Journal of Steroid Biochemistry, 1975, Vol. 6, pp. 717–722. Pergamon Press. Printed in Great Britain

LOCAL EFFECTS OF TOPICALLY APPLIED STEROIDS

V. PLACE and H. BENSON

ALZA Corporation, Palo Alto, California, U.S.A.

SUMMARY

The objective of using topically applied steroids is to obtain a local therapeutic response without concomitant systemic effect. This objective is rarely achieved by topical application of steroids because of the lack of controlled drug availability. Formulation, method of administration, and dosage regimen have a marked effect on their resulting tissue levels and efficacy. Therapeutic systems, on the other hand, fulfill the objective of localized response to topical application by virtue of their precise, preprogrammed method of membrane-controlled drug delivery. Two examples of controlled steroid administration are the ocular therapeutic system (Ocusert®), which is effective in treating superficial ocular inflammation but confines drug response to the eye; and the uterine therapeutic system (Progestasert®) which is effective in preventing conception but confines drug response to the uterus.

Local effects from topically applied steroids have been sought for many steroids. These steroids, corticosteroids, progestogens, estrogens, and androgens, have wide-spread clinical use for a remarkable variety of indications: inflammation, dermatoses, pruritis, acne, uveitis, asthma, ulcerative colitis, arthritis, contraception, and senile vaginitis. Controlled topical delivery of steroids by therapeutic systems offers new definition to these attempts.

INTRODUCTION

Steroids occur naturally by the thousands, and hundreds have been used in topical therapy with written prescription instructions such as "apply to the affected area several times each day." This is augmented and supported by somewhat more specific verbal recommendations such as "squeeze out as much as it takes to cover the area and rub it in well." After all, everyone instinctively knows how to put something on the skin. However, your experiences with patients will remind you how far afield they can go with such vague instructions; even the stratum corneum barrier of their skin cannot always protect them from injury. Although in today's discussion "topical steroids" will mean steroid administration to a specific location to obtain therapeutic effects limited to the site of application, unintended systemic effects also occur.

Early in the clinical use of steroids, recognition was given to the marked difficulties in administering these agents systemically—each agent is capable of affecting several target tissues—and the potential advantages of topical application for some therapeutic applications were explored. The objective of administering steroids topically became to obtain a local therapeutic response, but to contain the drug at the site of desired action such that no concomitant systemic effects occur. The success of this approach depends primarily on the formulation of the steroid preparation and the method and pattern of its application. Excessive amounts of drug applied indiscriminately may elicit adverse effects, either locally or systemically, instead of the desired local therapeutic response. A more rational drug program controls drug release to a minimum rate to maintain, throughout the active course of the treatment, the lowest drug concentration consistent with the achievement of desired therapeutic effect.

Our research has been to incorporate these principles into therapeutic systems which provide the optimum quantity of required therapeutic agent over time, rather than sporadically loading in more than needed with the consequent over- and under-dosage (Fig. 1). The concept and design of therapeutic systems have been presented earlier at this meeting by Dr. Zaffaroni.

The principles of controlled drug delivery through the use of therapeutic systems can potentially be applied to all therapeutic agents. Today, however, we will confine our discussion to the locally effective steroids: corticosteroids, progestogens, estrogens, and androgens; and illustrate the advantages of controlled drug delivery with two of our ocular and uterine therapeutic systems.

Corticosteroids

The anti-inflammatory steroids, corticosteroids, are used for local therapeutic effect in several fields: dermatology, ophthalmology, rheumatology, gastroenterology, and for respiratory allergies. In all of these uses, corticosteroids have a local pharmacological action that suppresses inflammation, controls local immune responses, produces vasoconstriction with clearing of edema, and decreases cell replication. Key to these effects is the last point, the control of cell replication [1]. The potency of an anti-inflammatory steroid can be determined by its ability to suppress fibroblast proliferation *in vitro* [2]. Since this broad cytotoxic potential exists, it is especially important to control steroid administration for optimum therapeutic response, without adverse concomitant effects.

