HORMONES AND THE TREATMENT OF STERILITY IN DAIRY CATTLE: A REVIEW*

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During the past few years considerable attention has been paid to the use of hormones as means of correcting infertility in live stock. In many animals in which disease is not very evident, derangements of the normal estrous cycle occur which should be amenable to this type of treatment. These include cases in which the cycle does not occur at all, possibly because the anterior pituitary gland is not functioning correctly or because the corpus luteum persists, preventing the regular cycle of events. Another type of hormonal disorder is found in the nymphomaniac in which the Graafian follicle fails to rupture and becomes cystic, thus causing the cycle to be interrupted. It also has been suggested that many cows with fairly regular cycles fail to conceive or to carry their calves to term because the corpus luteum or the uterus is not performing its function efficiently. Further, it has been suggested that resistance to diseases of the genital tract may be increased in some instances by reinforcing the normal hormonal mechanism. In this review, a list of the hormones available, their major functions and their best sources is given. This is followed by a statement of the point of view adopted by the writer and by an analysis of reports of the attempted use of these hormones in experimental work and in the field. This last part of the review deals with these problems as they are seen to occur in the field, i.e. the clinical condition is the basis of classification of the literature. As this part of the review is developed, certain gaps in our knowledge are pointed out as suggestions of the lines along which further data should be sought if progress is to be made. At the outset, it may be stated that the greatest need at present is for good assay methods so that hormone levels may be determined on individual cows. This is an important requisite if rational hormonal treatment is to become possible. Too much of the work, so far, has been along empirical lines, due not to shortcomings in the investigators but to their lack of effective tools.

HORMONES AVAILABLE

I. Anterior pituitary gonadotrophes
   a. Follicle stimulating hormone, causes growth of the Graafian follicle (after an antrum has been established) and spermatogenesis. Best source, horse pituitary; very little in cattle pituitaries, and not much in sheep or hog pituitaries.
   b. Luteinizing hormone, causes ovulation of a ripe Graafian follicle and formation of the corpus luteum, and also causes the cells of Leydig to secrete testosterone in the male. Best source, sheep and hog pituitaries.

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c. Prolactin, causes the corpus luteum to secrete progesterone. No known function in the male.

These hormones are proteins and are not likely to be synthesized for a long time, so the only source is from pituitary glands. Extracts of the glands contain a mixture of these hormones. Prolactin is separated from the others fairly readily and can be purified with relative ease. The other two are not separated readily and pure preparations, though they have been made, are not available. The writer's experience has been that pure luteinizing hormone can be prepared but not in sufficient quantity for use. Follicle-stimulating hormone is so soluble that it is not readily obtained pure. McShan and Meyer (34) destroy the luteinizing hormone of extracts by tryptic digestion which leaves the follicle stimulator more or less unattacked.

II. Other gonadotrophins

a. Chorionic gonadotrophin from the urine of pregnant women. Entirely luteinizing in its action.
b. Human ovariectomy or menopause urine. Entirely follicle stimulating in its action.
c. Equine gonadotrophin from the blood serum of mares between 45 and 150 days of pregnancy. Entirely follicle stimulating in its action.

One of the main difficulties in the use of gonadotrophic hormones in animals with their pituitaries intact (a method of procedure which is obligatory in therapy) is that all these hormones are acting in the presence of the animal's own pituitary hormones which tend to modify the activity of the injected material. Also, by their action on the ovary or testis, the balance is altered for better or worse.

