest.

Recent reports have suggested that in a few women steroids administered in early pregnancy may cause congenital anomalies. Progestogens administered for pregnancy tests are especially implicated (60, 69, 117, 118, 119, 120). The risk is small—probably no greater than 7 per 10,000 births (85)—and probably occurs only in conjunction with "some type of maternal predisposition" (118).

In an attempt to avoid administration during pregnancy, the first injection of Depo-Provera or Norigest is usually given within a few days after menstruation.

**DEBATE OVER CANCER RISKS**

Suspicion that Depo-Provera might stimulate certain cancers has repeatedly delayed approval of the drug in the USA. A controversy over whether the injectable increases the incidence of cervical carcinoma in situ, a possible precursor of invasive cancer, is still unresolved. Several years ago researchers found that both Depo-Provera and Norigest produce breast nodules in certain test animals. Subsequently, however, many scientists have concluded that the results of these animal studies cannot be extrapolated to humans.

**Cervical Carcinoma in Situ**

Some statistics suggest, but do not prove, that cervical carcinoma in situ may occur more often among Depo-Provera users than among nonusers. Among 10,333 women who used the injectable for a total of 14,891 woman-years, 35 cases of carcinoma in situ were reported (152), but because there was no control group in this study, it is difficult to evaluate these data (44).

An attempt has been made to compare the rates found among Depo-Provera users with age and race adjusted
carcinoma in situ rates from US surveys conducted by the National Cancer Institute (NCI) (152). Such a comparison between separate studies, however, leaves a wide margin for possible inconsistency and bias. Depending on the age, race, location, regimen, and, to a lesser extent, the statistical method used, rates of cervical carcinoma in situ among Depo-Provera users range from less than one to more than nine times the age and race adjusted rates in the U.S. population (37, 152). For the usual regimen of 150 mg/3 months, the risk is 1.55 times the adjusted US rate (152), a difference which is “statistically and clinically insignificant” (44).

USFDA officials, faced with the problem of how to interpret the inconclusive statistics, twice nearly approved Depo-Provera for contraceptive use and twice withheld approval because of objections from Representative L. H. Fountain, chairman of a congressional subcommittee concerned with intergovernmental relations. It was Fountain who, in 1974, first made an issue of the apparently higher incidence of carcinoma in situ among users of Depo-Provera. He has argued that the statistics raise enough doubts about the safety of the injectable to justify keeping it off the market (37).

Responding to Fountain’s objections, the USFDA examined the data, and it concluded that no increased risk could be proved. The agency pointed out that almost all of the carcinoma in situ cases among Depo-Provera users occurred within the first two years of drug use:

> From all that we know about carcinogenesis, . . . such early tumors cannot be considered as drug related; the absence of a lag time of 3 to 10 years or more is at variance with the known toxicological behavior of chemical carcinogens (146).

The USFDA also argued that the statistics about Depo-Provera raise no more concern than has been raised about the possible carcinogenicity of oral steroidal contraceptives already marketed with USFDA approval (146, 147). Despite these arguments, further protests from Fountain led to another postponement of USFDA approval, which, as of March 1975, remains in effect. The agency will hold an open hearing in April 1975 to discuss the carcinoma in situ issue with experts on “contraception, epidemiology, and carcinogenesis” (147).

Only two studies of cervical malignancies among Depo-Provera users have been conducted with control groups for reliable comparisons, and both were too small to be statistically significant. A Chilean study found no difference in the rates at which cervical growths occurred in Depo-Provera users and in IUD users. But, for unknown reasons, women who chose the injectable were more likely to have a cervical malignancy before beginning contraception than those who chose the IUD (18). In a Belgian study which included Depo-Provera, abnormalities and malignancies, as determined by Papanicoulau cervical smears, occurred less than half as often among the users of continuous progestogen contraception as in a control group using no hormonal contraception (54).

Papanicoulau smears taken during the Peruvian field trials of Norigest produced no evidence that the injectable increased the incidence of cervico-vaginal abnormalities (75).