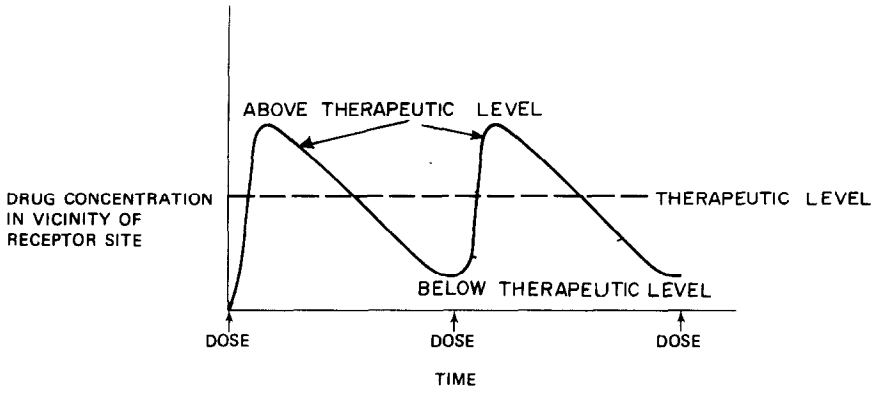

Fig. 1. Pulse administration of drugs can result in periods of overdosage and underdosage.

Therapeutic objectives from local corticosteroid effects are: to control non-infective inflammation, block antigen/antibody reactions, suppress erythema and tissue proliferation, and control the cellular replication in psoriasis.

The ability of steroids to suppress cell production may also have toxic manifestations however: inadequate tissue replication, delayed wound healing, wound separation, thinning of skin and scar tissue, atrophy, telangiectasia extending to actual tissue destruction, and, in some cases, ulceration.

Dermatology. The potent topical dermatological preparations have a marked local pharmacological effect which suppresses inflammation. The Stoughton–McKenzie assay [3] and subsequent procedural refinements [4, 5] have made it possible to screen the anti-inflammatory potency of a large number of steroids based on this local vasoconstriction. Effectiveness of the method of administration of steroids has been evaluated by the vasoconstriction assay. The vasoconstrictor assay has also been used to evaluate vehicle effects on the bioavailability of corticosteroids. The availability of drug from a topical formulation to the skin depends on two consequent events: diffusion of drug from the vehicle and diffusion of drug to the target tissue. Although the latter process, diffusion of steroid through the human skin, is slow and rate-limiting with normal skin [6], the former controls the rate and amount of drug presented to the skin surface and may influence the rate of skin penetration as well.

Vehicle, occlusion, and frequency of administration combined contribute as much to the effectiveness of topical skin preparations as the steroid molecule. A method of presentation of a steroid that precisely patterns the rate of drug availability can therefore be expected to improve local therapeutic results without systemic or local side effects. Therapeutic systems providing controlled drug delivery are not available for dermatologic use, but significant progress has been made in ophthalmologic therapy.

Ophthalmology. In the field of ophthalmology, topical steroids have been extremely effective in controlling conjunctival inflammations, as well as some cases of anterior uveitis of either non-specific or antigen origin. The use of an antigen model in immunized rabbits [7] has made it possible to evaluate the relative effectiveness of patterns of steroid administration [8].

Two ocular therapeutic systems currently under development continuously deliver steroid to the eye (Fig. 2). The efficacy of the therapeutic systems, one for prednisolone acetate and the other for hydrocortisone acetate, was compared over a 96-h period in rabbits with the efficacy of equivalent daily doses of steroid given intermittently by eyedrops. Inflammation scores, based on a daily evaluation of the lids, conjunctiva, cornea, and iris show a marked difference between the control eye and the eye treated with 50 μg prednisolone acetate as eyedrops 5 times a day and the continuous delivery of 10 μg/h prednisolone acetate with an ocular therapeutic system (Fig. 3). With the latter, inflammation is completely controlled after 96 h. Comparable results have been obtained with hydrocortisone acetate topical administration. The continuous delivery of either steroid from an ocular therapeutic system was more efficacious than the corresponding steroid given as intermittent pulses by eyedrops. In comparing the two

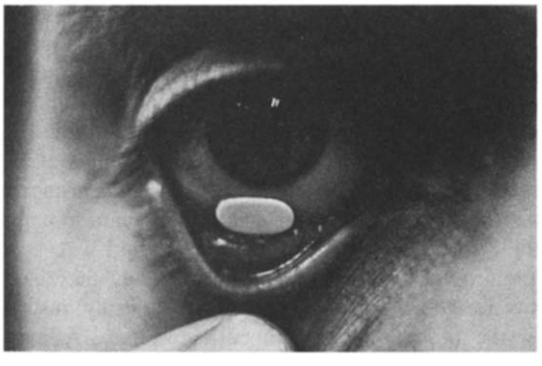

Fig. 2. An ocular therapeutic system that delivers anti-inflammatory steroid to the eye.