III. Sex steroids.

a. Estrogens. These hormones, secreted by the theca interna cells of the Graafian follicle and by the placenta, cause the psychic symptoms of heat, increase the blood supply to the endometrium, activate the myometrium and reduce the alkalinity of the vaginal secretion, thus promoting the liquifaction of the uterine seal. Estradiol is the most potent, then estrone and estriol. They are slightly soluble in water and much more so in oil, and usually are injected in the latter medium. This causes slow absorption and, in practice, as they are given as esters (e.g., estradiol monobenzoate) absorption is very slow, indeed. These hormones also cause the pituitary to change from follicle stimulating to luteinizing hormone secretion.

b. Progesterone, secreted by the corpus luteum, causes glandular growth of the endometrium and, in general, inhibits the activity of estrogens. It also is essential for the implantation of the embryo and probably is essential in the cow for the maintenance of pregnancy for the greater part of the period of gestation.

c. Androgens. These are secreted by the cells of Leydig of the testis. They are responsible for sexual desire and for the maintenance of the accessory
sex organs in the male. Testosterone is the most powerful, followed by andro-
sterone.

All these natural steriods are obtained from animal sources, estrogens from
pregnancy urine, androgens from the urine of males and progesterone from
corpora lutea. They also are synthesized, especially in the case of progesterone,
beginning with certain sterols of vegetable origin. The use of natural estrogens
rapidly is being replaced by the synthetic estrogens of group IV, below.

IV. Synthetic estrogens.

These do not occur in nature and are relatively simple in structure. They
also have the advantage that they may be fed, not being destroyed in the gut as
are the natural estrogens to a large extent. They have the biological properties
of the natural estrogens.

a. Diethylstilbestrol (stilbestrol).
b. Hexestrol.
c. Octofollin.
d. Dienestrol, now being tried extensively, as it is more water soluble than
the preceding and consequently is absorbed more easily, with a correspondingly
more rapid and shorter action.

Our experience with diethyl stilbestrol has been that it is so slowly ab-
sorbed and excreted that it has a prolonged action, which may be detrimental
to the return of normal sexual function. All the estrogens, both natural and
synthetic, if given over a sufficiently long period cause nymphomania, with the
usual symptoms, sinking round the tail head and liability to bone fracture,
found in chronic cases. If given in pregnancy in sufficiently large doses, they
cause abortion.

V. Other hormones

a. Oxytocin. This hormone, secreted by the posterior pituitary gland, causes
the myometrium to contract. It is used either as such, or in the crude prepa-
ration, pituitrin, to hasten birth or to expel the retained placenta. Estrogens,
by their action in stimulating the spontaneous activity of the myometrium, have
much the same effect.

b. Thyroxin. This hormone, secreted by the thyroid gland, controls the
basal metabolism and thus is essential for the efficient function of every cell of
the body. There is evidence from gynecology that hypothyroidism often is as-
associated with infertility, so this hormone must be considered in any account of
hormone therapy. A synthetic form, thyroprotein, is available. It has the ad-
antage over most hormones that it is not destroyed by the digestive juices, so
it may be fed to the animal to be treated.

THERAPEUTIC USE OF HORMONES

The philosophy of the writer regarding the therapeutic use of hormones in
the treatment of infertility stems largely from observations in an experiment
made to test the usefulness of estrogens for this purpose (Asdell et al., 7). In
this work, cows free from brucellosis, with no obvious signs of disease or abnormality and with fairly regular heat periods were treated with estrogens. The reason for selecting this method of treatment was that, since heat periods were fairly regular, the pituitary and ovaries probably were functioning normally but that the uterus was at fault. Estrogens were indicated since they increase the blood supply to the endometrium, thus giving a chance for better nutrition of that organ, and since they also stimulate the myometrium, thus improving the chance of normal function if that part of the uterus were at fault. The cows were bred naturally whenever they were in heat. Forty-two per cent of the treated cows conceived, but a control group had been included in the design of the experiment, and, of these, 50 per cent conceived in a fairly reasonable time. It is obvious that both in field trials and in experimental work this factor of spontaneous recovery must be taken into account. Adequate controlling is essential and it very rarely is found. The extent to which spontaneous recovery may affect the deductions varies with the criterion of sterility. Diagnosis of sterility by one veterinarian was followed by 12.5 per cent of spontaneous recovery; in our experiment, which may be regarded as fairly typical of the usual diagnosis in the type of infertility treated, the spontaneous recovery rate was 50 per cent; spontaneous recovery following diagnosis by another veterinarian was 85 per cent. This variation emphasizes the need for adequate controls in each trial which is made.

