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Indications for Therapy with Progestational Agents

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The post war explosion in the rate of discovery and release of new potent pharmacological agents for general prescription has written a new chapter into the medical text books, that of "Iatrogenic Disorders". I mention this before passing on to discuss the indications for therapy with progestagens to stress that the prudent physician must weigh in the balance the *need* for treatment and the risk of side-effects. While the issues can clearly be seen in the short-term use of potent drugs to deal with brief episodes in ill patients, it is more difficult to bring the issues into perspective when what is being contemplated is the long-term exposure of a well person to potentially noxious agents to achieve a socially desirable effect with or without justification on strict medical grounds.

In the main, the indication for the administration of a progestagen is the correction of disorders of function arising from a relative or absolute deficiency of progesterone. Typically, such a situation arises with the cessation of luteal function in the female menstrual cycle with which the following changes have been described as being coincident (Table I).

While these changes in biochemical and physical parameters must be regarded as physiological concomitants of the withdrawal of ovarian hor-

Table I

Changes after cessation of luteal function

1. Weight gain
2. Retention of Na^+ and Cl^-
3. Vasoconstriction
4. Increased capillary fragility
5. Presence of circulating fibrinolysin
6. Greater urinary excretion of gonadotrophins
7. Decreased circulating eosinophiles
8. Decrease in platelets
9. Increased release of adrenal formaldehydic steroids
10. Decreased serum diastase
11. Lowered circulating level of vitamin A
12. Low blood sugar
13. Stimulation of the pancreas
14. Greater tolerance for lactose
15. Creatinuria
16. Low alveolar CO_2 tension
17. Reduction in tissue and plasma monoamine oxidase
18. Decreased sexual excitability
19. Accelerated protein catabolism
20. Lower basal temperature

Table II

Clinical uses of progestogens

1. Amenorrhoeas	7. Contraception
2. Dysfunctional uterine bleeding	8. Mazoplasia and virginal breast hypertrophy
3. Essential dysmenorrhoea	9. Nymphomania
4. Endometriosis	10. Delay of menstruation
5. Premenstrual tension	11. Psychiatric disorders associated with progesterone withdrawal or imbalance
6. Adenomatous endometrial hyperplasia (carcinoma in situ)	12. Migraine

Table III

Six main criteria in selecting progestogen

1. Potency	4. Convenience
2. Specificity	5. Suitability to the subject
3. Safety	6. Economy

mones, both estrogens and progestagens, certain clinical entities have become recognised as attributable to pathophysiological reactions which can be corrected by the administration of a progestagen alone.

If I may be excused for indulging for a moment in semantics, the title of this present session of our seminar is open to double interpretation. "Indications for Therapy with Progestational Agents" can mean either the clinical and laboratory indices which point to the *need* for therapy with such compounds, an aspect which has been very well examined so far. To avoid repetition therefore, may I ascribe a second meaning to the title and suggest that it could also be taken to mean – "The Parameters by which the suitability of a progestational agent for use in therapeutics may be assessed."

If we look at the accepted and the possible or potential clinical applications for progestogens (Table II), one indication, contraception, above all others stands out as different and distinct for special consideration because the recipient of therapy will be, in most instances, a very normal and a very healthy young woman. Therefore, the choice of preparation to be administered to her over a possible protracted period of time requires a great deal more thought about its selection and suitability for the individual subject than appears to be the case in the vast majority of instances to-day.

Six main criteria should guide the physician in selecting the most suitable progestogen for a particular subject (Table III).

1. Potency

The relative potency of progesterone and progestational agents using the induction of withdrawal bleeding as an index can be seen from Table IV.

Table IV

Relative potency of progesterone and progestational agents

Agent	Dose (mg/day for 5 days)
Progesterone	90–100
Ethisterone	20– 30
Dydrogesterone	5– 10
Ro 4-8347	1– 4
Norethisterone	2.5–5
Medroxyprogesterone acetate	2.5–5
Ethynodiol diacetate	0.5–1

2. Specificity

It is clearly of importance that particularly when a substance is to be administered chronically that it should have precise and specific range of activity. The following table indicates the spill-over of hormonal effect associated with the principle progestational agents in common clinical use to-day and compares them with the activity of a new retrosteroid Ro 4-8347 (Table V).

3. Safety

With the exception of those progestogens which have a 17-alkyl substituent in their formulae, the progestational agents we are considering have so far in their pure form, been singularly free from toxic effect. The 17 substituted compounds share with methyltestosterone the risk of causing cholestatic jaundice.

4. Convenience

All of the preparations share the convenience of being effective in once daily oral dosage schedules.

5. Suitability to the subject

Obviously, it would be undesirable to add a further hormonal stimulus of the same character to a patient that already demonstrates clinical evidence of androgenic response or excess estrogenic response. For example, the patient with evidence of hirsutism with or without acne is liable to experience an exacerbation if treated with a progestogen which carries an androgenic overlay of hormonal activity.

The induction of monoamine oxidase by progesterone and certain progestogenic substances is associated with the occurrence of depression and loss of libido in some patients treated with progestational agents. Caution must therefore be exercised especially in patients with a known history of depression when the use of progestational steroids is contemplated.

Table V

Spill-over of hormonal effect associated with principal progestational agents in comparison with Ro 4-8347

	Progestational	Estrogenic	Androgenic	Anabolic	Antiestrogenic	Pregnancy maintenance
Norethynodrel	+	–	0	0	0	0
Norethindrone	+	0	+	+	+	0
Medroxyprogesterone acetate	+	0	+	?	+	+
Chlormadinone acetate	+	0	?	?	+	+
Ethynodiol diacetate..	+	+	–	0	+	0
Ro 4-8347	+	0	0	0	0	+

+ = Androgenicity in female rabbit fetuses.
? = No information available.

Progestational agents have been found useful in the management of many clinical conditions. The potency, specificity, safety and convenience of Ro 4-8347, a new retrosteroid progestational compound, must be taken as indications which warrant making it more widely available for clinical use with a view to diminishing the incidence of iatrogenic disorders precipitated by the use of non-specific progestational agents.

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Discussion

E. Diczfalusy: I noticed that you did not include in your list the homosteroid norgestrel which seems to be for the time being perhaps the most active on a weight basis.

A. Darragh: I have not had an opportunity of studying it, so that I did not include that on it.