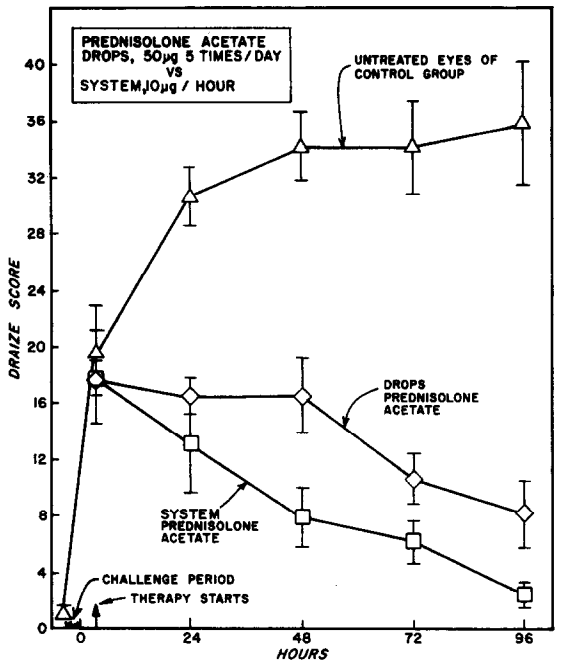

Fig. 3. The effect of prednisolone acetate eyedrops and ocular therapeutic system on inflammation in the rabbit eye.

steroids from ocular therapeutic systems, it can be seen that prednisolone acetate is 2 to 6 times more effective than hydrocortisone acetate (Fig. 4).

The distribution pattern of steroid among the various ocular tissues of an inflamed rabbit eye also varies with the method of administration [9]. With ^{14}C used as a tracer, an eyedrop regimen of hydrocortisone acetate, 250 μg given twice daily, was compared with an ocular therapeutic system releasing 10 μg/h. Measurements of tissue levels of ^{14}C were made from 8 to 96 h after the start of either regimen. With both regimens, the total quantity of ^{14}C in ocular tissues continued to rise throughout the 4-day treatment period and did so at comparable rates. However, at each time, the total quantity of ^{14}C in ocular and periocular tissues was approximately two times higher with the continuous than with the intermittent regimen, despite the fact that the total dose administered by the continuous regimen was only half that administered by the intermittent. Thus, by controlling the rate of continuous presentation with an ocular therapeutic system, a therapeutic regimen of hydrocortisone acetate could be localized to conjunctival structures.

The presently available ocular therapeutic systems in clinical tests appear to offer superior control of local inflammation and to potentially avoid the problems of loss of potent drug through the nasolacrimal duct and resultant adverse systemic effects [10, 11].

Arthritis. Another form of topical therapy results from the intra-articular injection of corticosteroids into the synovial lining of the involved joints of patients with arthritis. This is a relatively simple and safe procedure when only a few joints are involved and when there is little or no erosive damage already present. Relief of pain and swelling may be rapid and permit early and long-lasting mobilization of the affected limb [12]. However, like other local applications already mentioned, intra-articular injections are not without hazard. If an excess of steroid is administered, destruction of the synovial lining, cartilage, and surrounding tissues may result [13].

Gastrointestinal tract. Corticosteroids can be administered in the form of retention enemas [14] or rectal foams [15] to patients with ulcerative proctitis or mild ulcerative colitis limited to the sigmoid and rectum, or as adjunctive therapy to relieve rectal tenesmus in severe ulcerative colitis. Sigmoidoscopic examination for mucosal appearance, edema, and ulceration and symptoms of rectal bleeding, diarrhea, anorexia, weight loss, and abdominal pain generally show some improvement frequently within a month. The major beneficial effect of corticosteroids in the gastrointestinal tract may be the stabilization of the lysosomal membrane so that toxic hydrolytic enzymes normally contained within the sub-cellular particles may not damage the intestinal cells [16].

Although systemic absorption following application the rectal mucosa does occur, between 30 to 50% of an administered enema, the beneficial therapeutic effect seems to be confined to the rectal mucosa itself [14]. The therapeutic effect of hydrocortisone enemas is not related to the amount of steroid absorbed systemically, and since the acetate is absorbed less readily than the alcohol form, it should be the steroid of choice. Rectal foams appear to be more convenient for patient use than enemas, but it is not clear whether systemic absorption is decreased with this dosage form.