It has been hypothesized that continuous progestogen contraception would be more likely to stimulate carcinogenesis than cyclical combined estrogen-progestogen contraception because an unchanging hormonal environment might encourage mutant cells to multiply unchecked, whereas a changing hormonal environment might check this growth (124, 135). This has not been proved, however.

Breast Nodules and Cancer

Depo-Provera causes breast nodules in beagles. Norgest causes breast nodules in rats and mice, as do other nortestosterone derivatives. But no evidence suggests that the injectable progestogens have the same effect in women, and the applicability of the animal study results to humans is disputed.

Studies conducted by the USFDA in the late 1960s found that female beagles receiving the body weight equivalent of the human contraceptive dose of Depo-Provera developed persistent breast nodules (175) and beagles receiving 25 times the equivalent human dose developed malignant nodules and metastases (36). As a result, in 1970 the Upjohn Company withdrew from the market Provest, a combination oral contraceptive which contained medroxyprogesterone acetate. Chlormadinone acetate, another progestosterone derivative studied as an injectable and at the time used in some oral contraceptives, was also removed from the market because it had a similar effect. The USFDA allowed clinical trials of Depo-Provera to continue, however, reasoning that other effective oral contraceptives were available but that Depo-Provera appeared to be the only highly effective injectable (8, 36).

The results of the beagle studies renewed the ongoing controversy over the extrapolation of animal study results to humans. Some researchers argue that dogs, particularly beagles, react differently and are more sensitive to progestogen and progestogens than are women and usually develop a type of breast nodule rarely found in women (14, 115, 116, 169, 175). They also point out that primates given Depo-Provera have not developed breast nodules, to which the USFDA replies that monkeys are more resistant to breast nodules than women are (8, 36).

The only study which compared the incidence of breast nodules in Depo-Provera users with incidence in controls found no significant difference between the two (98). McDaniel, who conducted the study with 1,270 users of the injectable and 257 controls, called the beagle experiments “unfortunate and misleading.”

After Norigest was discovered to cause pituitary and breast nodules in rats, Schering AG stopped clinical trials (116) and removed the injectable from the market in Peru, the only country where it was available commercially (25).
Later studies revealed that in rats Norigest has strong estrogenic effects, rather than the progestational effects it has in rabbits and humans. Schering scientists postulate that this estrogenic effect in rodents causes pituitary proliferation and tumors and increases the secretion of prolactin by the pituitary. The increased prolactin overstimulates mammary growth and triggers the development of mutant cells. Because of species differences this does not occur in humans (116). To varying degrees, other nortestosterone derivatives also cause breast nodules in rodents. Because rodents appear to be inappropriate test animals, the USFDA has been willing to approve for human contraceptive use nortestosterone derivatives which have slight tumorigenic effects on rodents.

USFDA officials defend the agency’s general reliance on animal studies with the rationale that, while evidence of tumorigenic effect in animals does not mean the drug will cause tumors in humans, evidence that it is not tumorigenic in animals allows a drug to be marketed with “a certain measure of assurance” of its safety for humans (8). They emphasize, however, that the agency’s decisions are based on US conditions which may not apply in other countries:

The risk-to-benefit principle alone is bound to vary from country to country, requiring variations in interpretations of results obtained in tests for toxicology, carcinogenicity and other multi-phased complexities arising from such investigations. Different interpretations and their consequent utilization by different agencies in different countries must be made by the responsible agencies on their merits for prevailing conditions and in the best public interest (8).

PROGRAM ISSUES

The advantages of injectable progestogens—effectiveness, convenience, ease of administration, and lack of inhibition of lactation—make them popular with a large number of both users and clinicians. Nevertheless, the place of injectable progestogens in a comprehensive family planning program has not yet been fully determined. With lactating women or women whose families are complete, injectables may be both popular and appropriate, but, from the program planner’s point of view, the overall effect could be the substitution of injectables for IUDs or sterilizations. With nulliparous women or those who want more children, many family planning officials still urge caution and limit the use of injectables.

