E-ISSN: 2618-0618
P-ISSN: 2618-060X

www.agronomyjournals.com
2024; SP-7(3): 388-393
Received: 20-01-2024
Accepted: 24-02-2024

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Insect growth regulators for insect pest control: A review

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DOI: https://doi.org/10.33545/2618060X.2024.v7.i3Se.504

Abstract
When certain biochemical pathways or processes necessary for insect growth and development are regulated or inhibited, insecticides with growth-regulating characteristics (IGR) may have unfavorable effects on insects. Certain insects exposed to these substances may die as a result of aberrant hormone-mediated cell or organ development regulation. Some insects may perish as a result of either an aberrant termination of the embryonic stage itself or a prolonged exposure to other mortality causes (such as vulnerability to natural enemies, climatic circumstances, etc.) during the developing period. Insect growth regulators can be derived from plants or from a combination of synthetic and natural substances. Nowadays, research is being done on the chemical makeup of naturally occurring insect hormones, with the goal of creating analogs or mimics that will work against insects. The parallels, nevertheless, in some of biochemistry among vertebrates and invertebrates may result in the limited development of IGRs. Contamination of the environment also makes it difficult for businesses to produce substances that offer more ecologically or environmentally sound insect pest control. We considered using insect growth regulators instead of commercial insecticides as part of our ongoing search for novel, physiologically active compounds made from natural sources.

Keywords: Insect growth regulators, insect pests, insect hormones, natural resources

Introduction
The growth, development, and metamorphosis of insects are impeded by substances known as insect growth regulators, or IGRs. Among the non-hormonal substances known as precocenes (Anti JH) and chitin synthesis inhibitors are IGRs, which also comprise synthetic analogs of insect hormones like ecdysoids and juvenoids. An insect's natural hormones that are involved in growth and development are as follows: Activation hormone (AH) is another name for brain hormones. Neutrophils in the central nervous system (CNS) known as neurosecretory cells (NSC) release AH. Juvenile hormone (JH) is produced by activating the corpora allata. 2. Neotinin (JH): Another name for juvenile hormone. Behind the brain of an insect, there are paired glands called corpora allata that release this substance. Their function is to maintain the larvae in their juvenile state. It has been determined that JH I, JH II, JH III, and JH IV belong to distinct insect groups. As the larva matures and pupalises, the concentration of JH falls. While JH III is present in adult insects, JH I, II, and IV are found in larvae and are crucial for the development of the ovaries in adult female insects. 3. Ecdysone: MH stands for moulting hormone. Prothoracic Glands (PTG), which are located next to prothoracic spiracles, release the steroid ecdysone. Insects can only undergo moulting when ecdysone is present.

In adult insects, ecdysone levels drop and eventually become completely missing. Agricultural pesticides have avoided pest damage that could have cost many crops between 5% and 30% of their potential yield; nevertheless, they have caused a number of issues in the field, such as the death of beneficial insects, the emergence of secondary pests, and the emergence of pests resistant to pesticides. Insect Growth Regulators (IGRs) interfere with and disturb the larval and egg stages of an insect's life cycle. IGR, to put it briefly, is a type of "birth control" for pests that works to prevent infestations both now and in future, thus helping to keep pest populations under control.

Discovery of Insect Growth Regulators (IGRs)

The first account of the potential use of IGRs in insect control was in 1956, when juvenile hormone (JH) was isolated from the abdominal crude extract of the male Cecropia moths *Hyalophora cecropia* (L.). Topical application of the hormone prevented metamorphosis and subsequent multiplication of the insect. However, it was not observed until discovery of the "paper factor" in 1965 because the "paper factor" led to an understanding of the potential use of JH in insect development. Researchers at Harvard observed that cultures of the linden bug, *Pyrrhocoris apterus* L., which originally came from Czechoslovakia, had low egg hatch rates and that supernumerary larvae, rather than adults, were formed. Their investigations later showed that the abnormality observed was caused by the material in the paper towels (Scott, brand 150) used in the rearing jars. The active component of the paper towel, which was later identified as juvabione, came from the balsam fir, *Abis balsamea* (L.), the main pulp tree used in the United States paper industry (newspapers, magazines, etc.). Juvabione is a methyl ester of domatuic acid proven to be a very specific juvenile hormone mimic of the hemipteran family Pyrrhocoridae. The discovery of this highly specific substance led to industrial interests in JH as a tool in developing IGRs.