Further reflection pointed to the lack of logic in injecting hormones in empirical amounts when no information was available concerning the normal requirements of the cow and little on what various doses do to the cow's reproductive tract. Since that time, this situation has been corrected to a certain extent and the present knowledge on this subject has been brought together by Asdell (6).

Autopsy of the cows which did not conceive showed that, in most cases, disease of an erosive type had been present in the uterus, had damaged the cotyledons and then had cleared up. This also was borne out by the rather high abortion rate in the cows which conceived. Experience in this and in other instances leads the writer to believe that hormonal dysfunction is usually the result of disease factors which have upset the normal balance. In many cases, the structural damage which has been done is such that repair cannot be made. Primary hormonal imbalance in dairy cattle is by no means common. Functional sterility usually is the result of disease or of malnutrition.

In some types of infertility, the number of services needed for conception after treatment may be used with caution as a criterion of success, but even here a controlled experiment is preferable.

There has been too much tendency to apply hormones to all types of infertility on a shotgun basis without attempting to fit the treatment to the symptoms. As a result of this and due to the lack of controls, most of the work that has been done, both in the laboratory and in the field, must be taken with considerable reserve. In the account which follows, an attempt has been made to assess the reliability of the information given bearing this in mind. The method
of presentation is to consider different types of infertility separately. In practice, a combined therapy aimed at elimination of the casual agent and at rectification of the hormonal imbalance is indicated, but where this method has been used, assessment of the value of the hormonal therapy becomes problematical.

Generally speaking, the earlier literature is far more optimistic than the more recent. The earlier workers, particularly those on the European continent, often report "cures," apparently meaning that the symptoms have disappeared without indicating that the all-important conception has followed. Furthermore, in many reports, including recent ones, a few case histories are given describing successful treatments but with no reference to unsuccessful attempts.

THE FREEMARTIN

Attempts by the writer to modify the freemartin by the injection of estrogens have failed. In the four cases examined, the Mullerian ducts had lost the power of response to estrogens. As the gonad usually is a rudimentary cryptorchid testis, treatment with gonadotrophes is not indicated. Small gonads with ovarian stroma, but devoid of germinal epithelium, sometimes are observed but probably would not respond to gonadotrophes sufficiently to become functional.

INFANTILE OVARIIES

Infantile ovaries, with the consequent failure of the accessory organs to develop, are due to a variety of causes. They may be due to late development, genetic in nature, or to failure for other reasons not yet understood, but usually the condition follows malnutrition in early life. The condition seems to be more frequent in more northern latitudes and lack of sunlight may be a factor. This may not be the primary factor involved, since high latitudes suffer from prolonged winters with consequent lack of succulent feed and a prolonged dry feeding period. The condition usually is found in heifers towards the end of winter, and it often is diagnosed when a number of heifers have been running with the bull and a check discloses very few conceptions. This means that treatment usually is initiated in early spring, when feed and climatic conditions are improving. Successes are credited to the treatment without sufficient basis.

The logical treatment is to inject a gonadotrophic preparation, preferably one with follicle stimulating properties, such as equine gonadotrophin or horse pituitary. The reaction of the normal heifer calf before puberty has been investigated by Casida et al. (15) who used pituitary extracts, both fractionated and unfractionated. They found that a calf whose ovarian follicles had not developed antra failed to respond. A similar result has been obtained by Smith et al. (50) in the rat. Further investigation may show that this is a serious limitation to the activity of gonadotrophes. Casida et al. (15) also found that there is a real danger of producing superovulations and that the eggs shed have a poor capacity for fertilization. Zawadowsky and Eskin (59) have found that conceptions are rare in cows inseminated at the first heat following the injection of chorionic gonadotrophin (prolan). However, if the reproductive system
can be stimulated sufficiently, spontaneous ovulations subsequent to the induced one should be normal.

