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THE DEVELOPMENT OF DEPOT CONTRACEPTIVES

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SUMMARY

Implants of steroidal pellets were first used in 1937 to obtain prolonged release. There is published information to suggest that these were applied for contraceptive purposes. Other methods have since been developed to prolong the action of systemically administered steroids. Synthesis of steroid esters prolongs activity and some compounds in this category have contraceptive efficacy in the human. Prolonging activity by the synthesis of poly phosphate conjugates has clinical application with oestrogens. Crystal suspensions of some progestational steroids have prolonged activity and contraceptive action. Each of these methods suffers from the disadvantage of a large initial "pulse". This can be overcome partially by the use of silastic implants. The ultimate objective of "zero order" release is most likely to be reached by polymer steroid amalgams. Theoretically the latter project could be achieved by a solid slab with release solely dependent on polymer erosion; by copolymers where release is determined by erosion and diffusion; or by micro capsules where steroid release is determined by ion exchange in the membrane.

INTRODUCTION

It is sometimes unnecessary, usually difficult and always hazardous to attempt an allotment of primacy in a given scientific area. Nevertheless there is reason to believe that the development of Depot methods for the delivery of drugs and in this context, particularly contraceptive drugs, may prove ultimately to have more than passing historical significance. In this field it seems reasonable to allot primacy to the work of Deanesly and Parkes[9] who first demonstrated that prolongation of the effect of oestrogens could be obtained by implanting pellets into experimental animals. Initial animal enthusiasm was rapidly reflected by human use, and as this was in the fourth and fifth decades of the 20th century, used without the benefit of animal toxicology and certainly without the benefit of pharmacodynamic studies. It is no source of comfort in the eighth decade of this century to realise that we have been no more successful in predicting human response from animal studies than our predecessors.

An elaborate theoretical equation was evolved based on the assumption that the rate of absorption from these pellets at any time was proportional to the surface area; therefore the theoretical absorption rate should have related to this area but translation of theory to fact proved infinitely more difficult. In 1954 Cowie and Flux[7] indicated that the factors affecting systemic absorption and peripheral levels were far more complex, varying not just with the compounding of the tablet but also with the incorporated active steroid; for example although deoxycorticosterone acetate in one dose level and a derivative of testosterone behaved in the predicted manner in rats, different dosage of deoxycorticosterone acetate, cortisone or progesterone did not so behave.

The major clinical usage of these implants in reproductive biology appeared to be for the treatment of menopausal symptoms in women, some difficulties of pregnancy attributed to hormone deficiency and for steroid replacement in older men. Many of these papers had somewhat depressing titles—for example "Testosterone implantation; a clinical study of 240 implantations in ageing males" [23]. Most of these clinical studies were more notable for their anecdotal enthusiasm than the rigorous control of the experimental design.

Although no survey of the literature can hope to be complete, the only study of pellets related to contraception found is a publication by Emperaire and Greenblatt[13] in the French literature. This described the use of four pellets containing a total of 100 mg of estradiol, combined with "menses regulation" using an oral progestin. In a study of 70 patients, ovulation was inhibited for 6 months or more without undesirable side effects. The authors suggested in their conclusion that "this simple method...represents, without added risk, a new method of hormonal contraception for long term use".

Despite a decline of interest in pellets as originally introduced it is nevertheless not unreasonable to see these pellets as the progenitors of some methods now undergoing active development, which will be discussed in later sections of this paper.

CHEMICALLY MODIFIED STEROIDS

In 1930, during the bright dawn of steroid chemistry, Butenandt noted that esterification of steroids bearing an hydroxyl group augmented their biological effect and prolonged the duration of activity. In what must surely be a landmark in the transformation of chemical expertise to biological potential, Junkmann[18] in 1957 presented a comprehensive and detailed review of the effect of steroid esters in biological systems. Although lacking the current advan-

tages of technological progress such as radioimmunoassay, Junkmann demonstrated with great clarity their prolonged action and from well designed bioassays, the dose response effect of a large number of esters of different steroids. However there was clear evidence that release was not steady, initial injection being followed by a relatively rapid rise to a peak with a rapid fall and disintegration over a period of weeks, or in some cases months. There was no demonstration of a fixed rate of release, biological action, metabolism or excretion after injection of these steroid esters.