In addition to plant-derived insect growth regulators, other compounds are synthesized based on an understanding of the biochemistry and physiology of insect development, rather than the empirical or random synthesis and screen approach of pesticide discovery. This direct approach, coupled with the available techniques, led to the design or synthesis of more selective analogs with potential compatibility with integrated pest management (IPM) programs.

Major Groups of Insect Growth Regulators

Major Groups of Insect Growth Regulators Since the target sites of common insecticides on insects and mammals are known to be similar, it is desirable to develop insecticides whose primary target site does not exist in mammals for selective toxicity. IGRs may belong to this type of (selective) insecticides and can be grouped according to their mode of action, as follows:

Chitin synthesis inhibitors (i.e. of cuticle formation) and substances that interfere with the action of insect hormones (i.e. JHs, ecdysteroids)

Chitin synthesis inhibitors

The insect cuticle serves as an interface between the living animal and its environment; and forms the exoskeleton, supporting the linings of the gut, respiratory systems, reproductive ducts, and some gland ducts. It consists primarily of protein and chitin fractions. The latter comes in 3 forms, a, b, and g chitin, and is the b-(1,4) glycoside polymer of N-acetyl-D-glucosamine. In additional to the insect and crustacean cuticles, chitin is present in cell walls of fungi and protozoa, but is absent in vertebrates and higher plants. Synthesis of chitin depends on the action of the extra cellular enzyme chitin synthesis attached to the plasma membrane. However, this enzyme is produced as a zymogen (inactive) in the endoplasmic reticulum of the epidermis and has to be activated by proteases for chitin synthesis (Hepburn, 1985) [16]. Since proteases are important for activating chitin synthesis zymogens, these enzymes become potential targets for regulation by certain compounds, along with other key regulatory steps in the biosynthesis of chitin.

The first chitin synthesis inhibitor introduced into the market as a novel insecticide was benzoyl phenylurea, diflubenzuron (Miyamoto *et al*., 1993) [23]. It was considered a potent compound against larvae of common cutworm, *Spedoptera litura* (Fabr.) and *Cydia pomonella* L. Some of the structural modifications (derivatives) of the compound are more active than the parent compound. Aside from Lepidoptera, diflubenzuron has also been effective against Coleoptera and Diptera (G.ktay and Kosmalo 1990) [14]. Diflubenzuron and its derivatives were effective against insect pests and mites infesting field crops, and were relatively harmless to beneficial insect species. On the other hand, buprofezin, another chitin synthesis inhibitor, was used against homopteran pests including nymphs of brown planthoppers, *Nilaparvata lugens* (Stal.), leafhoppers, *Nephotettix cincticeps* (Uhler), whiteflies, *Bemisia tabaci* (Gennadius), and scale insects, Trialeurodes vaporariorum (Westwood), attacking fruit crops and certain species of Coleoptera and Acarina (Asai *et al*., 1985; Ellsworthip and Martinez, 2001) [8, 12]. Lefunuron, an orally administrated chitin synthesis inhibitor, was also used against fleas (Smith, 1995) [29], and it inhibited chitin synthesis and influenced the development of eggs and larvae. Female fleas biting lufenuron-treated animals produced infertile eggs as well as inhibiting larval development when feeding on oflea dirto that contained blood from the treated insect. This observation was probably because of lufenuron, which is not significantly metabolized and is thus excreted into the feces. Different groups of insect growth regulators, such as juvenile hormone analogues, chitin synthesis inhibitors, and one triazine derivative, were tested in a special larvicidal test. The chitin synthesis inhibitors were quite effective against multi-resistant Musca domestica strains, except for one strain with strong resistance against chitin synthesis inhibitors, developed after extensive treatments with benzoylphenylureas for several years (Pospischil *et al*., 1997) [27].