Most of the earlier workers used gonadotrophins, but the later ones have been relying upon the synthetic estrogen, diethylstilbestrol. The mode of action, if any, of this hormone is obscure. Several workers suggest that it acts by "jolting" the anterior pituitary, causing it to initiate a normal rhythm in the reproductive tract. Comment on this is reserved until the experimental results have been given.

Pighini (43) treated one heifer by grafting anterior pituitary tissue and injecting a crude anterior pituitary extract. She conceived. Asdell (5) treated 2 heifers with a crude anterior pituitary extract from sheep and both conceived, but not until they had been on grass for some time. Eisenbach (21) treated 15 heifers with 125 R.U. of chorionic gonadotrophin and 87 per cent conceived. Amilcare (3) treated 1 heifer with 325 R.U. of chorionic gonadotrophin without effect. Bottomley et al. (11) treated one heifer with chorionic gonadotrophins without result. Teunissen (55) treated 42 heifers with chorionic gonadotrophin; 26 came in heat and 18 conceived. He also treated 16 with equine gonadotrophin; 9 came in heat and 5 conceived. This gives 78 heifers treated with gonadotrophes with a pregnancy rate of 55 per cent.

Steinach et al. (53) treated 19 heifers with estradiol benzoate (Progynon B), 50,000 M.U. in one injection. Of these, 95 per cent came in heat within 2-4 days and 53 per cent conceived. Anderson and Bugg (4) injected 15 mg. of diethylstilbestrol dipropionate (the usual form in which this hormone is administered) into six heifers with small inactive ovaries. One came in heat, but none became pregnant. Allen (21) injected 18 heifers with the same substance and seven became pregnant. He notes that if heat was observed after the injections the chances of success were good and that the less the bodily development the poorer the outlook. Wright (56) injected 23 heifers with from 1,500 to 3,000 I.U. of stilbestrol; 5 came in heat and none conceived. It is not clear how long Wright persisted in his attempt to obtain pregnancy. Entirely negative results in experiments or trials of this nature are as difficult to explain as is 100 per cent success. If his report is omitted, 43 cows have been treated with estrogens with 40 per cent success.

On the basis of published results estrogen treatment of cows with infantile ovaries has been less successful than gonadotrophin treatment. Casida et al. (15), in their work with normal heifers, found the most successful treatment to be an initial injection of a follicle stimulator followed by an injection of luteinizer. This is a rational treatment, but it has not been followed in the field so far as published results show. Indeed, most workers have relied entirely upon luteinizer.

The idea that stilbestrol jolts the anterior pituitary into action is not supported by the results of this form of therapy. The effect of this substance upon the pituitary of the immature animal has not been worked out. More information is needed along these lines and also more is needed upon the condition of
the ovaries of those heifers which show no response, if there be one, to any form of therapy.

HYPOPLASTIC OVARIAN IN THE ADULT

The condition of ovarian hypoplasia in the adult has points of similarity to that of infantile ovaries, but the condition found seems to be more variable. One cause is malnutrition. The ovaries may vary from a condition in which small follicles are present, without heat periods and ovulations, to a complete fibrous degeneration. The rational hormonic treatment is to inject a follicle stimulator, and, in some cases, this is reinforced by the classical massage treatment. Reports on treatment are numerous. Perhaps it might be as well to begin their consideration with a report by Clark (16) that of 15 treated by massage alone, 14 conceived.

Spieler (51) treated ten cows with a mixed estrogen and anterior pituitary preparation (hormovilat) and nine conceived. Asdell et al. (7) treated three cows with a sheep anterior pituitary extract and two conceived. Hupka and Majert (27) gave 60 cows one or two injections of 125-200 R.U. of prolan (chorionic gonadotrophin), a very small dose by more recent standards, and 62 per cent came in heat, while 47 per cent conceived. They also report the injection of 20 cows, with 90 per cent in heat after one to five injections. Betti (10) treated nine cows of which eight were "cured." Amilcare (3) treated eight cows with 125 R.U. of prolan and all conceived. Eisenbach (21) treated six cows similarly and all were "cured." Menzani (35) treated 25 cows and 96 per cent came in heat. Pataki (42) treated 19 cows and 84 per cent came in heat. Koch (31) treated 34 cows which had anaphrodisia, a sequel to hoof and mouth disease. They received 250 R.U. of prolan, and conception at the first mating was recorded in 19 of them. Bottomley et al. (11) treated 19 cows and 6 conceived. Haisch (25) treated 12 and 11 conceived. Teunissen (55) treated 32 cows and 10 conceived. This gives a record of 165 cows treated with chorionic gonadotrophin with 50 per cent conceptions.

