Underlying data supporting:

Misjudging Early Embryo Mortality in Natural Human Reproduction

(Transcripts of Expert Witness Statements)

by Dr Gavin E. Jarvis

Department of Physiology, Development & Neuroscience,

University of Cambridge, Cambridge CB2 3EG, UK

This dataset consists of transcripts of scientific witness statements submitted as evidence in *R (on the application of Smeaton) v Secretary of State for Health* [2002] EWHC 610 (admin) (18 April 2002) (Case No: CO/928/01). They have been made available to enable readers to evaluate claims made in the main article and to see the full extent of the evidence presented to The Honourable Mr Justice Munby.

This dataset is available online here: https://doi.org/10.17863/CAM.53696.

Where no explicit consent to publish the statements has been obtained from a witness, the content has been redacted, except where that content has been quoted by Munby J. in his judgment or directly referenced by me in the main article.

The transcripts were made personally by me from photocopies of documents in the archives of the Claimant. Every attempt has been made to ensure that the transcripts are faithful reproductions of these photocopies. This means that typographical errors in the original documents have been retained and transcribed. Any errors of transcription are my responsibility and will be corrected on notification. A full unredacted transcript and copies of original documents will be supplied on request. Personal addresses will remain redacted.

This dataset may be updated in the future to incorporate corrections and/or provide unredacted versions of some witness statements - see metadata associated with https://doi.org/10.17863/CAM.53696 for notice of updated versions.

Gavin E. Jarvis, 3rd July 2020

Witness statements (WS) are listed in alphabetical order of witness surname.

Name of Witness	Date of signed WS	Pages	Referred to in main article as
Prof. Chris Barratt	22nd October 2001	2-3	*WSCB*
Prof. Peter Braude	10th July 2001	4-6	*WSPB*
Prof. Nigel Brown	3rd August 2001	7-11	*WSNB*
Prof. James Owen Drife	3rd August 2001	12-15	*WSJD*
Dr Peter Longthorne	3rd August 2001	16-20	*WSPL*
Dr John McLean	22nd October 2001	21-30	*WSJM1*
Dr John McLean	4th February 2002	31	*WSJM2*
Dr Connie Smith	12th July 2001	32-37	*WSCS*
Prof. Steven Smith	19th October 2001	38-41	*WSSS*

WITNESS STATEMENT OF PROFESSOR CHRIS BARRATT

I, Professor Chris Barratt of The University of Birmingham, will say as follows:

1. I have been instructed by the Claimant's solicitors to comment upon the role of sperm in the reproductive process. I understand it to be part of the case advanced by the Secretary of State and by Schering that one of the ways in which Levonelle acts is by impeding sperm motility and thereby preventing the sperm reaching the egg. The conclusion that I reach in this witness statement is that unless Levonelle is taken prior to or at the time of coitus, its effect upon preventing sperm reaching the site of fertilisation will be negligible. I briefly set out below my relevant qualifications and experience.
2. I have a PhD in reproductive biology (graduated 1985) and 18 years experience working with human infertility. I am the Scientific Director of the Assisted Conception Unit at the Birmingham Women's Hospital. We perform over 600 cycles of IVF/ICSI (intra cytoplasmic sperm injection) every year. In addition we are the regional NHS Centre for diagnosis and treatment of infertility.
3. I am also a Professor and Head of the Reproductive Biology and Genetics Research Unit at the University of Birmingham.
4. My area of expertise is male infertility. I am a member of several fertility committees. I am on the educational board of the World Health Organisation (Semen Analysis). I have written over 100 research papers in male infertility and have edited several textbooks on the subject.

Sperm And Human Reproduction

5. It is a commonly held view that sperm cannot ascend from the vagina to the oviducts outside a woman's fertile period. However, studies have shown this not to be the case, although the levels of sperm penetration are much lower than at times closer to ovulation. (Ash 1978: Templeton and Mortimer, 1982; Ramsewak et al 1990). A large scale study, conducted by Wilcox et al (New England Journal of Medicine, vol 333:No, 23: Dec 7,1995) found that the most likely days for conception to occur was the day of ovulation itself (where there was a 33% probability of conception) and the two days preceding ovulation (31% and 27% probabilities). However, he could not exclude a possibility of conception of up to 12% on the day following ovulation.
6. There are no specific studies that have used natural or donor insemination to determine the minimum time period from insemination to conception (fertilisation). Studies using in vitro fertilisation (test tube baby treatment) shows that fertilisation (formation of two pronuclei) occurs 16-24 hours after insemination of the egg with the spermatozoa.
7. Sperm are able to reach the oviducts within a very short time after insemination. A study by Rubinstein et al (Fert Steril 1951;2:51-19) conducted on 51 women, who had been inseminated prior to undergoing hysterectomies, found that motile sperm could already be present in the oviducts within half an hour of insemination The women in the study were undergoing a hysterectomy because of multiple or large fibroids, polyps or extensive endometriosis. As insemination was not confined to any particular time of the menstrual cycle the results demonstrated that sperm could be transported through cervical mucus to the oviducts at any time of the cycle. A more recent study using uterine flushing (Williams et al. Human Reproduction 1993;8: 2019-2026) showed that motile sperm were recovered from the uterus within 4 hours of coitus in 8out of 10 women.
8. Freshly ejaculated sperm does not have the ability to fertilise the ovum. In order to do this, the sperm needs to undergo a complex process termed "capacitation" which occurs in vivo and can be reproduced in vitro. Capacitation involves a series of biochemical and molecular events that prepare the spermatozoon for a full functional competence, i.e. formation of a viable embryo. These biochemical and molecular details are poorly understood in the human, but involve remodelling of sperm plasma membrane. Capacitation is also associated with the change in the pattern of sperm

motility termed “hyperactivation”. As yet it is unknown the minimum time it takes for human spermatozoon to capacitate. Studies in vitro suggest that it takes at least two hours from ejaculation for a sperm to be able to pass through the cumulus and penetrate the zona pellucida (out eggcoat). We do not know if this can be accelerated in vivo.