Mode of action of chitin synthesis inhibitors (CSIs)

Most CSIs are primarily used as larvicides. Treated larvae develop until molting, but fail to ecdyse due to inhibition of the synthesis of new cuticle, specifically, chitin biosynthesis. Diflubenzuron, for instance, when directly applied to Manduca epidermal cells *in vitro*, inhibited endocuticular deposition (Miyamoto *et al*., 1993) [23]. Moreover, chitin precursors of Pieris larvae ($_{14}$Cglucose), Manduca larvae ($_{14}$C-glucosamine), Mamestra larvae ($_{14}$C-acetylglucosamine) and Spodoptera (Boisduval) larvae ($_{14}$C-UDP-N- acetyglucosamine) were not incorporated into chitin in the presence of chitin synthesis inhibitors.

Although the precise mode of action of diflubenzuron and other CSIs is still unknown, 3 hypothetical target sites have been proposed, namely: inhibition of chitin synthetase (or its biosynthesis), inhibition of proteases (or its biosynthesis), and inhibition of UDP-Nacetylglucosamine transport through the membrane (Miyamoto *et al*., 1993) [23]. It seems unlikely, however, that the active metabolite hypothesis (*i.e.* action of proteases on zymogens) is correct because studies using diflubenzuron showed fast *in vivo* inhibition of chitin synthesis, while its metabolism in insects was relatively slow.

Although Leighton *et al*. (1981) [19] suggested that diflubenzuron inhibited chitin synthesis (i.e. by interfering with proteolytic activation of the zymogens), neither the presence of such zymogens in insects nor the inhibition of insect proteases has been found. Eto (1990) [13] further indicated that the most probable mechanism proposed is the disruption of the accessibility of the substrate. This hypothesis was demonstrated in a study using isolated *Mamestra brassicae* (L.) larval midgut tissue (Mitsui *et al*., 1984) [21]. It was shown that diflubenzuron

inhibited the incorporation of 14C-labeled glucosamine or NÐ acetylglucosamine into the chitin of the peritrophic membrane, when applied to either side of the insect midgut epithelial cell layers. However, when UDP-N-acetylglucosamine was applied inside the midgut, diflubenzuron did not inhibit chitin biosynthesis. These results suggested that the compound interferes with the transport system of UDP-N-acetylglucosamine across the biomembrane (Eto, 1990) [13]. The release of UDP-Nacetyl glucosamine from the epithelial cells was inhibited by diflubenzuron (Mitsui *et al*., 1984) [21]. Similarly, *in vivo* chitin synthesis from N acetylglucosamine of *N. lugens* nymphs was selectively

IGRs used in pest management

Ecdysoids

These compounds are synthetic analogues of natural ecdysone. When applied in insects, kill them by formation of defective cuticle. The development processes are accelerated bypassing several normal events resulting in integument lacking scales or wax layer.

Juvenoids (JH mimics)

They are synthetic analogues of Juvenile Hormone (JH). They are most promising as hormonal insecticides. JH mimics were first identified by Williams and Slama in the year 1966. They found that the paper towel kept in a glass jar used for rearing a Pyrrhocoris bug caused the bug to die before reaching adult stage. They named the factor from the paper as “paper factor”or “juvabione” They found that the paper was manufactured from the wood pulp of balsam fir tree (*Abies balsamea*) which contained the JH mimic. Juvenoids have anti-metamorphic effect on immature stages of insect. They retain status quo in insects (larva remains larva) and extra (super numerary) moultings take place producing super larva, larval-pupal and pupal-adult intermediates which cause death of insects. Juvenoids are larvicidal and ovicidal in action and they disrupt diapause and inhibit embryogenesis in insects. Methoprene is a JH mimic and is useful in the control of larva of horn fly, stored tobacco pests, green house homopterans, red ants, leaf mining flies of vegetables and flowers.

Potential Effects of IGRs on Non-Target Organisms (NTOs)

Chitin synthesis inhibitors

Chitin is a very important constituent of the cell walls of fungi and green algae, and in the integuments of invertebrates (arthropods), but it is absent among vertebrates. Since arthropods share a similar molting process, species-specificity to chitin synthesis inhibitors is less pronounced than that of JHAs (miyamoto *et al*., 1993) [23].