Kedrov (29) reports heat after treating cows with atrophic ovaries caused by underfeeding. His treatment consisted of injecting 1,000 M.U. of equine gonadotrophin, and he remarks that few of them conceived. Teunissen (55) treated two cows with the same type of preparation and both conceived.

Treatments with estrogens also have been numerous. Murphey et al. (38) treated two cows with an estrogen extract and both conceived. Steinach et al. (53) treated 66 cows by injecting 50,000 R.U. of estradiol benzoate (Progynon B) and 95 per cent came in heat. Bennewitz (9) gave 18 cows the same treatment; all came in heat and 54 per cent conceived. Ratti (46) reported heat in 44 of 55 cows similarly treated. Klüpper (32) reported 36 treated with 20 in heat and 14 pregnant with another estrogen (Unden). Allen (2) treated four cows and obtained four pregnancies, while Mirskaja and Kedrov (36) treated one group of seven cows with 16 to 30 mg. of stilbestrol and reported six in heat and one pregnancy. They treated 16 cows which did not come in heat after parturition in a similar manner. Four of these ovulated but only one
conceived. Teunissen (55) treated four with another estrogen (Dimenformon) without success. Finally, Zollinger (6) treated 36 cows with stilbestrol and 58.8 per cent conceived. The total number of cows treated with estrogens is 123 and, of these, 53 per cent conceived.

Amongst miscellaneous types of hormone treatment of this type of infertility may be mentioned a report by Deubler and Barnes (19), who treated 19 cows by injecting an extract of one or two ovaries or by feeding extracts of two ovaries in a capsule. Eighteen of these cows came in heat, but, as natural estrogens are not absorbed from the gut in small doses, the successes cannot have been due to estrogens. Stäheli (52) treated 51 cows by transplanting one or two ovaries. Of these cows 85 per cent came in heat and 61 per cent conceived. Frei and Stäheli (23) treated nine cows with “vethormone” of which six came in heat and five conceived. This substance is a mixture of ovarian, pituitary, thyroid and pancreatic hormones.

**SUBESTRUM**

The English workers have described a condition which they term “subestrum.” Animals which are classified thus do not come in heat, and small follicles are present in the ovaries but no corpora lutea. It appears to be a mild form of ovarian hypoplasia, and the type of treatment suggested should be the same as for that disorder.

Pataki (42) treated nine cows with 62 to 125 R.U. of chorionic gonadotrophin and seven conceived. Jensen (28) combined this treatment with uterine douches and ovarian massage. Of 47 cases treated, 46 came in heat and 79 per cent conceived. Zavadovskii (58) treated 92 cows with equine gonadotrophin. Heat was recorded in 56 and pregnancy in 39. Wright (57) treated 18 cows with 15 to 25 mg. of stilbestrol. Seven came in heat regularly after the treatment but none conceived. Durrell (20) treated twelve with semen in the cervix and three conceived. A cow treated with equine gonadotrophin conceived, but with testosterone propionate only one of six became pregnant. One cow treated with progesterone conceived.

**PERSISTENT CORPORA LUTEA**

The usual treatment for persistent corpora lutea is to remove these bodies by squeezing them from the ovaries. In some cases, attempts have been made to treat with hormones. Spieler (51) used an anterior pituitary extract in 20 cases with 14 conceptions. Hupka and Majert (27) treated ten with small doses of chorionic gonadotrophin and seven came in heat. Menzani (35) used the same treatment in 20 cases, and 13 cows came in heat. Eisenbach (21) reported all cured with 21 treatments, while Teunissen (55) obtained three pregnancies in six treatments with the same substance. Cameron (12) treated 46 cows with equine gonadotrophin. Twenty-one came in heat, and he obtained some pregnancies.

