Value of Attachment Schemes

Dr. Umfraville values the G.P. attachment system as a very useful path of communication. If, for example, an immunization programme is not going well the chief nursing officer can call in her nurses and tell them so and they can then subtly influence the doctors with whom they work. Another valuable link would be the involvement of G.P.s in maternity and nursing units with the local authority providing the nursing staff and the hospital service providing the hotel and hostel service. Co-ordination among the 100 or so G.P.s on a divisional basis could also lead to organized night and weekend rotas and eliminate the use of deputizing services.

Dr. Umfraville’s ideas about bringing Cogwheel into the community are in keeping with the concept of the “specialist in community medicine” which the recent Report of the Working Party of Medical Administrators under the chairmanship of Dr. R. B. Hunter advocated. The medical officer of health would cease to “manage” domiciliary midwifery, psychiatry, and other conditions which were in fact much better understood by obstetricians, psychiatrists, and other hospital-based specialists. Instead, he would be able to concentrate on the epidemiological and organizational aspects of health care for which he had been trained: on running a health data unit, collecting and presenting health information to, for example, the district medical teams which would appear in 1974, and to the Cogwheel medical executive committee.

Even so, Hunter had missed the opportunity, Dr. Umfraville thought, of dividing M.O.H.’s into two specialties—medical administrators and epidemiologists. Instead, all medical officers of health were to be converted into managers and epidemiology could be done either as a part-time activity of the community physician or full-time as an underling in the area or regional health offices. In 1974 a medical officer of health would acquire not only a new area committee but also two new employers—the area and regional authorities—whereas now he was a boss himself within the local authority. Dr. Umfraville did not regard it as likely that the specialist in community medicine would be treated as a consultant supplying a service as pathologists and radiologists do, but as a “dogbody” untangling patients caught between the social service department, the general practitioners, and the hospital; or “unblocking” hospital beds occupied by patients with social problems.

Nevertheless, the changes produced by the implementation of the Cogwheel, Seebohm, Hunter, and the 1974 reorganization could allow the experienced medical officer of health to develop a new and rewarding role for himself. For many, however, the changes will mean divided loyalties, and more direction—Dr. Umfraville was adamant that, whatever the protestations, the district, area, and regional structure could not avoid becoming hierarchical.

References

Today’s Drugs

With the help of expert contributors we print in this section notes on drugs in common use

Drugs in Infertility

British Medical Journal, 1972, 4, 167-170

Now that ovulation can be induced artificially great changes have occurred in the management of infertility. There is now a need to identify patients with defective ovulation so that suitable ones may be chosen for treatment.

Preliminary Investigation

Before any drug therapy is contemplated it is essential to have a full history from both partners, with particular reference to infertility. In most clinics this is usually obtained from the wife initially: general physical examination with special emphasis on pelvic assessment is followed by taking a biopsy specimen of premenstrual endometrium. Tests of tubal patency performed are mostly insufflation and hysterosalpingogram, though laparoscopy and dye instillation is sometimes more appropriate. At the initial visit the patient is carefully instructed to record her basal temperature and asked to bring the graph with her at every visit. By the time the other investigations have been completed, her chart will include records of several cycles and variation between cycles can be assessed. Finally, a specimen of seminal fluid from the husband is also analysed.

Absence of ovulation may be diagnosed by a monophasic temperature record, even in the presence of menstruation. It is supported by a failure to find secretory endometrium on biopsy and the presence of poor cervical mucus. There may be a history of oligomenorrhoea that may indicate at the first visit the subsequent need for induction of ovulation, but the preliminary investigation must still be completed.

Ovulation may now be induced. The drugs are expensive and the courses of treatment protracted, involving frequent attendances at the clinic, so there should be no other bar to pregnancy. The patient’s need for treatment of the infertility must be established and her full co-operation must be ensured by fully discussing all the factors relevant to the use of these “fertility drugs.”