Other and quite successful methods to prolong the action of a steroid by modification of its chemical structure or its physical presentation have been the development of crystal suspensions, the effect being related both to the concentration of drug and crystal size [20] and the development of polyestradiol phosphate complexes [10]. More recently other oligomeric steroids have been synthesised, either estrogen dimers, trimers, tetramers, or dimers of a progestin and estrogen. Coupling was achieved by utilizing a succinic acid bridge. These oligomers have prolonged action in some animals [28].

Despite this considerable chemical and physico chemical expertise, only two steroids with prolonged action have been widely used for contraceptive purposes in the human, one of these a crystal suspension (medroxy progesterone acetate) and the other a steroid ester (norethisterone oenanthate).

INJECTABLE PROGESTATIONAL CONTRACEPTIVES CURRENTLY AVAILABLE

After initial experience with its use in the treatment of endometrial carcinoma and endometriosis, medroxy progesterone acetate (Depo Provera), was first used as a contraceptive agent in the human in 1963 [21]. A great deal of the relevant literature has been reviewed by Rosenfield[24]. Given in a dose of either 150 mg every 3 months or 300 mg every 6 months by deep intramuscular injection this compound is a very effective method of contraception and has the added advantage that it will increase lactation in puerperal women. Its disadvantages are that there is a total disruption of the menstrual cycle, bleeding unpredictable both in time and in amount being common in early treatment cycles, while amenorrhoea is the rule if treatment is prolonged.

A further source of anxiety has been the very marked delay in the return of fertility after discontinuance of treatment. The reasons for this delay have remained obscure until recently, being variably attributed to a "massive assault" of this drug on the reproductive endocrine system to very prolonged retention in the muscle depot with correspondingly prolonged biological activity. A careful study by Schwallie and Assenzo[26] serves to clarify this problem well. They have indicated that "the prolonged amenorrhoea and anovulation is due to prolonged pharmacological levels of Provera in the circulation due to slower absorption from the injection site. The return of reproductive function occurs promptly upon disappearance of Provera from the circulation".

Although this work has provided a rational answer for a previously inexplicable problem, it nevertheless underlines the difficulty inherent in the administration of crystal suspensions. After the initial injection there is a very rapid increase in the level of steroid in biological fluids, far beyond that necessary for the desired biological effect. This is followed by decay in detectable plasma levels but the variability of the duration of action clearly underscores the fact that the release rate, metabolism, excretion and therefore the biological action of the compound is unpredictable in individual patients, poorly related to the amount of steroid administered and unrelated to the physical form—in this case the crystal size—of the suspension administered. While the desired clinical effect—control of fertility—is achieved, it is only at the expense of a high incidence of undesirable side effects and an unpredictable duration of activity.

A further difficulty that has delayed the more widespread introduction of this compound into the human is the problem of animal toxicology and its relevance to the human. In this specific instance it is induction of mammary tumours in the beagle bitch by this compound and other 17-acetoxy progesterone derivatives. This has made many regulatory authorities reluctant to approve their use for contraception in the human. There are obvious difficulties in the application of some of these animal findings to the human and satisfactory resolution is not easy. This problem is discussed in some detail by Hill and Dumas[16].

Experience with norethisterone oenanthate is not as extensive as with the crystal suspension discussed above. A summary of experience in 3851 women for 39,712 cycles indicated an overall pregnancy rate of 0·66/100 woman years [25]. Published data indicated the latitude of timing is not nearly as extensive as it might be with Depo Provera. There is good evidence that the pregnancy rate is increased substantially when the injection is given at intervals of 3 months instead of intervals of 12 weeks in a dose of 200 mg [12]. A study by Weiner and Johansson[29] has indicated that towards the end of the 12 week contraceptive protection there is restoration of apparently normal ovulatory function. This suggests that norethisterone oenanthate may have other mechanisms of action in contraception apart from inhibition of ovulation which appears to be the dominant action with Depo Provera and the predominant method in the first half of each treatment cycle with norethisterone oenanthate.

While the true pharmacodynamics of this steroid ester remain to be established. pending the application of sensitive, specific, accurate and precise radioimmunoassays for both the parent ester and the released active steroid, work using crude total radioactivity indicates that, as with Depo Provera, the release into biological fluids in both animals and humans is that of a skewed parabola with very rapid

rise to high initial plasma levels followed by a rapid but nevertheless unpredictable decay.

As with Depo Provera toxicological problems remain, although these have been rationalized better than in the case of the former compound. In rats, norethisterone oenanthate acts as an estrogen increasing prolactin secretion. Related to this estrogenic potency, this steroid ester increases the incidence of mammary tumours in rats. The fact that this is mediated by the pituitary has been indicated by the evidence from hypophysectomized rats where the compound has no such action[22].