9. I am sure that sperm which is capable of fertilising the ovum will be present in the ampulla of the uterine tube (where fertilisation takes place) within a short time of coitus and will certainly be present within 12 hours.

The effect of Levonorgestrel upon sperm transport

10. I am only aware of one study examining the effect of Levonorgestrel on sperm penetration (Kovacs et al 2000). The authors reported the significant reduction in sperm penetration approximately 12 hours after taking the progesterone-only pill. Levonelle is taken after coitus and usually at least 12 hours after coitus. By this time capacitated sperm are highly likely already to have reached the oviducts. Given that Levonorgestrel may take 12 hours to demonstrate a significant effect on the cervical mucus, and given that sperm are able to make it through the cervix very much faster than this therefore, for Levonelle to be effective in preventing sperm from reaching the site of fertilisation it would need to be administered many hours prior to coitus. If Levonelle is administered at any time subsequent to coitus its effect on sperm transport is likely to be negligible.

I, Professor Chris Barratt, believe that the facts set out above are true and that the opinions I have expressed are correct. I understand that it is my duty to help the Court on matters within my expertise and that this duty overrides any obligation to those who have instructed me in this matter.

(*Signed*: ‘C Barratt’)

Signed……

(*Dated*: ‘22/10/01’)

Dated……

WITNESS STATEMENT OF PROFESSOR PETER BRAUDE

1. [redacted]

2. [redacted]

[redacted]

3. [redacted]

4. [redacted]

5. [redacted]

6. [redacted]

[redacted]

7. [redacted]

[redacted]

8. It is to be noted that of the eggs that are successfully fertilised, a large number do not eventually become implanted in the uterine wall. Many do not develop normally at the cleavage stage, with the result that the cells die and the embryo degenerates. At this stage, the woman would not be aware of shedding the embryo, which would be about 0.1mm in size and would easily be lost in the normal daily discharge of cells from the uterus and the vagina. Even if the blastocyst stage is reached, that implantation will only occur where the endometrium is at the particular stage of development capable of receiving the blastocyst.
9. [redacted]

[redacted]

10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]

[redacted]

15. Although hCG may be detected in the urine of women, this is not confirmation of a viable nor of a continuing pregnancy. In a classic study by Wilcox et al[3] they found that using a sensitive radio-immunoassay, nearly one quarter (22%; 43/198) of women attempting pregnancy, showed a positive hCG but did not continue to miss their menstrual period or continue with a clinical pregnancy. In another study, using a highly sensitive non-routine assay, and testing the urine of 217 women over 1253 menstrual cycles, unsuspected early pregnancies occurred which failed spontaneously before the first missed period in between 11% and 27% of cycles depending on the cut-off used and the subgroup analysed. For accurate diagnosis using such assays they recommended that "urine collection begins 4 – 5 days before the expected next menses", thus confirming the inability to diagnose pregnancy reliably before this time.
16. [redacted]

[redacted]

[redacted]

[3] Incidence of early loss of pregnancy. (1988) Wilcox, Weinberg, O''Connor, et al, New England Journal of

[redacted]

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

[redacted]

5. [redacted]

[redacted]

6. [redacted]

7. [redacted]

8. [redacted]

9. [redacted]

10. [redacted]

11. [redacted]

[redacted]

12. [redacted]

13. [redacted]

14. [redacted]

15. [redacted]

16. [redacted]

17. [redacted]

18. [redacted]

19. [redacted]

20. [redacted]

21. [redacted]

The Incidence of Death of Fertilised Eggs

22. It is striking that the usual fate of a fertilized human egg is to die. The proportion of fertilized eggs that produce a live full-term baby (in the absence of contraceptive measures) is not known precisely, but is probably only 40%[1]. The other 60% die, at all stages from fertilization to late pregnancy. Perhaps 20% or so do not implant in the uterus; there are no systemic signs that fertilization has occurred, and the woman is unaware. The next common stage of conceptal death is soon after implantation, when the consequence can be a heavier than usual menstrual flow, perhaps somewhat delayed, which can be noticeable. [redacted]

[1] Edmonds D.K. , Lindsay K.S. , Miller J.F. , Williamson E. , Wood P.J. Early Embryonic Mortality in Women, Fertility and Sterility 1982 Vol 38 447-453.

[redacted]

23. [redacted]

[redacted]

[redacted]

WITNESS STATEMENT OF PROFESSOR JAMES OWEN DRIFE

I, PROFESSOR JAMES OWEN DRIFE of Department of Obstetrics & Gynaecology, D Floor, Clarendon Wing, Belmont Grove, Leeds LS2 9NF **WILL SAY AS FOLLOWS**:-