These patients are initially treated with clomiphene citrate, possibly after measuring basal oestrogen excretion beforehand, since higher values of this may indicate the possibility of successful induction of ovulation. The co-existence of amenorrhea presents a more complex problem. In addition to the above assessment, there must be a more elaborate investigation to exclude any organic process that requires treatment before the infertility is dealt with. The following investigations are performed in patients with amenorrhoea or in any patient before she is started on gonadotrophin therapy: measurements of
the serum protein bound iodine and serum thyroxine levels; glucose tolerance test; skull x-ray film; buccal smear and karyotype; two 24-hour urine specimens for 17-oestrogens, 17-hydroxy corticoids, total oestrogen, luteinizing hormone or total pituitary gonadotrophins. Laparoscopy should probably be performed at this point, if it has not been done already to examine the ovaries and to exclude unexpected tubal adhesions that may militate against conception.

The most frequent finding is that the results of all these tests are normal, and hence the probable diagnosis is hypothalamic amenorrhoea. Clomiphene therapy may then be started unless the patient has had an hypophysectomy or shows additional signs of hypopituitarism, when gonadotrophin therapy must be used.

**Induction of Ovulation**

**CLOMIPHENE**

First used in 1961 clomiphene citrate is now prescribed extensively as the initial agent for induction of ovulation. If menstrual cycles are occurring the drug may be given in an initial oral dose of 50 mg daily for five days, from the fifth or sixth day of the cycle, the first day being the first day of menstrual bleeding. Patients with the Stein-Leventhal syndrome tend to be more sensitive to clomiphene than others and therapy should be started on a dose of 25 mg daily. In patients with amenorrhoea treatment may be started arbitrarily so long as the temperature record indicates no recent ovulation.

**Side Effects**

The patient frequently experiences hot flushes while under treatment and though these are of no consequence she requires reassurance. Blurring of vision occurs occasionally; its cause is not known but it should engender caution in further treatment. Loss of hair or galactorrhoea is a rare problem. As a result of ovarian stimulation there may be mittelschmerz and a greater degree of stimulation may give rise to lower abdominal pain of varying severity. Pain of any consequence is usually associated with tenderness or enlargement of the ovaries and is frequent enough to warrant a vaginal examination of every patient before starting another course of treatment. If appreciable tenderness or enlargement is found further therapy should be withheld until this has resolved and then it may be wise to use a reduced dosage. Regular vaginal examinations forestall most of the instances of hyperstimulation caused by clomiphene.

If the temperature record shows no response to the initial course of clomiphene the dose may be increased by successive monthly increments of 50 mg to a maximum daily dosage of 200 mg. If no response is still achieved the investigations described above should be done before using gonadotrophins, always provided that the patient is still keen to continue.

Once ovulation has been induced as indicated by the temperature record, caution must be exercised in increasing the dose. If the length of follicular and luteal phases is roughly normal, if the rise in temperature is appreciable and well sustained during the luteal phase, then there should be no further dosage increase. The regimen may be maintained for up to another six consecutive cycles, maintaining clinical supervision and recording the temperature. Increase in dosage may result in deterioration of temperature response. Interestingly enough several pregnancies have occurred in patients up to six months following clomiphene therapy after long-standing infertility, perhaps as a result of longer term changes in the levels of follicular stimulating and luteinizing hormones or of the ratio between them. If the temperature records show a normal pattern the pregnancy rate is about 70%, particularly in patients with oligomenorrhoea, or secondary amenorrhoea. In both groups of patients any unduly long follicular phase can be shortened by increasing the dosage of clomiphene. The establishment of the normal time relationships within the menstrual cycle helps to maintain a regular coital pattern and improve the chances of conception.

**Anovular Cycles**

Patients with anovular cycles occurring at normal intervals show a lower response rate to clomiphene. Any such patient over 35 may be premenopausal and it may be worth estimating the urinary levels of luteinizing hormone at intervals at least 14 days after the last course of clomiphene. Excessive levels may be one of the earliest signs of the approaching menopause and ovarian refactoriness to stimulation. If the response to clomiphene is only a slow rise in temperature, or when this is brief or irregularly maintained, the chances of pregnancy are poor. In these patients the antioestrogenic effects of clomiphene are more pronounced and the cervical mucus is frequently scanty and viscid and postcoital tests give poor results. Urinary oestrogen assays may show low levels during the follicular phase. Preliminary results of treating these patients with menopausal gonadotrophins are encouraging; on the other hand treatment with human chorionic gonadotrophin during the luteal phase has given disappointing results.