Advantages

From the users’ point of view, injectables are attractive. Reports from family planning programs around the world show that, where women were offered a choice among contraceptive methods which included an injectable, between one-quarter and three-quarters chose the injectable (51, 74, 90, 125, 155, 172). Effectiveness, convenience, freedom from fear of forgetting (94), and the fact that husbands cannot interfere with its use (125) are major reasons for the popularity of the injectable (see Fig. 7). The mode of administration is also an asset. The attitude McDaniel and Pardthaisong found in Thailand holds true elsewhere as well (17, 51, 136):

...since the turn of the century, medicines given by needle and syringe have been widely regarded as more reliable, more effective, and more prompt in their actions than medicines taken orally. In the minds of many of the common people, a physician without a syringe is not a real physician at all, no matter how high his degree or other qualifications may be. Therefore a contraceptive to be taken by injection has a tremendous advantage over other methods (95).

An important advantage is that injectables do not inhibit lactation (43, 65, 183), as the estrogen-progestogen oral contraceptives sometimes do (10, 79, 82). In fact, the injectables may actually increase both the duration of lactation (43, 45) and the volume of milk (47, 65, 80). They are therefore preferable to oral contraceptives for postpartum use, especially in countries where mothers breastfeed their children for long periods (47).

An effective steroidal contraceptive which does not reduce lactation is welcome for two reasons. Firstly, in the postpartum period women are highly motivated to accept contraception (191, 192). Secondly, contrary to popular thought, ovulation and conception can occur before the end of lactation amenorrhea (170). Furthermore, in areas where a woman’s only access to medical care and advice is during childbirth, a single injection at that time can provide her with several months of protection against the next pregnancy (76). In an extensive review of the duration and contraceptive effect of lactation, Dr. Franz Rosa of the UN Fund for Population Activities (UNFPA) has recommended that progestogen-only contraceptives be provided to lactating women at least until menstruation recommences (138).

<table>
<thead>
<tr>
<th>Fig. 7. Advantages and Disadvantages of Injectable Progestogens Compared to Oral Contraceptives and IUDs.</th>
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<tr>
<td><strong>Advantages of Injectables Compared to Orals</strong></td>
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<tr>
<td>• More convenient to use. No daily pill taking.</td>
</tr>
<tr>
<td>• Freedom from fear of forgetting.</td>
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<tr>
<td>• No inhibition of lactation.</td>
</tr>
<tr>
<td>• No estrogen side effects or possible long-term hazards of estrogen.</td>
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<tr>
<td>• Husband cannot interfere with use.</td>
</tr>
<tr>
<td><strong>Advantages of Injectables Compared to IUDs</strong></td>
</tr>
<tr>
<td>• More effective.</td>
</tr>
<tr>
<td>• No pelvic examination or insertion procedure necessary.</td>
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<tr>
<td>• No risk of IUD side effects such as pain, perforations, or infections.</td>
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<tr>
<td>• Heavy bleeding less frequent.</td>
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| **Disadvantages of Injectables Compared to Orals**           |
| • Cannot be immediately withdrawn if harmful or distressing side effects occur. |
| • Greater possibility of disturbed menstrual patterns.       |
| • Possible delay in return of fertility.                     |
| • Self-administration not practical.                         |

| **Disadvantages of Injectables Compared to IUDs**            |
| • Need to return periodically for injections.                |
| • Possibility of disturbed menstrual patterns.              |
| • Possible delay in return of fertility.                    |
| • Carcinogenic issues still unresolved.                     |
Whether injectable progestogens alter the composition of breast milk is uncertain. While one research group found no significant differences in specific gravity, protein content, and fat content between the milk of Depo-Provera users and that of controls (80), another group reported significantly higher milk protein levels and decreased milk lipid and lactose levels (47). The injectable progestogens apparently do not affect the immunologic powers of breast milk (27).

Depo-Provera and/or its by-products (metabolites) can be found in the breast milk of women using the injectable (78), but whether this can affect an infant has not been determined. Radioimmunoassays, used to test for the presence of steroids in breast milk, cannot distinguish between the drug and its metabolites, and it is not known whether the metabolites are physiologically active. There have been no clinical reports of adverse effects on infants whose mothers were receiving progestogens, but additional research is needed on this point.