1. My name is James Owen Drife. I was born in 1947 and qualified as a doctor in Edinburgh in 1971. My qualifications are BSc(Hons), MB ChB, MD, FRCOG, FRCPEd, FRCSEd. After working in junior hospital posts in obstetrics and gynaecology in Edinburgh I was a lecturer in obstetrics and gynaecology in Bristol from 1979 to 1982, and then a consultant obstetrician and gynaecologist in Leicester. Since 1990 I have been professor of obstetrics and gynaecology at the University of Leeds, and an honorary obstetrician and gynaecologist to the General Infirmary at Leeds. I am vice-president of the Royal College of Obstetricians and Gynaecologists and an elected member of the General Medical Council. A copy of my Curriculum Vitae is at Exhibit "JOD1".
2. My clinical practice involves a weekly general gynaecological outpatient clinic in which I see patients suffering from all types of gynaecological conditions including cancer, and I advise on problems with contraception. I am on call on a regular basis for gynaecological and obstetric emergencies, and this work may involve delivering babies and caring for women who are having miscarriages. I supervise the termination of pregnancy service at the General Infirmary at Leeds and carry out surgical and medical terminations on a regular basis. My special clinical interest is reproductive medicine, and I was part of the IVF team in Leicester. I have a particular interest in contraception and have written extensively on the intrauterine contraceptive device, post-coital contraception and the oral contraceptive pill.
3. I have been asked by Schering Health Care Limited to provide an account of the meanings I ascribe to terms in everyday use in gynaecological practice today. The meaning of some terms has altered slightly during the thirty years that I have been practising medicine. There are two reasons for this. One is that knowledge has increased among both doctors and the public as a result of medical advances – in particular the introduction of IVF, the development of highly sensitive pregnancy tests and the refinement of ultrasound imaging, all of which occurred during the 1980s. The other reason is a growing sensitivity among doctors to the implications that medical language has for patients.
4. The meaning of the word **"pregnancy"** has not changed in relation to the later stages of gestation, but I consider that its meaning has changed in relation to the earliest stages. In the past, pregnancy was suspected when a woman missed her period and was confirmed by uterine enlargement, found on abdominal or pelvic examination. Nowadays, pregnancy is confirmed by a positive pregnancy test, which can be carried out on either urine or blood. It tests for HCG (human chorionic gonadotrophin), a hormone produced by the placenta or the cells destined to form the placenta. A pregnancy does not necessarily require the presence of an embryo or fetus. For example, a common complication of early pregnancy is an "anembryonic pregnancy", in which the pregnancy test is positive, the woman feels pregnant and the placental tissue is developing, but embryonic development has failed at a very early stage. Such a pregnancy can continue for two or three months before ending in miscarriage. Nor does a pregnancy have to be in the uterus: an "ectopic pregnancy" develops outside the uterus, commonly in the fallopian tube. Initially it may include a live embryo but the pregnancy almost always fails, usually around the second month. Bearing all these factors in mind, in my experience neither doctors nor women normally consider that a pregnancy has begun until the pregnancy test is positive, even when (as in IVF) an embryo has been placed inside the uterus. The pregnancy test does not become positive until HCG can be detected, usually around the time of the missed menstrual period.
5. In my view **"conception"** means the meeting of the sperm and the oocyte (that is, the egg or ovum). It is a term used more by lay people than medical people, but lay people nowadays are familiar with

the idea of the sperm meeting and being absorbed into the oocyte. This is in fact a process which takes place over some hours, rather than a single point in time.

6. **"Fertilisation"** refers to the process by which the sperm and oocyte meet and fuse. This process can now be observed in the IVF laboratory: it is known to involve a number of steps and take more than 24 hours. The outer wall of the sperm attaches itself to the outer wall of the oocyte, and then the walls dissolve and the nucleus of the sperm is transported to the nucleus of the oocyte. The two nuclei, each containing 23 chromosomes, fuse and form a full complement of 46 chromosomes. The new single nucleus then begins to divide, and when this is seen down the microscope it confirms that fertilisation has occurred. I think the term "fertilisation" covers the whole process I have described. I do not think there is any purpose in choosing a point during this process that could be defined as "conception".
7. **"Implantation"** means the process by which the cells destined to form the pregnancy bury themselves in the wall of the uterus. It is now known that fertilisation takes place in the fallopian tube, close to the ovary. The fertilised egg divides into two cells and then four, and so on, and while doing so it is transported down the fallopian tube, arriving in the uterus some 4-5 days after fertilisation. By this time it consists of a ball of cells (the "blastocyst") with a fluid-filled space at its centre. Most of the cells are destined to form the placenta and membranes. Within the blastocyst are a small number of cells (the "inner cell mass") which will become the embryo and then the fetus. The blastocyst adheres to the surface of the uterine lining (the endometrium), and then invades the endometrium to lie just under the surface. This remarkable process is ill-understood. We do not know why the blastocyst adheres to the endometrium, having (usually) avoided adhering to the lining of the fallopian tube. Nor do we know why it invades only the superficial layers of the endometrium but usually ceases invasion before reaching the muscular layer of the uterine wall. In my view the process of adherence precedes the process of implantation. Implantation itself starts when the blastocyst begins to bury itself in the endometrium. We do not know how long the blastocyst remains attached to the surface of the endometrium before starting to implant. The very earliest point that implantation could begin is 4-5 days after fertilisation. Its end point is also difficult to define as the invasion of cells into maternal blood vessels continues for days or weeks.
8. **"Miscarriage"** means the loss of a clinically recognised pregnancy. Since a pregnancy cannot be recognised until HCG can be detected, and HCG is not produced until implantation has been initiated, a miscarriage will not occur prior to implantation. As I have explained above, a clinically recognised pregnancy generally means that at least one menstrual period has been missed. Rarely nowadays a pregnancy test may be positive before a period is missed and if the period occurs a few days late it may be considered to be a very early miscarriage, but this applies to only a small number of cases. From various strands of evidence it has been calculated that in a normally cycling woman who is sexually active and not using contraception, conception will occur in about 85% of cycles. Of those fertilised eggs, around 15% will be lost before implantation begins. Of those which begin to implant, only about half will implant successfully. Of the half which do implant successfully (as shown by detectable HCG in the woman's urine), between one third and one half will be lost at the time of the menses. Overall, therefore, around 75% of all conceptions are followed by an apparently normal period.[1] These losses of fertilised eggs, whether before or after implantation in a cycle ending with normal menstruation, do not involve a clinically recognised pregnancy and are not covered by the term "miscarriage".
9. **"Abortion"** used to be the medical term for "miscarriage", and indeed still is as far as many doctors and textbooks are concerned. However, it is now recognised that for most lay people "abortion" means artificial termination of pregnancy. Increasingly doctors are using the word "miscarriage" when a pregnancy ends before 24 weeks' gestation. A pregnancy in which the embryo fails to develop

[1] Drife, JO. British Medical Journal 1983; 286:294.

used to be called a “missed abortion”, but “anembryonic pregnancy” is the most accurate medical term and “silent miscarriage” is increasingly preferred when talking to the patient.