Assays of urinary oestrogen have sometimes been thought to be essential in the management of therapy in patients with infertility but now that the induction of ovulation with clomiphene is becoming an everyday practice in the gynaecological clinic few laboratories could cope with the large number of requests this would entail. At present it seems preferable to reserve these assays for those cases in which defective luteal phases occur spontaneously or develop on treatment so that the underlying defect can be determined and therapy planned.

**GONADOTROPHINS**

The first pregnancy after the induction of ovulation with human pituitary extract was reported in 1958 and extensive work on dosage regimens has since been undertaken. Nevertheless, this material is in short supply, so for routine clinical use it has been replaced by human menopausal gonadotrophin (HMG), which is now available commercially as Pergonal (Searle) and Humegen (Organon). This latter has the advantage of giving different ratios of follicular stimulating to luteinizing hormones. If adequate ovulation occurs, either spontaneously or in response to clomiphene, there is no indication for using gonadotrophin therapy.

Treatment with HMG is planned to stimulate ovarian follicular growth directly and may be given by several different schedules. Two principal dosage regimens among many are daily injection and the alternate-day schedule. Whatever regimen is used, the most critical feature of treatment with gonadotrophins is monitoring the response. Though examination of the quality and quantity of cervical mucus is extremely useful in indicating clinical responses, once an optimum response of copious, watery mucus and good spinnaker have been obtained, there is no way of knowing whether the follicles have undergone hyperstimulation unless steroid assays (mostly the 24-hour urinary total oestrogen) have been done.

The object is to develop a single follicle with graded doses of HMG so that the urinary total oestrogen excretion lies between 50 and 150 μg/24 hrs at the peak of response. If the excretion value is less, follicular development will be insufficient, whereas if the level is higher probably more than one follicle will have been developed. The stimulated follicles will not liberate ova spontaneously in these patients with anovulation so that follicular rupture and ovulation then have to be achieved by injecting human chorionic gonadotrophin (HCG), which simulates the surge of luteinizing hormone in the normal patient. Further supplementary HCG is often given, but if the urinary oestrogen excretion is found to be too high then HCG injections must be withheld at all cost or else hyperstimulation will occur. The
signs of this condition are not apparent at the time of the HCG injection and only within the next few days do abdominal pain and ovarian enlargement occur. The ovaries may be readily palpable abdominally (even up to the umbilicus) and ascites, perhaps progressing to dehydration may follow; death has been reported.13 With appropriate monitoring, however, it is unusual to get more than ovarian enlargement and pain, but the latter may nevertheless be considerable. Hence unless a urinary oestrogen assay service is readily available it is not feasible to use HMG for induction of ovulation and though commercial assay services are available its use is largely restricted to hospital clinics.

The initial dose of HMG is two ampoules (75 IU follicular stimulating hormone), 75 IU luteinizing hormone per ampoule), given intramuscularly on alternate days (1, 3, 5, schedule). If there is no response, no treatment is given for one week and the dose is then increased by about a third in each course to a maximum of 20 × 75 IU follicular stimulating hormone and luteinizing hormone per injection. Pretreatment oestrogen assays should indicate low levels and the first injection is usually given six days after the onset of bleeding if any. If a response occurs, steroid excretion usually rises by the fifth day of treatment. Excretion then tends to rise steeply as the optimum dose is approached and the follicle usually reaches maturity by day 8, and improvement in the quality of the cervical mucus will also be noted. At this time the decision must be made whether HCG should be given. The decision is difficult, requiring considerable experience; the urinary collections and assay results are, of course, many hours behind the physiological events occurring at that time, so that the likely peak oestrogen excretion has to be estimated on the basis of the previous days’ excretions and the likely rate of rise. One advantage of the alternate-day schedule is that the rate of rise is likely to be slower than that found on the daily injection programme. When a response occurs, smaller adjustments in dosage may be required to achieve a peak urinary oestrogen excretion value within the expected range.

Injection regimens for HCG at the time of optimum response are also variable. They range arbitrarily from 500 IU daily for five days up to a single 6,000 IU injection or the HCG dose may be determined according to the luteal phase response to give the optimum HCG stimulus.13 Once HCG is given an autonomous luteal phase follows usually together with withdrawal bleeding if no pregnancy ensues.