Estrogens also have been used in this condition. Bennewitz (9) treated 15 cows with 50,000 R.U. of estradiol benzoate (progynon B); 94 per cent came
in heat, 75 per cent conceived, and 20 per cent became nymphomaniac. Küpper (32) treated 13 cows with a similar dose (Unden) and obtained seven pregnancies, mostly after one to two sterile matings. Mirskaya and Kedrov (36) treated 13 cows with estrogens but no pregnancies resulted.

**ABSENCE OF HEAT, CAUSE NOT GIVEN**

These cases of anaphrodisia may be due to ovarian hypoplasia or to persistent corpora lutea. Hancock (26) treated six cows with chorionic gonadotrophin and three conceived. Murray (39) used equine gonadotrophin (1,500 I.U.) in 19 cases, and 9 of these showed ovarian reaction. He also treated 35 cows with stilbestrol (20 mg.). Heat followed in a large proportion, but only one conceived. Glenney (24) also treated 12 with stilbestrol and two pregnancies resulted. Lentz (33) treated six with estrogens (folluelit) and four conceived.

**NYMPHOMANIA**

Nymphomania usually is treated by removal of the follicular cysts which cause the condition. In cases of long standing the cysts frequently have lost their lining of granulosa cells, and this presents a problem in hormonal treatment, since the rational hormonal therapy is to luteinize the follicles, thus breaking the deadlock in the cycle. Another complication may be the involvement of the central nervous system in the syndrome, as nymphomania is said to occur occasionally in the absence of large amounts of estrogens (Alba and Asdell, 1). An important paper on the condition and its treatment with hormones is that by Casida et al. (14). They point out that when extracts of sheep pituitary are injected the results differ with the site of injection. Subcutaneous injections produce follicular growth, while intravenous injections cause luteinization. Thus, the latter method is the one to be recommended in this particular form of therapy.

A wide variety of hormonal treatments have been attempted. Asdell (5) injected an extract of sheep pituitaries in four cases and obtained one conception. Walsh (56) injected twelve cows and seven conceived, while in two others normal cycles were restored. Casida et al. (14) made a very thorough test of this method using intravenous injections of sheep pituitary extract. They divided their cows into two groups of nymphomaniacs. Group 1 consisted of 71 cows which were nymphomaniac but without uterine complications. In 55 of them, corpora lutea formed, 52 showed normal heats and 46 were bred, with 32 pregnancies. Group 2 consisted of ten cows in which there were uterine complications. In this group, corpora lutea were formed in nine; normal heats followed in seven but none became pregnant. The only criticism which can be made is that many of the cows were in the incipient stages of nymphomania and the spontaneous recovery rate was not known. These workers also report that in 33 of the cows of group 1, cysts were ruptured, but that the degree of recovery in these cows did not differ from those in which the cysts were not ruptured. The total for this treatment is 97 cows injected, with 41 per cent of conceptions.
A luteinizing hormone, chorionic gonadotrophin, has been used by many workers. Koch (30) treated 35 cases and reported success in 30, with pregnancies in several. Niklas (41) treated 31 cows with 100 to 400 R.U. and had 20 cures, 11 of which were only temporary. He also reports treatment of 40, with 65 per cent conceptions. Haisch (25) treated nine cows and obtained six conceptions; Hancock (26) treated five with three conceptions; Deubler (18) had five injected cows and all conceived. Moore (37) treated 18; 12 ceased to be nymphomaniac, 10 had corpora lutea and 12 conceived. Teunissen (55) treated 12 cows and none conceived, while Durrell (20) records six treated, six conceptions. Lentz (33) used Folluetin and reported 16 conceptions in 17 cows injected. The total for this form of treatment is 112 cows of which 66 per cent conceived.