IMPLANTS

Following the initial demonstration that various steroids enclosed in dimethylpolysiloxane (Silastic) by Dziuk and Cook in 1966 [11], substantial clinical experience has accumulated in the contraceptive application of various steroids delivered from Silastic implants.

Although relatively effective [6, 8, 14, 27] there is substantial disruption of cyclical bleeding and technical problems of administration and discontinuance. Implantation of these capsules requires local anaesthesia, skin incision and insertion through a trochar while after dissolution and diffusion of the active steroid from the biologically inert Silastic capsule, removal is usually indicated.

Benagiano *et al.*[2] have indicated that with this method as usually applied, ovulation is not inhibited as a rule, the effect being not unlike that of the orally effective "mini pill".

While *in vitro* studies indicate that steroid release through Silastic follows Fick's law, permeation being proportional to surface area and inversely proportionate to membrane thickness, studies *in vivo* do not support that this postulate can be transferred to biological systems [19]. It is probably that encapsulation of the implant soon after insertion contributes to these differences. Similarly in human studies, Benagiano *et al.*[3] have shown that constant release, as indicated by total excretion of radioactivity, is not achieved until after two months from the time of implantation.

ZERO ORDER RELEASE

No method of delivery of any drug for systemic use has yet achieved zero order release. Currently whether the active compound is given as a tablet, as an injection or as an injection with sustained release qualities, initial release of the drug is rapid with a "pulse" effect; the result, therefore, is that the systemic levels of the active drug are for much of its life span either above or below the therapeutic level that is required. The first order kinetics that apply to virtually all current therapeutic delivery systems are complicated further by the formation of secondary and sometimes tertiary depots from storage and selective concentration elsewhere in the body with subsequent release from these subsidiary depots.

Based on a considerable body of data from study of tri-cyclic antidepressants and analeptic drugs it is assumed that if a predictable and constant systemic level could be assured by a sustained constant release, therapeutic results would be improved. The whole concept of zero order release is based on this theoretical desirability. In its simplest terms, zero order release depends on the design of a delivery system that will allow constant predictable release, independent of the amount of drug in the dose form. It should be emphasized that there is, as yet, no proof that even when it is attained, zero order release will be a substantial improvement in terms of contraceptive technology. Theoretically one could aim at the release of a drug in varying dose levels. For example a low dose release that would allow ovulation but inhibit fertility by mechanisms such as interference with sperm transport through the cervix, or a larger dose level release where the predominant action was central on the hypothalamus inhibiting ovulation.

Currently a great deal of work is being done to develop zero order release systems for systemic administration, the emphasis being either on implants or injectables. Three potential methods will serve to illustrate some of the approaches that are being used.

Two of these use polymer technology, the first utilizing water soluble polymers with degradable cross links, the release of the drug being related to both diffusion of the drug and hydrolysis of the polymer. The second utilizes a hydrophobic water insoluble polymer while the third utilises the ion exchange characteristics of membranes surrounding the active drug, release being determined by the nature of the membrane and the subsequent charge across this membrane.

HYDROPHYLIC CO-POLYMERS

One example of this approach has been described by Jackanicz[17]. It describes the incorporation of d-norgestrel into a solid matrix of poly-L-lactic acid. While zero order release could be obtained *in vitro*, this was not obtained when these polymer slabs were studied *in vivo*. Since the compound is hydrophylic there is release by both diffusion through the polymer compounded by the release of drug with erosion and hydrolysis of the polymer.

Theoretically a similar mechanism could be utilized with micro spheres which would then be suspended and capable of intramuscular injection. It seems likely that with some particular contraceptive steroids copolymers of polylactic and poly-glycolic acid would give better control of release for a predictable time and work is currently in progress utilizing this sytem.

HYDROPHOBIC POLYMERS

The most advanced work in this area is represented by the development of Alza's Chronomer TM systems [15]. Varous polymers have already been shown

to achieve local zero order release for pilocarpine in the eye and progesterone within the body of the uterus but the problems are more complex with implantation or injection of polymers into a muscle. The theory underlying the concept of the hydrophobic polymer is that the drug to be delivered is dispersed uniformly throughout the polymer; since it is hydrophobic there is no release by diffusion, release and discharge of the drug being totally dependent on erosion of the polymer at the body water–polymer interface. Theoretically it would be possible to incorporate two active compounds into a polymer in varying proportions, their release rate being dependent on the concentration of each drug within the polymer system.