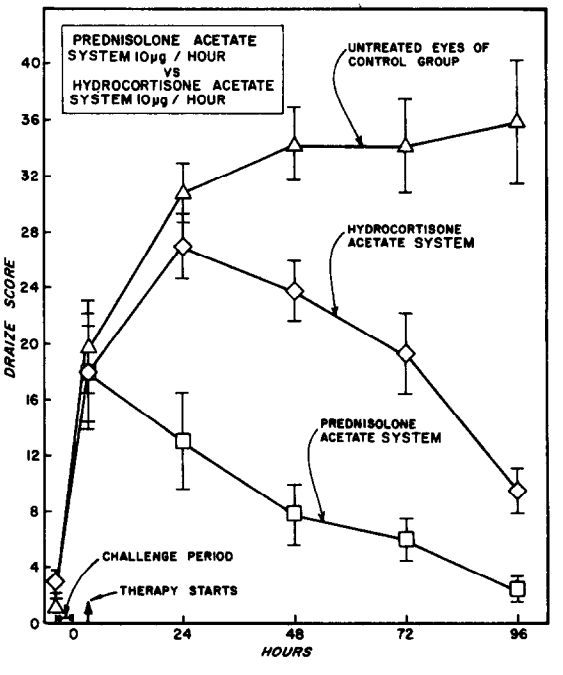

Fig. 4. The effect of prednisolone acetate and hydrocrotisone acetate ocular therapeutic systems on inflammation in the rabbit eye.

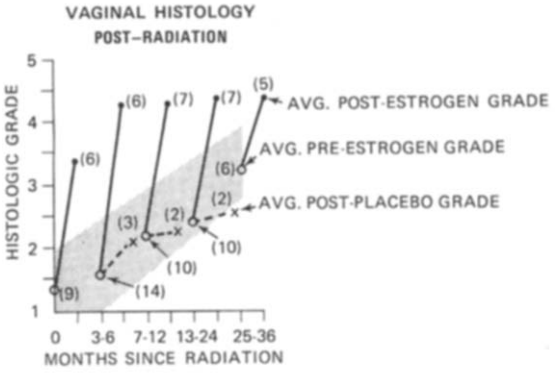

Fig. 5. The effect of estrogen on vaginal epithelium following radiation therapy for cervical cancer. Numbers in parentheses refer to the number of patients in each group (Pitkin and Bradbury, ref. 22).

Rhinitis and asthma. Corticosteroids are among the most effective agents available today for the symptomatic treatment of asthma and a wide variety of allergic respiratory conditions. Steroids directly relax smooth muscle in the respiratory tract and reduce histamine levels in lung tissue [17]. Because of this local action, topical steroid application in the upper respiratory tract by aerosol generally has a local therapeutic effect equivalent to or greater than that produced by systemic steroids and is achieved with lower dosage. While there is little doubt that some steroid reaches the systemic circulation following aerosol use, it is far less than amounts from other routes of administration, and adverse systemic effects seem to be greatly reduced [18]. Therapeutic efficiency could probably be heightened and systemic effects reduced further with aerosol formulations of the optimum particle size for deposition in the tracheobronchial tree [19].

Estrogens

Atrophic vaginitis. The local application of various estrogen formulations to estrogen-deficient vaginal tissues found with atrophic vaginitis has been recognized for many years as effective and convenient therapy [20]. The various side effects sometimes attributed to estrogens given orally or parenterally—nausea, vomiting, uterine bleeding—are avoided, even when the vaginal administration of estrogen continues for several years [21].

Senile or atrophic vaginitis is characterized by a diffuse redness of the vaginal walls, with occasional granular or ulcerated areas. During therapy, the epithelium is regenerated, vaginal cells increased in size and glycogen content and inflammation reduced [21, 22].

The effect of estrogen on the vaginal epithelium is illustrated with a study by Pitkin and Bradbury [22]. On a gradation scale of 1–5 where 1 means absent epithelium and 5 means mature stratified squamous epithelium, estrogen therapy for three months converts vaginal epithelium of average score of 1·5 to an average score of nearly 3·5, following completion of radiation therapy for cervical cancer (Fig. 5). Even more pronounced effects were observed when topical estrogens are applied to patients who were three months or longer post-radiation.

Dermatology. Estrogens appear to have equivocal effects on aging skin [23, 24] and sebaceous gland activity [25].