Individual patients respond to different doses and a test dose of pregnant mares’ serum has been used to predict the likely dose level of HMG.14 The response in an individual patient to the same dose of HMG may be variable and the clinical response and the urinary oestrogen response do not always match. These difficulties combine to produce a definite risk of hyperstimulations and multiple pregnancies, though this is substantially reduced by careful clinical management and appropriate monitoring of steroid excretion. If hyperstimulation occurs there must be no further HMG or HCG given until the ovaries have returned to normal size and steroid excretion is basal. Treatment of the acute episode should be conservative if possible.

About 70% of patients treated with HMG have ovulatory steroid patterns and of these about 70% conceive, giving rise to a pregnancy rate of 50%. When apparent ovulation has been achieved, treatment is usually continued for four to six cycles at the same dose level to try and achieve pregnancy. If conception has not occurred by then or if there is no response to the maximum dose treatment is stopped and the patients are advised to consider adopting a child if this is acceptable.

Ovulation may also be induced by cyclofenil (F6066) a compound similar in structure to clomiphene and only just introduced into this country, though it has been used extensively in Europe. It is said to have an additional affinity for the corpus luteum15 but definitive clinical studies to assess its role in treating the defective luteal phase are still lacking. Another related compound, ICl 46,474 has been used16 but is not yet freely available.

Norethisterone, 5 mg three times daily, and dydrogesterone, 10 mg three times daily, have been used to supplement the luteal phase from days 15–25 of the cycle. Each results in the satisfactory maintenance of cervical temperature levels but the former can induce bizarre endometrial changes. Neither has been associated with a notable pregnancy rate and in view of the contraceptive effect of the follicle stimulating hormone it is tempting to question whether pregnancy is present, as the test result is likely to be abnormal, this is not a sensitive test. If it is not possible to achieve pregnancy it does not seem rational to use either as primary therapy unless a specific isolated deficiency of progesterone has been identified.

Thyroxine should be used as replacement therapy only when there is demonstrable hypothyroidism.

Oral contraception is frequently prescribed empirically hoping to induce a rebound increase in fertility. There is no evidence from controlled studies that this is so and it seems more logical to investigate the infertility.

**Recurrent Abortion**

As a double-blind controlled trial between 17hydroxyprogesterone caproate and placebo resulted in the same pregnancy salvage rates of patients with recurrent abortion,11 it is difficult to understand how hormone therapy in this condition can be of more than psychotherapeutic value. Certainly, treatment with other progestogens in pregnancy is contraindicated because of their potential androgenic effect.

**Endometriosis**

Progestogen therapy has an important role in treatment of endometriosis, either in early disease diagnosed at laparoscopy or in more extensive disease before or after conservative surgery. Pseudopregnancy may be induced with nor-ethisterone, beginning with 20 mg daily and increasing the dose by 10 mg daily if any vaginal spotting occurs. Amenorrhoea may be maintained at 40 to 60 mg daily for three to nine months depending on the severity of the disease. Atrophy of deposits of endometriotic tissue may also be induced by oral contraceptives but if pseudo-pregnancy is to be maintained the daily oestrogen dosage will need to be increased to more than 100 μg. There is no evidence for an increase in thromboembolism on these regimens.18

**Male Infertility**

If the result of the sperm count is normal, then the man requires no drug therapy and any abnormality in depositing the sperm in the vagina (as detected at the postcoital test) is attributable to poor technique or psychosexual difficulties. Investigation of an abnormal sperm count begins with a check on the technique of collection and a repeat count after an appropriate interval. If the result of this second test is also abnormal, then the man should be examined, with particular emphasis on secondary sex characteristics and the presence of an external genitalia. His wife should also be investigated and a postcoital test arranged.

No abnormality is found on physical examination of many men with low sperm counts. Unfortunately, a frequent finding is that only 20% or fewer of the existing sperms are motile—and this abnormality is extremely difficult to influence with treatment. Another not uncommon finding is the presence of small soft testes. Testicular biopsy in men with low counts will identify any destruction of sperm elements within the seminiferous tubules as well as showing the state of the Leydig cells. It is then feasible to assess whether a response to stimulation is possible. After treatment of any varicocele, drug therapy is the only course available. Azoospermia associated with normal histology on biopsy is obstructive in nature and cannot be treated by drugs.