Among the species in aquatic ecosystems affected by IGRs, crustaceans and a few other aquatic species are the endangered organisms sensitive to chitin synthesis inhibitor applications. This is because insects and crustaceans contain the same molting hormones. For instance, diflubenzuron (at ppm levels) affected the survival, larval development, regeneration and reproduction of macrocrustaceans (Nimmo *et al*., 1980) [26]. Miura and Takahashi (1974) [22] reported that crustaceans and shrimp were extremely sensitive to diflubenzuron, showing LC50 of about 0.1-1.0 ppm, which is comparable to the mosquito LC50 of about 0.7 ppm. In addition to the direct effects of CSIs in aquatic ecosystems, the reduction of aquatic organisms (which are an important component in the food chain) shifted the feeding habits of other species. The bluegill sunfish, Lepomis macrochirus Rafinesque, shifted its feeding habits from feeding on cladocerans (e.g. crustaceans) and copepods to chironomid midges and terrestrial insects (Ables *et al*., 1977) [6].

The effects of diflubenzuron on terrestrial NTOs, however, tend to be minimal compared to the effects of conventional insecticides. Adults of *Trichograma pretiosum* (Riley), *Apantels marginiventris* (Cresson), and *Voria ruralis* (Fallen) as well as the survival of the F1 generation were not affected (Wilkinson *et al*., 1978) [5]. A decrease in egg hatch was observed in the lacewing Chrysopa carnea Stephens, and in the nymph survival of *Gaucheries punctipes* (Say) due to diflubenzorun treatment (Apperson *et al*., 1978; Medina *et al*., 2002) [7].

In addition to the diflubenzuron effect on terrestrial NTOs, 2 ecdysone agonists, halofenozide and methoxyfenozide, caused premature induction of larval molting and incomplete pupation in affected larvae of the multicolored Asian lady beetle, *Harmonia axyridis* (Carton *et al*., 2003) [1].

Juvenile hormone analogs

Methoprene (Altosid ¨EC4) showed no adverse effects on Rotifera, Platyhelminthes, Nematoda, Mollusca, Arachnida, or Pisces. Field applications do not produce long-term disruptions in the population levels of crustaceans, altough at multiple applications of 302g a.i./ha to experimental ponds, it significantly affected the populations of certain aquatic insects (e.g. the mayfly, *Callibaetis pacifucis Seeman*, the dytiscid beetle, *Laccophilus* sp. and the hydrophilid beetle, *Tropisternus lateralis* (F.) (Norland and Mulla, 1975).

With respect to predators, the lacewing, Chrysopa carnea Stephens, and lygaeid bug, *Geocoris punctipes* (Say), tolerated high doses of JHAs. However, the lady beetle *H. convergens* and *Coccinella septempunctata*, were sensitive to many JHAs (Hodek *et al*., 1973; Kosmalo and Erkin, 1984) [17-18]. In other studies, the effects of JHAs were enhanced depending on the methods of application. For instance, the topical application of methoprene did not affect the predaceous mite *Amblyseius brazilli* except at concentrations as high as 1000 ppm, but with methoprone-treated pollen at 100 ppm egg laying was inhibited (El-Banhawy, 1977) [11]. Similarly, JHAs did not show significant adverse effects on parasites. The LD50 for eggs of the gypsy moth, *Porthetra dispar* L., was 6.3 ng/egg, but the dose that produced deleterious effects on the egg parasites, *Ooencyrtus kuwanai* (Howard), was 63 ng/egg (Granett and Wesoloh, 1975) [15]. *Hydroprene*, *triprene*, and kinoprene were found to adversely affect Aphidius nigripes Ashmead, the parasitoid of the potato aphid, *Macrosiphum euphorbiae* Thomas (McNeil. 1975) [20], but the overall adverse effects of JHAs on parasitoids were less than those of broad-spectrum conventional insecticides.

Many highly eusocial bees such as honeybees (Apinae) and stingless bees (Meliponinae) practice age polyethism, in which different groups of individuals perform a different ensemble of tasks as they age. Young workers, for example, are responsible for brood and queen care and nest maintenance, while older workers are involved in foraging activities. Since JH is involved in the regulation of age polyethism in the honeybee, *Apis mellifera* L. (Robinson and Ratnieks, 1987) [28], it is probable that JHAs will have adverse effects on this species. Indeed, the topical application of 200 µg methoprene to adult worker honeybees caused a premature shift from the brood nest to food storage region, precocious foraging behavior, and premature production of alarm pheromones. At the same time, efficient pollination of insect-pollinated crops can be achieved due to the induced foraging effects of JHAs. Although treatment significantly shortened the life span of worker honeybees

(Robinson, 1985) [28], bumble bee broods fed with a sucrose solution containing pyriproxyfen or fenoxycarb developed normally (De Wael *et al*., 1995) [2].