Androgens

Rejuvenation is a core desire, but a Dorian Gray approach will satisfy most people—just reverse the ravages of aging from showing on the skin. Toward this end, Papa [24] found that testosterone has a rejuvenating or ameliorating effect when applied to aging human skin for six months. Clinically evident changes in 75% of the subjects such as effacement of wrinkles, hair growth, and augmented sweating were present. The histologic improvement from testosterone application was even more uniform and striking, particularly in the epidermis where the disorderly cytologic and histologic alterations were reversed. In contrast to the corticosteroid destructive changes to the skin, androgens had the capability of thickening the epidermis by both increasing cell size and number of cell layers. The observed effects were entirely local for neighboring and distant skin did not show any changes, nor was systemic administration over extended time comparably effective.

Progestogens

Progestogens are the keystone to the successful development of oral contraceptives. Outside the uterus, oral contraceptives have a variety of systemic effects, many unrelated to conception. Within the uterus, the progestogen component of oral contraceptives produces secretory changes in the endometrium that are manifested by the failure of "corkscrew" development in the glands and by an associated pseudo-decidual change in the stroma [26]. The efficacy of the oral minidose progestogens may be related to this local effect [27].

The natural hormone progesterone, of course, also causes secretory transformation of the estrogen-primed endometrium—indeed, this is the basis for

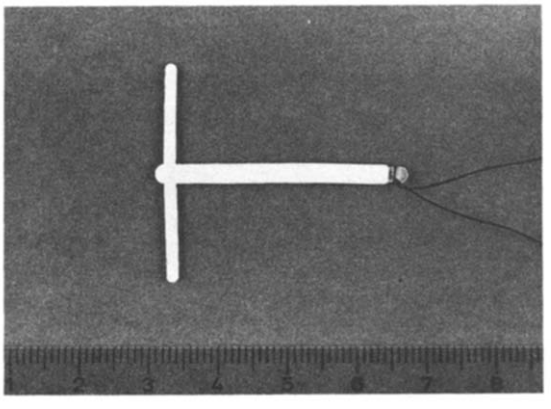

Fig. 6. Progestasert® (progesterone) uterine therapeutic system, 65 μg/day for one year. Dimensions are in cm.

the definition of "progestational"—but progesterone has not been useful in the past as a contraceptive [28] because of its high rate of metabolism throughout the body [29]. We felt that if we could deliver progesterone directly to the uterine lumen with a therapeutic system, we could effect endometrial changes that would prevent conception without the systemic steroid effects seen with oral contraceptives. Only about 65 μg/day progesterone—less than that secreted in 1 day by the midluteal phase ovary—is necessary for reliable contraception with this local administration [30, 31].

The Progestasert® (progesterone) uterine therapeutic system designed for this purpose contains a progesterone reservoir housed in a T-shaped structure which is inserted into the uterus (Fig. 6). It is important that the Progestasert® system's contraceptive effect depends primarily on the hormone released rather than on a conventional IUD effect of the platform. This means that the platform can be designed, not specifically for contraception, but for maximum retention and patient comfort. The T-configuration was chosen on the basis of studies described by Tatum [32] which indicated its high rate of retention and its superiority to other IUDs in minimizing bleeding and pain. The platform itself does not provide effective contraception [33]. Thus, though the Progestasert® system by virtue of its intrauterine placement, is akin to IUDs, it differs basically from the IUDs in a functional sense. It is, in essence, a method of steroidal contraception that localizes the effects of the hormone [34].

The mechanism of contraceptive action of progesterone applied directly to the uterine lumen has not been established. It is likely that cervical mucus changes which deter sperm passage [35], and biochemical alterations in the endometrium which change sperm survival, functionality, and capacitation [36] are involved, as well as the expected histological effects on the endometrium. Biopsies taken after the Progestasert® system had been in the uterus for various periods were histologically evaluated on a single-blind basis. Endometrial suppression was the most common finding. For this study a suppressed endometrium was characterized as one with small glands exhausted of secretions and lined with small, cuboidal, eosinophilic epithelium and surrounding edematous tissue [35]. No indications of cellular abnormalities or hyperplasia were present, even among the specimens taken after at least 12 months of exposure to the Progestasert® system.

CONCLUSION

Topical administration of these various steroids has numerous local therapeutic applications without the widespread systemic effects associated with systemic administration. The inherent safety from this approach is not guaranteed, however, when there is no control over the rate and quantity of drug presented. Precision drug delivery of steroids offers new definition to these attempts toward the safe and locally effective topical administration of steroids.

