Clinical pathology—déjà-vu?

Clinical investigation in a specialised laboratory¹

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It is now more than 50 years since, in 1927, Sydney Campbell Dyke banded together the growing number of pathologists to form the British Pathologists' Association, which later became known as The Association of Clinical Pathologists. Dyke had a wide-ranging interest in medicine, unlike some of his successors, who have relinquished their clinical affiliations and have retired to the confines of their laboratories.

Under the influence of men such as Dyke, clinical pathology expanded into a discipline in which one had to be an expert in a wide range of pathological subjects and to have knowledge not only of their laboratory aspects but also of their clinical applications. With the advancement of medical science, however, it is no longer possible to be an expert in all aspects of the discipline, and many have neglected the clinical aspects.

Challenges are appearing on all sides. Within our laboratories some of the technical staffs believe that they should be in charge and that the medical pathologist should interest himself only in what are termed 'clinical matters'. This point of view has been propounded in the search for an elevation in status and the additional salary benefits that normally accompany it. The possible effects on the patient appear to have been overlooked.

Some clinical colleagues have also encroached upon the pathologist by the establishment of small personal laboratories, particularly within university hospitals. In these laboratories, research projects quickly blossom into a routine service to the patient, resulting in the exclusion of the pathology laboratory and the clinical pathologist.

Although the days of Dyke are over, it is essential

that clinical pathology remains a specialty attractive to medical men and women. It is only the medically qualified, scientifically trained person who is in a position to determine rationally the types of test to be introduced and how they should be carried out and to examine the results critically in order to determine if they are providing valid information which helps in the diagnosis and treatment of the patient. At the instigation of the Department of Health and Social Security and the Royal College of Obstetricians and Gynaecologists, the endocrinology laboratory at the Jessop Hospital, Sheffield was chosen as one of three laboratories to develop a trophoblastic tumour screening service for the entire country. This service, together with the subsequent recognition of the laboratory as a supra-regional laboratory for certain steroid and polypeptide hormones, has been supplemented by clinical facilities both in the treatment of trophoblastic disease and in the field of female and male infertility. These laboratory-clinical services will now be considered in more detail.

The trophoblastic tumour screening service

It is accepted that women who have hydatidiform moles have a relatively high risk of malignant sequelae, particularly during the two years after evacuation. In European populations, over 90% of moles die out spontaneously. It is in the remainder that, if treatment is not given, the inevitable progress of the mole may result in the death of the woman.

In our experience, 8% of patients registered for follow-up have required treatment. There is general agreement that, if chemotherapy is required, prompt treatment should be administered as drug-resistance increases in frequency with longer intervals between removal of the mole and the start of chemotherapy. Since 1973 the policy in this country has been to select patients for treatment on the basis of regular measurement of human chorionic gonadotrophin

¹A shortened version of the first Dyke Memorial Lecture given on Wednesday, 24 January 1979, at the South Staffordshire Medical Centre, Wolverhampton WV10 0QP

(HCG), which provides a guide to the persistence of trophoblast after evacuation. The registration scheme gives all gynaecologists access to the laboratories in London, Sheffield, and Dundee and provides a choice of follow-up procedures. The referring consultant retains control and responsibility for the patient, unless a request is made for the specialist centre to undertake such treatment as may be needed.

Under the most widely used follow-up procedure, a prepaid kit is despatched by the laboratory to the patient. Samples of urine are returned and, after analysis, the HCG result is sent directly to the referring gynaecologist. Assays are performed initially at weekly intervals and then at two-weekly intervals until normal levels are reached. Subsequently estimations are made monthly until the end of the first year and three-monthly during the second year. During the first six years of the scheme (1973-78) 1093 women have been registered with the Sheffield laboratory. Currently, 200 new cases are notified each year. Patients are advised not to become pregnant during the two-year follow-up period because of the difficulty in differentiating the source of the HCG.

INCIDENCE

The incidence of the disease for the Sheffield area has been computed as 1:1200 live births. It seems unlikely that this figure will differ markedly from that for the United Kingdom as a whole but it is markedly different from that in countries such as Taiwan where there is a reported incidence of 1:120. Reasons for this difference are unknown. Analysis of the Sheffield figures according to the age of the patient has demonstrated a marked increase in the incidence of trophoblastic disease over the age of 35 years (1:506) and an even greater incidence over the age of 45 years (1:17).

TREATMENT

During the six-year period 84 patients have been treated. The first 58 are currently reported, a minimum two-year interval having been allowed for possible recurrence. Three types of treatment have been used, the principal cytotoxic agent being methotrexate with folinic acid rescue.