Neem-or AZ based IGRs are highly selective, but their potential adverse effects on beneficial organisms cannot be discounted. Isolated cases of ecdysial failure in certain parasitoids were reported. However, this type of IGR is generally safe for non-target and beneficial organisms (e.g., honeybees, parasitic wasps, spiders, earwigs, ants, and predaceous mites) (Mordue and Blackwell. 1993) [25].

Chitin synthesis inhibitors

Benzoyl phenyl ureas have been found to have the ability of inhibiting chitin synthesis *in vivo* by blocking the activity of the enzyme chitin synthetase. Two important compounds in this category are Diflubenzuron (Dimilin) and Penfluron. The effects they produce on insects include: Disruption of moulting, Displacement of mandibles and labrum, Adult fails to escape from pupal skin and dies and Ovicidal effect. Chitin synthesis inhibitors have been registered for use in many countries and used successfully against pests of soybean, cotton, apple, fruits, vegetables, forest trees and mosquitoes and pests of stored grain

A new approach to insect pest control is the use of substances that adversely affect insect growth and development. These substances are classified as "insect hormone mimic" or "insect growth regulators" (IGRs) owing to their effects on certain physiological regulatory processes essential to the normal development of insects or their progeny. They are quite selective in their mode of action and potentially act only on target species. The action of IGRs, however, should not be confused with other synthetic insecticides, such as organophosphates and carbamates, since these chemicals interfere with other physiological processes but do not regulate the development of normal insects. An IGR, therefore, does not necessarily have to be toxic to its target, but may lead instead to various abnormalities that impair insect survival (Siddall, 1976) [4]. Interestingly, most of the IGRs that have shown effectiveness against insect pests cause the rapid death of the insect through failure of a key regulatory process to operate or function. IGRs generally control insects either through regulation of metamorphosis or interference with reproduction (Riddiford and Truman, 1978) [3]. Compounds developed to disrupt metamorphosis ensure that no reproductive adults are formed. Those that specifically interfere with reproduction may include the development of adults with certain morphogenetic abnormalities that reduce their reproductive potential. Adults may be sterile or possess abnormally developed genitalia, which hinders the mating process or the capacity to produce fertile offspring. Chitin synthesis inhibitors, the insect cuticle serves as an interface between the living animal and its environment; and forms the exoskeleton, supporting the linings of the gut, respiratory systems, reproductive ducts, and some gland ducts. It consists of protein and chitin fractions. In the 1970, Benzoyl phenyl ureas, compounds with high degree of selectivity and low mammalian toxicity were discovered by scientists at Philips-Duphar, Netherlands. Actually it was a attempt for development of weed control agent but the product was found to be more effective as an insecticide showing delay in toxicity when the insect next molted.

Because CSIs interfere with the polymerization of chitin, this mode of action has been targeted for control of several different insect pests. CSIs cause abnormal deposits of endocuticle that accumulate during molting, specifically uridine diphospho-N-acetylglucosamine monomers thereby preventing chitin synthesis. This produce a weakened cuticle and causes mortality when the pro-cuticle is subjected to the stresses of ecdysis and cuticular expansion. Consequences of CSI toxicity also include mortality in the absence of metamorphosis and include swollen appendages, decrease in locomotion, inability to eat due to dislocation of mandibles, malformed or absent peritrophic matrix, as well as suppressed fecundity and egg viability.

Benzoyl Phenyl Ureas (BPU)

Benzoyl phenyl urea, an important type of insect growth regulators, acting on the larval stages of the Lepidoptera insects by inhibiting chitin synthesis have been rapidly developed after the introduction of the first benzoyl phenyl urea diflubenzuron in 1972. Besides diflubenzuron, hexaflumuron, lufenuron, penflzuron, noveluron, tefluenzuron and chlorfluazuron were some of other widely used IGRs. Benzoyl phenyl urea have a unique mode of action coupled with a high degree of activity on target pests and low toxicity to non-target organisms, that is why they have attracted considerable attention for decades and have become a new tool for integrated pest management.