In a family planning program injectables offer the advantage of quick, easy, and infrequent administration. McDaniel has found that, if a woman returning for an injection has no complaints, she can be processed in 60 to 90 seconds. This includes time for a short interview with a doctor or nurse-midwife, paperwork, and the injection itself (95). Dispensing both Depo-Provera and oral contraceptives, one of McCormick Hospital’s mobile family planning clinics routinely serves 800 women in one day and 1,500 in the next on two stops near Thailand’s border with Burma (93) (see Fig. 8). The six-month regimen saves even more clinic time and resources, but it provides a woman less contact with health personnel should questions or problems arise.

The injectable progestogens can be administered by jet injector (126, 143), and evidence from animal studies indicates that use of the jet may reduce the variation from one woman to the next in the return of fertility after discontinuation (177). Both Depo-Provera and Norgestrel can be stored without refrigeration for up to five years.

Like oral contraceptives, the injectables have a great potential for wider distribution and use. Paramedical personnel can easily give injections. Dropping the requirement that a woman have a pelvic examination before starting an injectable would also broaden its acceptance in many areas, since some women will refuse to seek contraception if pelvic or general physical exams are required (86, 139). In developing countries the benefits of wider distribution of both injectable and oral contraceptives, especially in terms of the potential reduction expected in maternal mortality rates, outweigh the risks (139) (see Population Report A-2). For these reasons McDaniel does not require pelvic exams in his Thailand program.

We feel that furnishing family planning services to a large number of women, without the “luxuries” of general physical and pelvic examinations and cancer detection, is more important and fruitful than serving a few, and discouraging many, in an attempt to cling too rigidly to more academic and professional medical standards (81).

Despite the advantages of injectables, many family planning officials have been reluctant to permit the unrestricted use of Depo-Provera. They have been concerned because the drug could not be withdrawn quickly if a problem arose, although this has not proved a problem in actual practice (94). More importantly, they have feared that Depo-Provera might cause permanent infertility. There has been no proof that injectables can cause sterility, and, if they do, it occurs very rarely. But officials and clinicians are aware not only that undesired infertility could have disastrous emotional and social consequences for the woman involved, but also that the reputation of a family planning program and of family planning itself could be ruined if people thought they had been deceived about the reversibility of the method. Thus, even in countries such as Jamaica, Malaysia, and Thailand, where Depo-Provera is now offered through national family planning programs, restrictions have been placed on its use. In Jamaica, only women whose families are complete may obtain Depo-Provera. The World Health Organization (WHO) has imposed the same restriction on Depo-Provera supplied by UNFPA. The International Planned Parenthood Federation (IPPF), though still without an official policy, unofficially advises its affiliates against giving Depo-Provera to young women with few children (139). In Nairobi, the Family Welfare Center, which obtains Depo-Provera from IPPF, restricts the injectable to women over 30 with five or more children and to those who, with their husbands, sign consent forms (51).

In the Thai National Family Planning Program, a woman using Depo-Provera must have at least two living children and want no more. If, after using the injectable for "a period of time," she still wants no more children, she will be urged to discontinue the injectable and to accept sterilization. The Thai National Ministry of Health hopes that Depo-Provera, a recent addition to the national program, will attract new participants to family planning
Table 5—Usage of Depo-Provera Reported by Family Planning Associations Supplied by the International Planned Parenthood Federation, 1971-74, and Planned IPPF Deliveries, 1975

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<tbody>
<tr>
<td>Africa</td>
<td>7,140</td>
<td>22,526</td>
<td>106,768</td>
<td>129,130</td>
<td>241,000</td>
</tr>
<tr>
<td>Indian Ocean</td>
<td>2,128</td>
<td>9,157</td>
<td>13,030</td>
<td>38,360</td>
<td>77,000</td>
</tr>
<tr>
<td>Middle East &amp; North Africa</td>
<td>0</td>
<td>100</td>
<td>4,055</td>
<td>7,000</td>
<td>13,000</td>
</tr>
<tr>
<td>South East Asia &amp; Oceania</td>
<td>28,460</td>
<td>53,300</td>
<td>83,017</td>
<td>161,874</td>
<td>177,000</td>
</tr>
<tr>
<td>Western Hemisphere</td>
<td>20,331</td>
<td>22,421</td>
<td>35,382</td>
<td>45,932</td>
<td>114,100</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>21,519</td>
<td>23,338</td>
<td>23,082</td>
<td>18,000</td>
<td>18,000</td>
</tr>
<tr>
<td>TOTAL</td>
<td>79,578</td>
<td>130,842</td>
<td>265,334</td>
<td>400,296</td>
<td>640,100</td>
</tr>
</tbody>
</table>