Teunissen (55) has used equine gonadotrophin in three cases, but none conceived.

Estrogen treatments also have been tried. Murphey et al. (38) treated one cow without success. Lentz (33) used stilbestrol in one case without success. Dancey (17) used the same substance on four cows; three improved and two conceived.

Progesterone has been used by Carlson (13), who recorded five pregnancies in five cases. Smith (49) treated ten cows and all symptoms disappeared. Bellomo (8) records the "effective" treatment of five cases with progesterone. Durrell (20) has tried testosterone propionate in two cases without success.

One gains the impression from some of these reports that other forms of treatment than hormonal injections alone have been resorted to and this makes several of the most optimistic reports difficult to accept at their face value.

**CYSTIC OVARIIES WITHOUT NYMPHOMANIA**

The exact significance of this classification is somewhat obscure. It may include cases in which the cysts occur in the corpora lutea or in the ovarian adnexa (mesovarium, parovarium). Spieler (51) treated 22 cows with an anterior pituitary extract and 77 per cent conceived. Casida et al. (14) used a similar treatment intravenously in 13 cases; nine produced corpora lutea, ten had normal heats and four conceived. Deubler (18) treated two cows with chorionic gonadotrophin and both conceived.

**COWS WITH HEAT PERIODS BUT NO CONCEPTION**

The type of cow in which heat periods are regular to irregular presents a most important problem, because they give the opportunity for breeding, but much time is wasted due to the delays in getting them pregnant. From the investigators point of view, they pose difficult problems, since, in the absence of obvious lesions, it is difficult to know when to begin treatment as sterile cases. Probably many of the cows with irregular heats represent a group of early aborters.

A further difficulty in assessing the results of treatment lies in the fact that in these cows their state of relative infertility may represent the degree of fer-
tility of the bull to some extent. A relatively infertile bull is not so successful with this class of cow as is a very fertile one. A rational hormonal method of treatment is not obvious, and many kinds of therapy have been attempted. In this class of infertility, controls are more essential, if that is possible, than in any other, and they rarely are found.

Spielser (51) treated 15 cows with an anterior pituitary extract and 93 per cent conceived. Asdell et al. (7) treated 11 cows with a sheep pituitary extract and four conceived. These cows had failed with previous estrogen treatment.

Eisenbach (21) used chorionic gonadotrophin in the small dose of 125 R.U. He reported that 12 cows were treated and all were cured. Bottomley et al. (11) treated 19 cows with 2,500 R.U. and obtained six pregnancies. In a group of cows in which difficulty was experienced in obtaining conceptions, the percentage of successful services was compared in treated and untreated cows. For the experimental cows services with treatment were 57 per cent effective, for untreated services 7 per cent, while for control cows, not deemed in need of treatment, services were 58 per cent successful. The authors draw the conclusion that treatment restored the average fertility to the level of the controls.

Durrell (20) treated ten cows and four conceived. Durrell (20) also has treated 24 cows with equine gonadotrophin, and 11 conceived to the first heat during or following therapy, a result which he interprets as showing the beneficial effects of the injections. He also treated three cows with equine gonadotrophin and progesterone and obtained one conception.