The most commonly used regime consists of methotrexate given at 50 mg per day intramuscularly on day 1 and repeated at 48-hour intervals for four doses. Thirty hours after each dose 6 mg of folinic acid are administered intramuscularly. This constitutes one course of treatment, and patients are given either four or six courses of treatment according to their classification into low- or high-risk categories. Those in whom the interval between

evacuation of the mole and treatment is less than six months, and where there is no evidence of metastatic spread, constitute the low-risk category. A single, high-dose regime has also been tried, consisting of vincristine, 2 mg intravenously, followed 30 minutes later by the intravenous infusion of 2.5 g methotrexate in 500 ml normal saline administered over 6 hours. Folinic acid rescue is started 2 hours after the completion of the infusion, 6 mg being given intramuscularly 6-hourly for 12 doses.

The third dosage schedule is reserved for the resistant cases and involves the use of combinations of methotrexate, vincristine, actinomycin D, cyclophosphamide, vinblastine, and adriamycin (the 'triple regime').

RESULTS OF TREATMENT

Thirty-one patients were treated on the standard methotrexate-folinic acid regime and 27 went into remission. The remaining four required more aggressive therapy; using the 'triple regime' three were successfully controlled.

Twenty-seven patients were treated on the single-dose methotrexate-folinic acid regime with 22 successful remissions. The remaining five were subsequently treated with the standard regime, four going into remission. Although the practical advantages of a single-dose regime are obvious, it was considered that the failure rate was unacceptably high, and this form of treatment has now been abandoned. The one failure on both regimes was then treated using the 'triple regime', with hysterectomy and radiotherapy to an unresectable pulmonary focus: she remains in remission.

One patient only has died, to give an overall remission rate of 98.3%.

Reproductive physiology

The investigation and treatment of ovulatory dysfunction has become a prime responsibility of this laboratory. It became evident, from an earlier study, that the normally accepted parameters of ovulation, although possibly appropriate in normally menstruating, normally ovulatory women, did not always apply in infertile women regardless of menstrual habit.

The accepted signs and symptoms of ovulation include the mid-cycle biphasic shift of body temperature, the presence of a secretory endometrium during the luteal phase of the cycle together with the appropriate appearance of histochemically detected endometrial enzymes, the presence of a corpus luteum during the luteal phase, and the hormonal picture consisting of a mid-cycle surge of oestrogens and luteinising hormone with a subsequent elevation

of progesterone and its urinary metabolite pregnanediol during the luteal phase.

In many instances it has been shown that there is considerable disagreement if multiple signs and symptoms of ovulation are searched for in the same women. It has been demonstrated that in some infertile women the well-established parameters of a biphasic temperature chart and a secretory histological picture are out of step with all other determinants of ovulatory function. The routine investigations carried out in this unit on all referred patients consist of baseline hormonal estimations of pituitary, ovarian, and adrenal activity in urine starting on day 3 of the cycle and at three- or four-day intervals thereafter. On occasions additional samples are collected between days 11 and 16 to determine more accurately the time of ovulation. A blood sample is also taken for the determination of thyroid and liver function and the level of prolactin.

TREATMENT

Where a defect in ovulation is demonstrated three types of treatment have been used, namely, pituitary gonadotrophin, ovarian stimulants such as clomiphene citrate, and bromocriptine. Up to the end of 1978, 249 pregnancies have been achieved in women who have previously been routinely treated in gynaecological clinics and in whom there was a mean duration of infertility of four years: this represents a success rate of just over 40%.

Pituitary gonadotrophin

Interest in this field was initially stimulated by the work of Gemzell in Sweden. He was able to demonstrate that in an appropriate clinical situation gonadotrophin extracted from pituitary glands obtained post mortem was extremely efficacious in inducing ovulation. A similar procedure has been used in Sheffield.

Pituitary gonadotrophin is reserved for the

amenorrhoeic women who do not exhibit hormonal evidence of ovarian failure. It is administered intramuscularly, the dose being titred by the ovarian response in terms of urinary oestrogen production. An attempt is made to induce a steadily rising level of oestrogen over nine days, at which time 5000 IU HCG, which is luteinising in its activity, is administered. This should bring about ovulation of the developed follicle. Using this technique, we have so far achieved 58 pregnancies. Of these, 42 have ended in live births and 16 have aborted. The breakdown of these results is shown in Table 1. As will be observed, there is a high abortion rate (27.6%) and a high multiple pregnancy rate (17.2%).