*Sudan only. **Thailand only. *Approximate. **Hong Kong only.*

Sources: IPPF Reports to Donors (56,57,58).

rather than draw women away from sterilization procedures, the number of which has been rapidly increasing recently. Depo-Provera is currently available only at National Family Planning Program hospitals and health centers staffed by physicians—some 300 out of about 4,000 program outlets (180). However, a study has been started to evaluate the use of auxiliary midwives to prescribe and administer the drug.

The McCormick Hospital program in Chiang Mai, Thailand, which was one of the first to offer Depo-Provera, takes a less stringent approach. The only requirement for new acceptors of Depo-Provera is that they have demonstrated their fertility by a previous pregnancy. McDaniel, who directs the program, reports that this requirement "is only to protect the reputation of the program from the accidental giving of Depo-Provera to an already sterile couple" (94).

In Malaysia national family planning officials also have restricted Depo-Provera. The injectable is available through 10 National Family Planning Board (NFPB) clinics with attending medical officers to women who have "already demonstrated their fertility" and have completed their families. The NFPB requires that women receive physical and pelvic examinations before starting Depo-Provera and checks for breast nodules with every injection. Also, they must be told individually about all possible side effects, including menstrual cycle disruption and "possible infertility" (132).

Had USFDA approval of Depo-Provera gone into effect, it would have placed special requirements on the use of the injectable in the USA. In its approval statement the agency wrote that Depo-Provera was intended for "those patients in need of contraception who cannot accept more regimented methods or in whom other alternatives are either contraindicated, unreliable, or otherwise unacceptable." Before a woman could have received her first injection, she would have had to give her consent after reading a brochure which explained the known and suspected side effects and risks of Depo-Provera. Also, pharmacies, private doctors, and family planning clinics would have been required to report back to the Upjohn Company on their distribution or use of Depo-Provera. If harmful effects were later discovered, the company then would have been able to notify doctors, who in turn would have contacted their patients (146). Because USFDA approval never took effect, these requirements were never instituted.

Fig. 9. Partial List of Countries Where Depo-Provera is Available as a Contraceptive Through Commercial Channels and/or Family Planning Programs, 1974-1975

Some countries where Depo-Provera for contraception is available:

**Western Hemisphere:**
- Argentina
- Barbados
- Bolivia
- Chile
- Colombia
- Costa Rica
- El Salvador
- Grenada
- Guatemala
- Honduras
- Jamaica
- Malaysia
- Mexico
- Panama
- Peru
- St. Kitts
- St. Lucia
- St. Vincent
- Surinam
- Trinidad
- Paraguay

**Middle East & Africa:**
- Afghanistan
- Botswana
- Egypt
- Gambia
- Ghana
- Iraq
- Iran
- Kenya
- Lebanon
- Liberia
- Lesotho
- Malagasy
- Mauritius
- Nigeria
- Rhodesia
- Saudi Arabia
- Seychelles
- Sierra Leone
- South Africa
- Sudan
- Tanzania
- Tunisia
- Uganda
- Seychelles

**Far East, South Asia & Pacific:**
- Bangladesh
- Hong Kong
- Indonesia
- Khmer Republic
- Korea
- Malaysia
- New Zealand
- Sabah
- Sarawak
- Sri Lanka
- Thailand
- Philippines
- Pakistan
- Vietnam
- Singapore

**Europe:**
- Belgium
- Denmark
- Federal Republic of Germany
- Federal Republic of Netherlands
- France
- Spain
- Sweden
- United Kingdom
- United States
- Venezuela
- Hungary