10. **“Abortifacient”** is not a word in everyday use among gynaecologists. It refers to a drug which causes a miscarriage, as defined above. There are few drugs which can do this reliably. One is the antiprogestogen *Mifepristone*, (usually used along with a prostaglandin). Mifepristone antagonises the effects of progesterone, the hormone which maintains pregnancy. Mifepristone can be used in early pregnancy, up to nine weeks from the last menstrual period but is not used before the pregnancy test is positive. I would use the term “abortifacient” to describe a drug that acted after implantation had occurred and would not used to describe a drug that could prevent or inhibit the implantation process. Levonelle / Levonelle-2 (hereafter “Levonelle”) is a progestogen (ie. It acts like progesterone). As progestogens are used clinically to support pregnancy in its early stages (particularly after IVF), I consider from a biological point of view it is impossible to believe that the same drugs could act as abortifacients. I am sure that if fertilisation has occurred, Levonelle acts to prevent or disturb adhesion of the blastocyst, before implantation begins.
11. In my view **pregnancy begins** when the pregnancy test is positive, some ten to fourteen days after conception. My reasons relate to the large numbers of fertilised oocytes which are believed to be lost during the normal menstrual cycle. I do not believe these can be described as “pregnancies”. When teaching students, I describe the process of spermatogenesis, ovulation and fertilisation as a continuum with implantation and early pregnancy development. I reserve the term “pregnancy” for the phase after implantation. When talking to patients, I would not use the term “pregnancy” until a pregnancy test was positive or a menstrual period had been missed.
12. I consider that dating the **start of life** from a particular point in time is not helpful in a clinical sense or indeed possible in a scientific sense. I agree with those who have pointed out that DNA (the self-replicating molecule within the chromosomes) is immortal. It perpetuates itself endlessly, sometimes in the cells of the human body and sometimes in the sperm or the eggs. This continuum is uninterrupted, except if an individual dies childless.
13. I have not studied the **Human Fertilisation and Embryology Act** in detail as it became the law after I left Leicester, where I was part of the IVF team. I am, however, familiar with its main points and I find its provisions relating to biology helpful.
14. It has been suggested that **Levonelle** may interfere with implantation, or at least that this possibility cannot be ruled out. As stated above, I am willing to accept that Levonelle could interfere with the adhesion of the blastocyst to the surface of the endometrium, but I do not believe that Levonelle can interrupt the process of implantation once it is under way. Therefore I do not believe that Levonelle causes miscarriage. As discussed above, in my view “miscarriage” means the loss of a clinically recognisable pregnancy after a menstrual period has been missed. Therefore I do not believe that Levonelle procures a miscarriage, even if the definition of miscarriage were to be extended to include the loss of an implanted pregnancy along with a menstrual period.
15. In 1967, when the Abortion Act became law, I was a third-year medical student and I had not yet seen patients on the gynaecology wards. By the time I began gynaecology, in 1969, I had heard of the potentially lethal dangers of illegal abortion. I remember my first case of septic abortion because of the anxiety it caused me, but happily the infection responded to treatment, I have heard from various colleagues about the distress they felt when treating women infected after illegal abortion. I am now Medical Director of the Confidential Enquiry into Maternal Deaths in the UK and when I lecture on this subject I point out that in the late 1960s thirty women a year died in the UK from septic abortion. This total took several years to fall and has remained zero since 1985.
16. I have been involved in providing contraceptive services and termination of pregnancy services for almost thirty years. I have thought a great deal about the implications of my actions. I have discussed them with students, written about them in medical and lay publications (including the correspondence column of The Times) and debated them in the context of ethics courses and

religious discussions. I have been fully aware of my duty to comply with the 1967 Abortion Act: almost every week for 29 years I have filled in the Abortion Act forms as part of my work in the termination service. I take these duties very seriously because I am conscious of my moral duty as a doctor and a teacher, and because I am aware that any lapse from the requirements of the Act could render me liable to prosecution. I have never at any time felt that the provisions of the Act referred to the prescribing of Levonelle, or the insertion of an intrauterine contraceptive device, or the prescribing of a progesterone-only pill. Although I carry out abortions, I have never felt that prescribing PC4 or Levonelle, or fitting a coil or prescribing a progesterone-only pill is procuring an abortion. Some of my colleagues do not carry out abortions because of their deeply-held views, but they are happy to prescribe PC4 or fit an IUCD or prescribe progestogen-only contraception. I do not know of any gynaecologist who feels that these contraceptive methods are procuring abortions. Indeed, colleagues who oppose abortion are – like me - keen to prescribe these contraceptives in order to reduce the need for abortion. Even though abortion is now safe in this country, it is distressing for all concerned – women and doctors. Levonelle is highly regarded because it reduces the number of cases in which a woman needs to consider abortion.

17. After preparing this statement I read the witness statement of Professor Peter Braude, dated 10th July 2001. I agree with Professor Braude's statement. He refers to "attachment" of the blastocyst whereas I have referred to "adhesion": I consider that the two terms mean the same thing.

Statement of Truth

18. I believe that the facts set out above are true and that the opinions I have expressed are correct. I understand that it is my duty to help the Court on matters within my expertise and that this duty overrides any obligation I have to those who have instructed me in this matter.