**GONADOTROPHIN**

A eunuchoid appearance may be supported by the results of laboratory studies showing abnormalities of a hypothalamic-pituitary function: low urinary or plasma gonadotrophin levels and low plasma testosterone values together with radiological evidence of retarded bone age. A skull x-ray film may exclude the presence of an organic lesion. Patients with this rare con-
dition may respond to HMG therapy given for many months, and a normal sperm count and pregnancy have been reported. Additional HCG may be administered but given alone this drug may induce some hyalinization of seminiferous tubules and does not produce a normal sperm count. Overt hypogonadism occurring after puberty seems to be rare.

**CLOMIPHENE**

Clomiphene may be given to men with low sperm counts with either normal or small testes at a dose of 50 mg daily for three months, as the time taken for sperm to mature is 69-72 days. The spermatogonia A cells are stimulated by this regimen but depressed if higher dosages are used. A post-treatment sperm count will indicate the response, but most workers have found that this has been disappointing.

**MESTEROLONE**

This recently introduced androgen (1α-methyl-5α-androstane-17β-ol-3-one) is said to have a substantial advantage over methyltestosterone in that it does not suppress endogenous testosterone production. It may improve the sperm count and the fructose and prostaglandin content of semen and pregnancies have been reported after using it for treatment at doses up to 25 mg three times a day, nevertheless, more data are needed. Methyltestosterone depresses the levels of endogenous testosterone and since it is likely to depress sperm production it cannot be recommended.

**References**


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**Any Questions?**

We publish below a selection of questions and answers of general interest.

**Keloid Scarring after Scald**

*What is the risk of a keloid scar developing after a scald?*

Keloids are only seen in scalds severe enough to produce skin loss. This can be in very small areas only. Scalds can be of varying degrees of intensity. Firstly, there are the superficial lesions where skin is damaged but not destroyed in full thickness. Such a lesion is seen when very hot water or a brew of some kind comes into momentary splash contact with the skin. The resulting lesion can be expected to heal within 10-14 days and skin grafting is not called for since no skin is lost. The scars of such a lesion should not become keloidal.

Secondly, the condition of “mixed deep burn” is practically indistinguishable from that described above during the first few days after the burn. After a few days it becomes clear that there are areas of partial skin loss with many small areas of full thickness loss. Sometimes there are large areas of deep burn which were not apparent at first. It is only at 10 days that an exact assessment of the skin loss can be made. Early grafting is indicated in all burns cases where skin is lost, but in the vast majority of the second group and in the deeper burns resulting from the more prolonged application of extremely hot materials, such as molten metals and napalm, keloids are the rule rather than the exception. The risk of keloids forming in a scald can be diminished by early skin grafting.

Children are particularly prone to keloid formation; so are adult patients with pigmented skin. It is sometimes believed that an apparently superficial scald can be made more extensive and indeed result in almost total loss of skin if infection supervenes during treatment. While this may be true the initial scald must have been deeper than was at first suspected. It means that antibiotics are indispensable even in apparently superficial lesions.

**Treatment of Rheumatoid Arthritis in Pregnancy**

*A 25-year-old woman with one child (6 years old) has rheumatoid arthritis for which she is receiving gold therapy and indomethacin, as well as soluble aspirin. She wants another child—what advice should be given to her?*

If the patient is only moderately disabled by her arthritis there is no strong contraindication to her undergoing one further pregnancy. The first child would benefit considerably from a sibling provided that the mother is likely to be able to cope with the demands of both children, with or without extra help, during the inevitable recrudescences of the disease. Gold therapy must be stopped before she becomes pregnant because of the risk of toxic effects early in foetal life.

Pregnancy frequently induces a remission and salicylates alone may be a sufficient treatment. Stronger antirheumatic therapy will be needed to cope with the likely relapse after delivery. If indomethacin, phenylbutazone, or even corticosteroids are needed it would be wise to curtail breast-feeding. Gold therapy can be restarted but exerts its effect very slowly. Preparation should be made for some extra help when she returns home—if possible for six months—to diminish the additional stress of household duties.