Clomiphene citrate

Clomiphene acts by competing with oestrogens for receptor sites in the hypothalamus, leading to an increase in the output of gonadotrophins. This in turn stimulates the maturation and endocrine activity of the ovarian follicle and subsequent development and activity of the corpus luteum. It is administered at a dose level of 50 mg per day for five days, starting where appropriate on the fifth day of the cycle. The dose may be increased in subsequent cycles in the absence of a response. All patients collect 24-hour samples of urine for the six days after completion of the course of treatment to assess oestrogen output, and on days 20 and 22 for the estimation of pregnanediol as an assessment of luteal function. In subsequent courses collections of urine are made only on days 20 and 22 provided that the surge of oestrogen production was previously noted.

Using clomiphene citrate and its related drugs, we have been successful in obtaining 165 pregnancies. The breakdown of these pregnancies is shown in Table 1 and is very different from the figures obtained with pituitary gonadotrophin. The multiple pregnancy rate is 2.4% and the abortion rate 10.9%. Clomiphene citrate has been found to be of greatest

Table 1

Outcome of pregnancies induced by FSH

Total number of pregnancies 58

Livebirths 42	Single	35
	Twins	4
	Triplets	2
	Quads	1
Abortions 16	Single	13
	Triplets	3

Abortions

27.6% of the total number of pregnancies ended in abortion

Multiple pregnancy

17.2% of the total number of pregnancies were multiple

16.6% of the livebirths were multiple

18.7% of the total number of abortions were multiple

Outcome of pregnancies induced by clomiphene citrate

Total number of pregnancies 165

Livebirths 143	Single	141
	Twins	2
	Single	16
Abortions 18	Twins	1
	Triplets	1

Abortions

10.9% of the total number of pregnancies ended in abortion

Multiple pregnancy

2.4% of the total number of pregnancies were multiple

1.4% of the total number of livebirths were multiple

11.1% of the total number of abortions were multiple

Table 2 Range of prolactin levels—patients treated with bromocriptine and the occurrence of pregnancy

	Prolactin (mIU/l)					
	< 360	361-500	501-800	801-1000	1001-1500	> 1501
Total number of patients	10	19	41	13	10	8
Total number of pregnancies after treatment	0	3	7	3	4	4
% pregnant	0	15.8	17.0	23	40	50
Total number of patients excluding all known infertility factors	8	11	21	5	6	6
Total number of pregnancies after treatment	0	3	5	2	3	4
% pregnant	0	27	24	40	50	66

use in the oligomenorrhoeic and regularly menstruating but anovulatory women. Adequate ovarian function is essential, and there should be no evidence of a gross elevation of FSH and LH levels. Most of the pregnancies with clomiphene citrate have occurred (62%) within the first three courses of treatment. It is also surprising that a number of women became pregnant within three months after the routine six courses of treatment (24%).

Bromocriptine

The ability to estimate prolactin and the concurrent development of bromocriptine has markedly altered treatment patterns in a number of patients. As with all new methods of treatment there appears to be an over-emphasis on its use at the present time.

Bromocriptine acts at two sites, indirectly in the hypothalamus as a dopamine agonist, thus increasing the release of prolactin inhibitory factor, and directly on the pituitary gland to inhibit the release of prolactin from the cells of that organ. The total number of pregnancies so far induced by the use of bromocriptine is 26: these were all in patients with elevated prolactin levels. Figures are currently available for the first 102 treated patients. So far in this group there have been 21 pregnancies. From Table 2 it will be observed that there is a high incidence of pregnancy in those patients with the higher levels of prolactin excretion when first estimated. The converse is also clearly demonstrated.

Donor insemination

Infertile patients are referred to this laboratory

because of azoospermia or severe oligospermia, and after hormonal investigation treatment is often begun with either mesterolone or clomiphene citrate. There remains a group of men in whom treatment does not elicit a response, and these are considered for donor insemination. To this group must be added those in whom there is an unacceptable risk of congenital abnormality or inherited disease, and those with a severe history of Rhesus incompatibility.

About 240 new couples are seen each year. They are initially referred for discussion and subsequent endocrine investigation. In suitable cases, donor insemination is offered, and the timing of insemination is based on the hormonal patterns found. Over 100 pregnancies have now been induced, between 50 and 60% of the referred women obtaining their desired pregnancy.

Clinical pathology and those who practise this specialty are at a crossroads. The bridge between the laboratory and the patient must remain. The alternative is a further isolation of the laboratory and eventual domination by non-medical personnel; this would be to the detriment of the patient. We must become, if this has not already occurred, latter-day Sydney Dykes, expand from our 'laboratory shrines', and, in the best traditions of the founder of The Association of Clinical Pathologists, extend our influence as versatile experts both in the laboratory and in various specialised clinical fields.

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