REFERENCES

1. Fisher L. B. and Maibach H. I.: *Archs Derm.* **103** (1971) 39–44.
2. Berliner D. L., Gallegos A. J. and Schneebeli G. L.: *J. Invest. Derm.* **48** (1967) 44–49.
3. McKenzie A. W. and Stoughton R. B.: *Archs Derm.* **86** (1962) 608–610.
4. Place V. A., Valazquez J. G. and Burdick K. H.: *Archs Derm.* **101** (1970) 531–537.
5. Poulsen B. J., Burdick K. and Bessler S.: *Archs Derm.* **109** (1974) 367–371.
6. Ostrenga J., Steinmetz C. and Poulsen B.: *J. Pharm. Sci.* **60** (1971) 1175–1179.
7. Aronson S. B., Goodner E. K., Yamamoto E. and Foreman M.: *Archs Ophthal.* **73** (1965) 402–412.
8. Keller N. Longwell A. M. and Birss S. A.: *The Association for Research in Vision and Ophthalmology*, Sarasota, Florida, May 6, 1973. *Archs Ophthal.* (1975) In the Press.
9. Birss S. A., Keller N. and Longwell A. M.: *The Association for Research in Vision and Ophthalmology*, Sarasota, Florida, April 25–29, 1974.
10. Burch P. G. and Migeon C. J.: *Archs Ophthal.* **79** (1968) 174–176.
11. Nursall J. R.: *Am. J. Ophthal.* **59** (1965) 29–30.
12. Gifford R. H.: *Med. Clin. N. Am.* **57** (1973) 1179–1190.
13. Hollander J. L., Jessor R. A. and Brown E. M.: *Bull. Rheum. Dis.* **11** (1961) 239–240.
14. Farmer R. G. and Schumacher O. P.: *Am. J. Gastroenter.* **54** (1970) 229–236.
15. Scherl N. D. and Scherl B. A.: *Dis. Col. Rect.* **16** (1973) 149–151.
16. Wall A. J.: *Med. Clin. N. Am.* **57** (1973) 1241–1252.
17. Aviado D. M. and Carrillo L. R.: *J. Clin. Pharm.* **10** (1970) 3–11.
18. Niesenbaum L.: *Annal. Allergy* **28** (1970) 367–370.
19. Robillard E., Lepine C. and Dautrebande L.: *Can. Med. Assoc. J.* **86** (1962) 363–366.
20. Kyriazis G. A. and Balin H.: *Pa. Med.* **73** (1970) 32–34.
21. Karnaky K. J.: *J. Am. Geriat. Soc.* **13** (1965) 820–827.
22. Pitkin R. M. and Bradbury J. T.: *Am. J. Obstet. Gynec.* **92** (1965) 175–182.
23. Brown R. K.: *J. Am. Med. Women's Assoc.* **21** (1966) 493–499.
24. Papa C. M.: *J. Soc. Cosmetic Chem.* **18** (1967) 549–562.
25. Strauss J. S., Kligman A. M. and Pochi P. E.: *J. Invest. Derm.* **39** (1962) 139–155.
26. Ferin J.: In *Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents.* Pergamon Press, New York, Vol. II (1972) 245–273.
27. Martinez-Manautou J.: *Excerpta Medica Int. Con. Ser.*, Amsterdam, **133** (1967) 999–1004.
28. Pincus G.: *Vitam. Horm.* **17** (1959) 307–324.
29. Lin T. J., Billiar R. B. and Little B.: *J. clin. Endocr. Metab.* **35** (1972) 879–886.
30. Pharriss B. B., Erickson R., Bashaw J., Hoff S., Place V. A. and Zaffaroni A.: *Fert. Steril.* **25** (1974) 915–921.
31. Scommegna A., Avila T., Luna M., Rao R. and Dmowski P.: *Obstet. Gynec.* **43** (1974) 769–779.
32. Tatum H. J.: *Am. J. Obstet. Gynec.* **112** (1972) 1000–1023.
33. Brenner P. F., Cooper D. L. and Mishell D. R.: *Am. J. Obstet. Gynec.* **121** (1975) 704–706.
34. Zaffaroni A.: *Acta endocr. Copenh.* **85** (1974) 423–434.
35. Martinez-Manautou J., Aznar R., Maqueo M. and Pharriss B.: *Fert. Steril.* **25** (1974) 922–926.
36. Rosado A., Hicks J. J., Aznar R. and Mercado E.: *Contraception* **9** (1974) 39–51.