THE POLIN MEMBRANE

This concept was developed by Dr. Herbert Polin from his observations on the electroplak of the electric eel. It depends on the micro encapsulation of the active compound—in this instance a steroid—by a membrane with ion exchange capabilities and then the envelopment of these multiple micro capsules in a further envelope which allows injection as a bolus. The physical chemistry underlying this methodology is complex and is described in some detail by Bretscher[4]. Current *in vitro* studies indicate that zero order kinetics can be sustained for more than 90 days using norethisterone as the active component [1].

The concept of zero order release although very attractive theoretically, does bring with it added dimensions of toxicology. It is now necessary to determine not only the toxicology of the active compound but also the toxicology and biodegradability of the polymer or other releasing mechanisms. Thus use of solid slabs such as biodegradable implants certainly raises the need to exclude the possibility of induction of solid state carcinoma and a great deal remains to be learnt of the metabolism, excretion and possible toxicity of the variable polymers that will be utilised. Nevertheless these newer delivery systems do promise the best hope of improvement on the currently available but unsatisfactory depot contraceptive agents.

REFERENCES

1. Beck L. R. and Polin H.: Personal Communication (1974).
2. Benagiano G., Ermini M., Carenza L. and Donini P.: *Acta endocr., Copenh.* **73** (1973) 347–359.
3. Benagiano G., Ermini M., Carenza L. and Rolfini G.: *Acta endocr., Copenh.* **73** (1973) 225–246.
4. Bretscher M. S.: *Science* **181** (1973) 622–629.
5. Butenandt A.: *Z. physiol. Chem.* **191** (1930) 140–156.
6. Coutinho E. M., Mattos C. E. R., Santanna A. R. S., Filho J. A., Silva M. C. and Tatum H. J.: *Contraception* **5** (1972) 389–393.
7. Cowie A. T. and Flux D. A.: *J. Endocr.* **11** (1954) 255–260.
8. Croxatto H., Diaz S., Vera R., Etchart M. and Atria P.: *Am. J. Obstet. Gynec.* **105** (1969) 1135–1138.
9. Deanesly R. and Parkes A. S.: *Proc. Roy. Soc. Lond. S. B.* **124** (1937) 279–298.
10. Diczfalusy E.: *Endocrinology* **54** (1954) 471–477.
11. Dziuk P. J. and Cook B.: *Endocrinology* **78** (1966) 208–211.
12. El-Mahgoub S. and Karim M.: *Contraception* **5** (1972) 21–29.
13. Emperaire J. C. and Greenblatt R. B.: *Gynec. Practique* **20** (1969) 327–334.
14. Ermini M., Rolfini G. and Benagiano G.: *Acta endocr., Copenh.* suppl. **177** (1973) 135.
15. Heller J.: Personal Communication (1974).
16. Hill R. and Dumas K.: *Acta endocr., Copenh. suppl.* **185** (1974) 74–84.
17. Jackanicz T. M., Nash H. A., Wise D. L. and Gregory J. B.: *Contraception* **8** (1973) 227–234.
18. Junkmann K.: *Recent Prog. Horm. Res.* **13** (1959) 389–419.
19. Kincl F. A. and Rudel H. W.: *Acta endocr., Copenh.* suppl. **15** (1971) 5–30.
20. Lens J., Overbeek G. A. and Poldermann J.: *Acta endocr., Copenh.* **2** (1949) 396–404.
21. McDaniel E. B. and Pardthaisong T.: *Contraception* **8** (1973) 407–414.
22. Neumann F., von Berswordt-Wallrabe R., Elger W., Graf K-J, Hasan S. H., Mearing M., Nishino Y. and Steinbeck H.: *Acta endocr., Copenh.* suppl. **185** (1974) 315–350.
23. Reiter T.: *J. Am. Ger. Soc.* **11** (1963) 540–550.
24. Rosenfield A. G.: *Am. J. Obstet. Gynec.* (1974) **120,** 537–548.
25. Schering A. G.: *Material on Noristat/Depot Contraceptive* (1973).
26. Schwallie P. C. and Assenzo J. R.: *Contraception* (1974) **2,** 181–202.
27. Tatum H. J.: *Contraception* **1** (1970) 253–263.
28. Taubert H-D and Kuhl: *Steroids* **5** (1974) 613–626.
29. Weiner E. and Johansson E. D. B.: *Acta endocr., Copenh.* (1974) in press.