The value of estrogens has been studied by several workers. Murphey et al. (38) treated six cows with estrogens and four conceived. Frank (22) used ovarian extract (without corpora lutea) on 35 heifers and 90 per cent conceived. In 50 cows, about 90 per cent conceived to the first service and 10 per cent to the second. Zupp and Murphey (61) treated two cows without success. Spieler (51) used a complex mixture containing estrogens and obtained 93 per cent conceptions in 15 cows. Risse (47) used the same preparation (hormovilan) on 85 cows and reported 16 per cent conceptions. Asdell (5) used estradiol benzoate in eight cases and two conceived. Clark (16) treated 41 cows which had averaged 4.6 unsuccessful matings with a saline douche, and 35 conceived after an average of 1.9 further matings. He also used saline douches and injected an ovarian extract in 17 cases which had previously been treated with saline douches. Ten conceptions resulted in this group. Mirskaya and Kedrov (36) treated 11 cows with estrogens and only one pregnancy followed. Asdell et al. (7) injected 31 cows with estradiol benzoate and ten conceived. This is 32 per cent. Of 18 controls, 55 per cent conceived. The first group, as it is reported here, contained several cows which had failed to conceive as controls and which were treated subsequently. The average number of services per conception in the treated cows that became pregnant was 3.0, while in the control group (without treatment), 1.7 services were required. The evidence from this experiment neither supports the view that estrogens improve fertility nor that it lowers the number of services required per conception. In one field
test in which the cows treated were regarded as poor prospects, two of ten conceived. In another herd 17 cows were treated, 15 of them conceived but five aborted subsequently. Accuracy of diagnosis thus is an important factor in assessing results, especially in this type of infertility.

Durrell (20) treated four cows with progesterone and obtained one conception. Ruegg (48) fed testes to eight cows, seven became normal and four conceived. It is improbable that any hormone was absorbed by these cows.

At this stage, it hardly seems necessary to comment further upon this group of infertile cows.

OTHER CONDITIONS IN THE COW LEADING TO INFERTILITY

Metritis is a causal factor, or a contributory one, in many cases of infertility. Haisch (25) treated 25 cows with Lugol’s solution together with injections of 25 R.U. of chorionic gonadotrophin. He states that 19 were cured. Spieler (51) treated seven cows with an anterior pituitary extract and six conceived. Anderson and Bugg (4) treated three with stilbestrol. One was improved and two not. Glenney (24) reports that stilbestrol has some effect in improving cows with pyometra.

Haisch (25) treated 23 cows suffering from vaginal prolapse with 250-1,000 R.U. of chorionic gonadotrophin and reports 17 cured and four others improved.

Stilbestrol has been recommended as an aid to the expulsion of the retained mummified fetus. Stuart (54) treated one cow with 25 mg., together with posterior pituitary extract. The fetus was expelled. One cow treated with stilbestrol alone failed to respond. Anderson and Bugg (4) also failed with one cow. Powell (45) tried one cow with chorionic gonadotrophin without effect; later she responded to stilbestrol. Murray and Robertson (40) treated one cow with stilbestrol without effect.

SEXUAL INACTIVITY IN BULLS

A good deal of work has been done on the use of various hormones upon sterility and sexual inactivity in bulls, but very little of it has been reported in the literature. In general, it may be said that, judging from results obtained with other species, when spermatogenesis ceases entirely the prognosis is unfavorable.

Pighini (43) treated eight bulls with anterior pituitary grafts and six became active again. Bottomley et al. (11) treated three bulls which produced semen with low sperm motility by injecting chorionic gonadotrophin and all were improved. Durrell (20) treated four bulls with low ability to mount with 300 mg. of testosterone propionate; all responded favorably, but in one the response was temporary. Reineke (46) treated 14 bulls with thyroprotein. Ten were improved in their libido, and conception rate improved in four of them.

GENERAL REMARKS

It has been a depressing task to bring the literature on the hormonal treatment of sterility together. Very little of the work is controlled adequately, and
much of it is anecdotal in character. The complications in work of this nature are such that it is difficult to devise critical experiments, but in view of the importance of sterility much more of this critical type of work should be done. Where adequate controls have been set up, horionic treatment has failed to demonstrate efficacy. Another feature is that in any definite type of infertility the average percentage of response is about the same whatever the treatment. Such uniformity seems to show that the type of treatment with these boundaries means little; other factors leading to a fairly uniform rate of recovery are at work. These conclusions do not mean that horionic treatment necessarily is worthless. They mean that we know too little about the exact rôle played by the horions and about the dosages that should be employed. Much more groundwork needs to be done and many more critical field trials. Also, in field trials, the worker has tended to neglect the recommendations of the physiologist. He has worked on a shotgun basis without fitting the treatment, in most cases, to the type of infertility encountered.

REFERENCES

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