(*Signed*: 'James Drife')

Signed……

Professor James Owen Drife

(*Date*: '3rd August 2001')

Dated……

WITNESS STATEMENT OF DOCTOR PETER NORMAN LONGTHORNE

I, DR PETER NORMAN LONGTHORNE of (*personal address redacted*) **WILL SAY AS FOLLOWS**:-

1. I am Medical Director of Schering Health Care Limited ("Schering"). I am also a registered medical practitioner and hold the qualifications of Bachelor of Medicine, Bachelor of Surgery, Member of the Royal College of Surgeons, Licentiate of the Royal College of Physicians, Diploma of Royal College of Obstetricians and Gynaecologists and Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians. I joined Schering in 1980 as a Medical Advisor, having practised medicine in hospitals in the United Kingdom and as a Principal in general practice. From 1982 I held the post of Head of Clinical Research at Schering, before becoming Medical Director in 1987. I became Marketing Director from late 1991, returning to become Medical Director in March 1995.
2. I make this Witness Statement with the authority of Schering in support of Schering's intervention in this Judicial Review as an interested party. Schering opposes the application of Mr Smeaton on behalf of The Society for the Protection of the Unborn Child for an Order quashing the Prescription Only Medicines (Human Use) Amendment (No. 3) Order 2000 and a declaration that: (a) the Prescription Only Medicines (Human Use) Amendment (No. 3) Order 2000 is ultra vires the Secretary of State; (b) a person who administers Levonelle-2 to a woman with the intention of causing an embryo which exists to be expelled commits an offence under s. 58 of the Offences Against a Person Act 1861; and (c) a person who supplies Levonelle-2 intending that the patient use it for a like purpose commits and offence under s. 59 of the Offences Against the Person Act 1861.
3. The information in this statement is either within my own knowledge or has been supplied to me by employees of Schering and its affiliates at my request. Where information has been supplied to me by others or has been derived from reading documents I identify my source and I believe that information to be true.
4. Schering is an English registered company whose ultimate parent company is Schering AG of Germany. Schering is the distributor in the United Kingdom of Levonelle-2 and Levonelle, providing supplies to the wholesalers from whom pharmacists buy their stocks. The manufacturer of Levonelle-2 and Levonelle is Gedeon Richter Limited ("Gedeon Richter"), a Hungarian company, which carried out the research which led to the development of Levonelle-2. The product licence in the United Kingdom is held by Medimpex UK Limited, who represent Gedeon Richter in the United Kingdom with Schering noted as the distributor on the product licence and packaging.

Levonelle and Levonelle-2

5. Levonelle-2, the predecessor to Levonelle, was launched by Schering in the United Kingdom in February 2000 as a prescription only medicine. Generally, Levonelle-2 can only be dispensed by a pharmacist if the patient presents a prescription signed by a registered medical practitioner. Both Levonelle-2 and Levonelle are marketed as medicinal products which may be used by women as contraception in emergencies after otherwise unprotected sexual intercourse has taken place. They consist of two tablets containing 0.75 mg of a synthetic steroid hormone, levonorgestrel, which mimics the action of progesterone, a hormone produced naturally by the ovary and by the placenta. The data sheet recommends that one tablet is taken by the woman as soon as possible after intercourse, and in any event not more than 72 hours after intercourse. The second tablet is taken 12 hours later. Levonorgestrel, at lower doses, is also a constituent of other oral contraceptive pills designed to be taken throughout a woman's menstrual cycle.
6. Levonelle-2 remains on the market as a prescription only medicine. Levonelle is an identical formulation to Levonelle-2, save that, pursuant to the Prescription Only Medicines (Human Use) Amendment (No.3) Order 2000, it is designated a pharmacy only medicine. This means that it can be

sold by a pharmacist to a woman over the age of 16 for use as an emergency contraceptive without the requirement for her to present a prescription. The circumstances under which pharmacists may supply Levonelle are the subject of guidance issued by the Royal Pharmaceutical Society, the professional body with which all dispensing pharmacists are registered and which regulates their practice. A copy of that guidance is at Exhibit "PNL1" to this statement. The package containing Levonelle contains a patient information leaflet which provides information required by European pharmaceutical legislation and the text of which is approved by the United Kingdom Licensing Authority. The leaflet includes information to assist the patient to use Levonelle safely and effectively. A copy of the patient information leaflet for Levonelle is exhibited as exhibit "PNL2" to this statement. The patient information leaflet is required to be consistent with the data sheet for the product that is in turn approve by the Medicines Control Agency ("MCA") at the time of licencing and is now normally described by the European expression, "Summary of Product Characteristics". The MCA is the executive agency through which the Licensing Authority (consisting of the relevant Ministers) exercises regulatory control over the supply of medicinal products.

7. I note that in the detailed Statement of Grounds served by the Claimant the references throughout are to Levonelle-2, and that Levonelle-2 is referred to in the second and third declarations sought by the Claimant. Since the regulations concerning the supply of the prescription only medicine have not changed, it appears that the Claimants may have intended to refer to Levonelle, the pharmacy only medicine which was launched this year.

The History of Emergency Contraception

8. Combined oral contraceptive pills containing both oestrogen like synthetic hormones ("oestrogens") and progesterone like synthetic hormones ("progestogens") have been widely available in the United Kingdom since the 1960s. Combined oral contraceptive pills are believed to rely primarily for their contraceptive effect on the suppression of ovulation. One tablet is taken each day throughout a women's menstrual cycle with one week's break, during which the women will have a withdrawal bleed, shedding the endometrium which lines the uterine cavity.
9. During the 1970s, researchers demonstrated that combinations of oestrogens and progestogens at higher doses than those contained in standard combined oral contraceptive pills could be effective in preventing pregnancy if taken after sexual intercourse had taken place. The Department of Health and Social Security ("DHSS") in the United Kingdom became aware that some doctors were recommending that patients took two tablets of a combined oral contraceptive pill, Eugynon 50, immediately after intercourse, followed by two tablets 12 hours later, with the aim of reducing the risk of pregnancy where either no other contraceptive measures had been taken or those measures might have failed. This use was outside the recommendations of the product licence for Eugynon 50 and the practice was, rightly, regarded by the MCA as unsatisfactory. The DHSS, therefore, specifically asked Schering, the manufacturer of Eugynon 50, to seek a marketing authorisation for a product expressly designed to be an emergency contraceptive pill. Schering did so and subsequently launched a product called Schering PC4. PC4 contained exactly the same combination of hormones, in the same quantities, as was contained in Eugynon 50. The package contained only 4 tablets, however, and the formulation was licensed specifically for use as an emergency contraceptive measure, Schering having satisfied the Licensing Authority, and its advisory body the Committee on Safety of Medicines, as to the safety, quality and efficacy for this use. PC4 was launched as a prescription-only medicine in October 1984. In 1999, 949,000 packets of PC4 were sold; in 2000, 422,000 packets were sold.
10. It has been Government policy for some time to improve women's access to emergency contraception in order to reduce the numbers both of medical abortions and unwanted pregnancies. Schering declined an invitation by Stephen Dorrell, the Secretary of State for Health in 1995, to make