Some countries where Depo-Provera for contraception is not available:

- Brazil
- Canada
- India
- Japan
- Japan
- Sweden
- United Kingdom
- United States
- Venezuela

Sources: Heywood (49,50); IPPF (58); Nortman & Hofstatter (116).
Despite caution and restrictions on Depo-Provera, its use has grown in recent years. At least 10 countries now offer the injectable in their national family planning programs, and use for contraceptive purposes has been approved in 64 countries. Two international donor organizations, IPPF and UNFPA, now supply Depo-Provera, but the US Agency for International Development (USAID) does not, since it does not supply drugs which have not been approved by the USFDA for use in the USA.

IPPF is currently the largest international supplier of injectable contraception. In 1975 IPPF plans to provide approximately 640,000 three-month doses of Depo-Provera to family planning clinics in 41 countries (58). This could provide one year of contraception for almost 150,000 women (124). Requests to IPPF for Depo-Provera have grown rapidly over the past several years, both in terms of the number of programs requesting the injectable and the amounts requested (see Table 5). The largest IPPF shipments in 1974 went to Thailand (140,000 three-month doses), Sri Lanka (35,000 doses), Uganda (12,000 doses), Kenya and Costa Rica (10,000 doses each) (58).

UNFPA began supplying small quantities of Depo-Provera in 1972. In 1972 and 1973 UNFPA shipments ranged from 220 to 10,000 doses and went to six countries (19). In 1974, at a cost of $.71 (US) per three-month dose, UNFPA ordered $200,000 (US) worth of Depo-Provera for Thailand, $38,000 (US) worth for Jamaica, and $600,000 (US) worth to be turned over to IPPF for distribution to its affiliates (19, 137).

UNFPA has set aside a small portion of its 1975 contraceptive supplies budget—to up to $200,000 (US) out of almost $4 million—to buy either Depo-Provera or, if WHO gives its approval, Noristerat (Norigest), depending upon which manufacturer submits the lower bid price.

UNFPA also supplies injectable contraception only once, and it does not plan to do so again because of reservations about side effects. In 1974 SIDA provided 100,000 three-month doses of Depo-Provera to Malaysia's national family planning program (164). In 1975 and coming years, the Malaysia National Family Planning Board intends to obtain its supply of injectables from UNFPA (132).

National family planning programs which offer Depo-Provera include those in Jamaica, Guatemala, Thailand, Malaysia, Hong Kong, Khmer Republic (Cambodia), Botswana, South Africa, Rhodesia, and Uganda. The fees for injections which these programs charge to users vary. In Jamaica, for example, injections, like all other contraceptive supplies, are free. In Hong Kong in 1974 the fee ranged from no charge to $1.40 (US) per injection, depending on ability to pay. Other fees per injection in 1974, expressed in US dollars, included: Botswana, $.43; Guatemala, $.50; Khmer Republic, $.30; Rhodesia, $.41; and Uganda, $.70 (121). The new Thai pilot program charges a service fee of $.75 for each injection, as does the McCormick Hospital program (94).

Total Depo-Provera Sales

Through commercial channels and sales to international donors, the Upjohn Company has sold close to 11 million doses of Depo-Provera since 1968. The company's Belgian affiliate, Upjohn S.A. Purus, manufactures the drug for international distribution. Upjohn affiliates in Colombia, Mexico, Korea, the Philippines, South Africa, and Argentina produce Depo-Provera for use within their own countries but do not ship to other nations. The drug is now commercially available as a "contraceptive," "anovulatory agent," or "anti-conception compound" in 64 nations, including 19 Western Hemisphere countries, 13 Middle East countries, 17 African, 8 European, and 7 Far East countries (49) (see Fig. 9).

Though doubts have clouded the history of injectable progestogens and important questions remain unanswered, use of Depo-Provera has grown in recent years. Barring conclusive proof that the injections cause cancer, their use probably will continue growing. In fact, injectables may become the first contraceptives produced by modern technology to win acceptance in the developing countries while lacking approval in most major industrialized nations.

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hydroxyprogestosterone 17-acceptors; new's class of potent proges-