The *in vivo* or in situ (isolated integument incubated in a tissue culture medium) studies showed that chitin synthetase catalyzing the incorporation of UDPN-acetylglucosamine (UDP NAGA) to chitin was clearly inhibited by BPUs. However, all of the subsequent studies trying to prove some action of BPUs on any part of the chitin synthesis pathway in insects in cell free systems (rather than *in vivo* and in situ) failed. In addition, BPUs showed no inhibitory actions on fungal chitin synthetase *in vivo* as well as in cell free systems, which have roughly equivalent chitin synthesis pathways as insects. Therefore, the action mechanism of BPUs remained unanswered.

Moulting hormones

The brain/molting hormone ecdysone initiates the molting process and induces metamorphosis.

Precocenes

The compounds which would antagonize the insect hormone activity and derange the insect‟s development are called as "Precocenes" because of their ability to induce precocious metamorphosis of the immature insects. The mode of action of precocenes seems to be the prevention of JH biosynthesis corpora allata, since application of exogenous JH can reverse their action.

IGRS from neem

Leaf and seed extracts of neem which contains azadirachtin as the active ingredient, when applied topically causes growth inhibition, malformation, mortality and reduced fecundity in insects.

Hormone mimics from other living organiss

Ecdysoids from plants (Phytoecdysones) have been reported from plants like mulberry, ferns and conifers. Juvenoids have been reported from yeast, fungi, bacteria, protozoans, higher animals and plants.

Resistance to Insect Growth Regulators

There were predictions that insects could not become resistant to their own hormones, since no demonstrable proof of the evolution of any new JH by insects has been advanced (Bowers, 1990) [10]. According to laboratory experiments, however insects can develop resistance to JHAs. However, no serious field resistance to JHAs has been reported to limit their use in pest

control. Cross-resistance between organophosphates, benzoylphenylureas or diflubenzuron has been suspected among organophosphate-resistant populations of the codling moth, *Cydia ponomella* (L.) (Moffit *et al*., 1988) [24]. Zhang *et al*. (1998) [30] also investigated cross-resistance to IGRs in the pyriproxyfen-resistance housefly, Musca domestica populations. They showed that although the housefly which possessed 880-fold resistance to pyriproxyfen had no cross-resistance to diflubenzuron, it showed medium cross-resistance to 2 other juvenile hormone analogs, fenoxycarb and methoprene. Elbert and Nauen (2000) [31] tested buprofezin and pyriproxyfen against second instar nymphs and eggs of the tobacco whitefly, Bemisia tabaci. Their results showed there was lower buprofezin resistance while pyriproxyfen resistance was not obvious. The ineffectiveness of diflubenzuron in controlling the tufted apple bud moth, *Platynota idaeusalis* (Walker), was attributed to the increased levels of enzymatic detoxification, which were also observed in organophosphate-resistant insects (Biddinger *et al*., 1996) [9]. The resistance in these chitin inhibiting types of IGRs indicated that multi-resistance factors (generally enzymatic detoxification) that allow insects to metabolize various groups of insecticides may confer some cross resistance to benzoylphenylureas and probably other IGRs. The carboxylesterase activity that contributed to the resistance of the tufted apple bud moth to organophosphates may also be important in conferring resistance or tolerance to diflubenzuron in various strains of the tufted apple bud moth (Biddinger *et al*., 1996) [9].

Conclusion

Most synthetic insecticides are toxic to all animals including human beings. Although many insecticides can be used safely, a few are persistent in the environment and a small number have multigenic, carcinogenic and teratogenic effects on human beings and domestic animals. Furthermore their magnification in the food chain sometimes threatens non-target organisms. These facts have become of deep concern to agricultural and health scientists, producers and consumers alike. Based on the previous discussion, IGRs represent the newest of all approaches to operational and commercial insect control. Their species or stage-specificities that were higher than those of conventional insecticides offer a good alternative for a selective insect pest control that is in harmony with existing IPM programs. IGRs generally have a good margin of safety for most non-target biota including invertebrates, fish, birds, and other wildlife. They are relatively safe for human beings and domestic animals. Although CSIs are broad-spectrum compounds, the mode of action between the targets and non-target organisms (e.g., crustaceans) should be considered. Similarly, JHAs are generally selective, but the last stage of some NTOs will potentially suffer morphogenetic effects or anomalies, while crustaceans will probably have defective reproductive systems (albeit reversible).

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