PC4 available as a pharmacy-only medicine. Schering was concerned about the possibility of adverse reactions taking place in women who. Against advice, used PC4 several times during one menstrual cycle.

11. In 1998 Schering became aware of collaborative studies which the World Health Organisation had undertaken with Gedeon Richter of Hungary. These compared the efficacy and side-effect profile of emergency contraceptive preparations containing combinations of oestrogens and progestogens, as in PC4, with formulations containing only a progestogen, levonorgestrel, as in Levonelle-2 and, subsequently, Levonelle. These studies had shown conclusively that Levonelle-2 was both more efficacious than PC4 in reducing the risk of pregnancy and had a superior side effect profile. The underlying reason for this appeared to be that the incidence of nausea and vomiting often caused by the oestrogen component of PC4 type formulations was reduced significantly in women taking levonorgestrel-only formulations. Women were, thus, much more likely to build up the appropriate levels of hormones in their bloodstream required for those hormones to exert a contraceptive effect.
12. In 1999, the Department of Health became aware of Schering's intention to market Levonelle-2 as a prescription-only medicine. The Department of Health renewed its interest in the provision of emergency contraception through pharmacies and began active discussions with Schering and the MCA about the possibility of redesignating Levonelle-2 as a pharmacy-only medicine. Schering concluded that the risk of serious adverse reactions arising due to improper use of Levonelle-2 was much less than would have been the case with PC4. This is because the more significant of the side-effects associated with such hormone combinations -circulatory disorders such as venous thromboembolism- are related to the oestrogen content of PC4, and Levonelle-2 does not contain any oestrogen. Schering, therefore, considered it safe to move cautiously towards rescheduling as a pharmacy-only medicine, a formulation containing 0.75 mg of levonorgestrel for use as an emergency contraceptive in women over the age of 16.
13. Levonelle-2 was launched in the United Kingdom in February 2000 . In that year 707,563 packs of Levonelle-2 were distributed by Schering, mainly to wholesalers. A relatively small number of packs were sent directly to hospitals. Levonelle was launched in January 2001 and, to the end of June 2001, 229,364 packs had been sold. The total sales for Levonelle-2 from launch currently stand at 1,118,324 packs.
14. The sales of PC4 have declined since the launch of Levonelle-2 and Levonelle. Schering now intends to discontinue the supply of PC4. It remains the case, however, that PC4, Levonelle-2 and Levonelle are much safer than any form of medical termination and, indeed, less hazardous to a women's health than pregnancy. The risk of a woman living in the United Kingdom dying as a result of pregnancy is around 1 in 10,000 pregnancies. The risk of a woman living in the United Kingdom dying as a result of a medical termination of pregnancy is around 1 in 500,000 terminations. There have been no deaths reported to Schering as a result of a woman having taken PC4, Levonelle-2 or Levonelle.

Mechanisms of Action of Levonelle-2

15. I have discussed the issues raised by Mr Smeaton's application with Dr Teodora Perger and Dr Andrea Mecz, experts in the medical affairs department of Gedeon Richter Limited. They have provided me with a summary of the current state of knowledge as to the mechanisms of action of Levonelle-2 and Levonelle. I am informed by Dr Perger and Dr Mecz that there are not sufficient scientific data available at this time to identify with certainty all of the mechanisms of action of Levonelle-2 and Levonelle as emergency contraceptives, or to assess precisely the relative importance of one possible mode of action over another. It is possible that more than one mechanism of action exists, and that the importance of different mechanisms of action varies depending on the cycle date on which treatment is started.

16. The risk of a women becoming pregnant at any time of her menstrual cycle varies according to the time from ovulation at which intercourse takes place. If unprotected intercourse takes place around the time of ovulation the risk of pregnancy is 29-30%. If unprotected intercourse takes place 14 days either before or after ovulation the risk of pregnancy is in single figures. The WHO research referred to above[1] showed that, of the 30 percent of women having unprotected intercourse who would have become pregnant, 95 per cent would not become pregnant if they took levonorgestrel in the first 24 hours after intercourse. If levonorgestrel is taken up to 72 hours after unprotected intercourse, pregnancy would be prevented in only 58 per cent of these women.
17. Non-clinical pharmacological studies of levonorgestrel show that it has a preferential affinity for progesterone receptors and, thus, exerts a negative feedback effect on the control of ovulation, both at the level of the pituitary gland and on the ovary. Effectively, the woman's body mistakes the levonorgestrel for naturally produced progesterone and, in a sense, is deceived into thinking that ovulation has already occurred. The regulatory processes in the brain and in the ovary that, generally, prevent the release of more than one egg in any one cycle are, thus, brought into play.
18. The post-coital administration of two tablets containing 0.75 mg levonorgestrel could, theoretically, prevent pregnancy by interfering with a number of physiological processes, including ovulation, release of pituitary gonadotrophins, sperm transport, the consistency of cervical mucus, the contractility of the fallopian tubes and implantation.
19. Levonorgestrel is contained in low doses in some progestogen-only pills used for ongoing contraception on a daily basis. Such doses prevent ovulation in about half of all cycles. It is reasonable, therefore, to assume that the post-coital administration of significantly higher doses of levonorgestrel suppresses or delays ovulation if given sufficiently in advance of the day of ovulation.
20. Some studies have shown effects on cervical mucus that could, within a few hours after administration, impair sperm transport to the upper genital tract. It is generally believed that cervical mucus acts as a reservoir for sperm, allowing fertilisation to occur some days after coitus. It is also known that levonorgestrel acts reasonably quickly to thicken cervical mucus. It is, thus, reasonable to assume that, within a few hours after unprotected sexual intercourse, sperm could become trapped in the cervical canal, owing to the action of levonorgestrel on cervical mucus.
21. Some studies have also shown alterations in the microscopic appearance of the endometrium after the administration of levonorgestrel which could represent effects on its receptivity and the likelihood of an implantation of an embryo. However, because the risk of pregnancy declines significantly on the cycle days immediately following the day of ovulation, and because the efficacy of levonorgestrel declines the longer treatment is delayed, Dr Perger and Dr Mecz consider this theoretical mechanism of action to be less likely, or at least less important, than pre-fertilisation mechanisms of action. Furthermore, levonorgestrel would not stop the implantation process f it had already begun which will not be the case if levonorgestrel is taken within 72 hours of possible fertilisation, since this only begins to occur about 4 or 5 days after unprotected intercourse has taken place.
22. In general, Dr Perger and Dr Mecz believe that the predominant mechanism of action of levonorgestrel exerts its effect prior to fertilisation. The major risk of pregnancy is concentrated in the six days leading up to and including the day of ovulation. It is, therefore, likely that emergency contraceptives work, at least some of the time, by suppressing ovulation. The pivotal WHO study in 1998 showed that the efficacy of levonorgestrel was significantly and inversely related to time since unprotected intercourse. This finding was replicated by Ho & Kwan [2] and the association was more pronounced with a levonorgestrel regimen than with the PC4 type regimen. If emergency contraceptives acted consistently after fertilisation to prevent implantation, one would not expect

[1] Lancet 8th August 1998 Vol 352 No 9126 428-433
[2] Human Reproduction 1993 Vol 8 no 3, 389-392

to observe a significant decline in efficacy the longer treatment is delayed after unprotected intercourse.

23. I know of no research which contradicts the views of Drs Pegler and Mecz, nor am I aware of any research which would enable a woman, her doctor or pharmacists to determine which mechanism or combination of mechanisms operates on any individual occasion when Levonelle-2 or Levonelle is taken.
24. The mechanisms of action of PC4 are the same as that of Levonelle-2 and Levonelle. There is no evidence that there is any difference at all in the mechanism of action of the three products.
25. Levonelle-2, Levonelle and PC4 cannot induce the abortion of an established pregnancy. It has been observed that some women do become pregnant despite having taken PC4 or Levonelle-2. Those pregnancies continue uninterrupted and no adverse effects have been observed on foetal development.
26. The administration of PC4, Levonelle-2 or Levonelle does not induce a withdrawal bleed; the endometrium is not shed. Although some women will find their menstrual period begins later than usual and a few find that it begins earlier than usual, in most women the next menstrual period after taking Levonelle-2 or Levonelle occurs at the expected time.

Conclusion

27. Schering does not believe that PC4 or Levonelle-2 or Levonelle is an abortifacient and does not supply these products to pharmacists with the intention that they should be used to procure a miscarriage or abortion.
28. I believe the contents of this Witness Statement are true.

(*Signed*: 'Peter Longthorne')

Signed…….

Dr Peter Longthorne

(*Dated*: '3rd August 2001')

Dated……..

WITNESS STATEMENT OF DR JOHN McLEAN

I, John McLean, of (*personal address redacted*), will say as follows:

1. I was formerly a Senior Lecturer in Anatomy and Embryology in the Faculty of Medicine at the University of Manchester from 1972 until 1992 and am currently an Associate Specialist in Genitourinary Medicine in the Manchester Centre for Sexual Health in the Manchester Royal Infirmary where I have been employed as a doctor dealing with sexually transmitted diseases since 1976.
2. I qualified MB BS with honours from the University of Durham in 1959. After pre-registration house posts in the University Teaching Hospital I completed a degree in Physiology, obtaining a BSc with first class honours, from the University of Durham in 1961. After teaching Anatomy in the University of Manchester for one year I spent the following year working in a Mission Hospital in Africa and a further year as a General Practitioner in Northumberland.
3. I then returned to an academic appointment in the University of Newcastle and was awarded an MD in 1968 for research on the Immunology of Pregnancy. Having previously obtained the first part of the Fellowship of the Royal College of Surgeons I then began a rotating surgical appointment in the University Teaching Hospitals in Newcastle upon Tyne.
4. I was then appointed to a Lectureship in Anatomy at the University of Newcastle and a Medical Research Council's Clinical Research Fellowship in Edinburgh before taking up my appointment as Senior Lecturer in Anatomy in the University of Manchester in 1972. With the support of the Vice Chancellor of the University of Manchester I undertook 3 clinical sessions per week in the Department of Genitourinary Medicine in the Manchester Royal Infirmary in 1976. These clinical sessions continued until 1992 when I retired from my University post. Since that time I have been in full-time employment in Genitourinary Medicine.
5. My clinical involvement in Genitourinary Medicine arose from my research interests in the antigenicity of spermatozoa, the immunosuppressive function of seminal plasma, the antigenicity of the conceptus, the process of implantation and the structure and function of the female reproductive tract. My joint appointment in basic medical science and clinical medicine enabled me to supervise a number of medical graduates for post-graduate degrees in these research areas which resulted in some 60 publications.
6. Throughout my University career I was primarily responsible for the teaching of human anatomy and embryology to undergraduate and postgraduate medical students as well as acting as an external examiner for the Universities of Sheffield, Southampton, Glasgow and London and as an examiner for the Royal College of Surgeons of England and the Royal College of Surgeons of Ireland.
7. I have been asked by Coningsby's Solicitors to give an account of the first two weeks of human embryogenesis and the incidence of unrecognised early embryo loss. In addition I have been asked to consider the possible public health consequences of making emergency hormonal contraception available without the need for medical oversight.

THE FIRST TWO WEEKS OF EMBRYOGENESIS

8. In normal circumstances pregnancy begins with internal fertilisation following sexual intercourse. If sexual intercourse is to be fertile it must take place during the appropriate period of the woman's ovarian cycle.
9. The ovary produces two major hormones, oestrogen (estradiol) and progesterone. Their secretion is controlled by a complex mechanism involving the hypothalamus within the brain and the pituitary gland situated at the base of the brain. The hypothalamus produces luteinising hormone releasing factor (LRF) which brings about the synthesis and release of both follicle stimulating hormone (FSH)

and luteinising hormone (LH) by the pituitary. These latter two hormones are referred to as gonadotrophins since they stimulate the secretion of other hormones from the ovary and the testis. Both FSH and LH are produced simultaneously but in different ratios at different times in the ovarian cycle. At the beginning of each cycle a cohort of immature ovarian follicles (each containing an immature female germ cell i.e. an oocyte) begin to mature in response to FSH secretion. As the follicles mature the cells surrounding them secrete oestrogen, which repairs the endometrium (lining of the uterus) shed at the previous menstrual flow, and a small amount of progesterone. At about day 8 of the cycle one of the follicles becomes dominant and continues to grow while the others regress. As the time of ovulation approaches the oestrogen secretion increases and reaches a peak about 24 hours before ovulation, an event which occurs at mid-cycle, about day 14. The increased secretion of oestrogen causes a change in the character of the mucous produced within the cervical canal. Until that time the cervical canal is occluded by thick white mucous but with impending ovulation mucous secretion increases and its character changes to facilitate the ascent of spermatozoa into the upper reproductive tract should coitus occur. Just prior to ovulation LH secretion increases significantly and this surge of secretion is considered to be the stimulus for ovulation and the release of the oocyte into the fallopian tube.

After ovulation the follicle from which the oocyte has been released is converted into the corpus luteum, which continues to secrete oestrogen and secretes significant amounts of progesterone. The initial effect of progesterone during the first 24-36 hours after ovulation is to alter the character of the cervical mucous to form a barrier that isolates the cavity of the uterus from the vagina and, as a coincidental effect, to raise the basal body temperature. The principle role of progesterone however is to prepare the endometrium for implantation of the embryo if fertilisation has occurred. The peak of progesterone secretion occurs about 5 days after ovulation and the embryo, if fertilisation has occurred, begins to implant on the sixth postovulatory day.

It is probable that these two ovarian hormones influence the motility of the fallopian tube. At the time of ovulation the fallopian tube carries spermatozoa towards the ovary while the after ovulation and fertilisation the tube carries the embryo towards the uterus.

There is a complex “negative feedback mechanism” operating between the gonadotrophins (FSH and LH) and the secretions of the ovary. As the serum concentrations of oestrogen and progesterone rise in response to the secretions of the gonadotrophins so secretion of the gonadotrophins falls. At the end of each infertile ovarian cycle the serum concentrations of oestrogen and progesterone fall dramatically and gonadotrophin secretion increases to bring about the maturation of another cohort of ovarian follicles and the commencement of another ovarian cycle.

10. The following account of the first two weeks of human embryogenesis is an edited form of my contributions to the third (1987), fourth (1995) and fifth (in press) editions of Haines & Taylor “Obstetrical and Gynaecological Pathology” edited by H Fox and M Wells, published by Churchill Livingstone and my contributions to the first (1988) and second (1999) editions of “The Vulva” edited by C M Ridley, published by Churchill Livingstone. These contributions are fully referenced and individual references will therefore not be included in this account. Additional detail of the events involved in the first two weeks of human embryogenesis are described in “Developmental Stages in Human Embryos” by O’Rahilly and Muller 1987, Publication 637, Carnegie Institution of Washington. Any pertinent references not included in the above publications will be given at the end of this section.
11. Pregnancy and embryogenesis begin with fertilization when the spermatozoon and oocyte fuse to form the zygote or conceptus. Each of the participating gametes contributes more than a million genetic units to the single cell oocyte in an arrangement unique to that human being. He normal haploid set of 23 chromosomes in each gamete yields a zygote with the diploid set of 46 chromosomes. The first eight weeks of gestation constitute the embryonic period during which the essential form of the human infant is established. Indeed the crucial events of human development

occur during the first quarter of gestation. Thereafter maturation and growth occur and continue postpartum, throughout childhood and into adulthood.

Because development is a continuous process various means have been used to identify and tabulate the progression of events during normal human embryogenesis. The founder of the Department of Embryology ant the Carnegie Institution in Washington, Franklin Mail, was the first to introduce staging into human embryology. His observations, and those of George Streeter, his successor at the Carnegie Institution, form the basis upon which the first eight weeks of human development are described in 23 Carnegie stages. These stages are used by all embryologists to tabulate the sequence of events taking place during the first 8 weeks of human development. In this account the reference point will also be the postovulatory age, i.e. the length of time since ovulation, related to the Carnegie stage. Since ovulation and fertilization are closely related in time the postovulatory interval is an adequate measure of embryonic age.

12. Much of the available information on embryogenesis is derived from traditional embryological studies. However, with the advent of assisted conception and the establishment of the Human Fertilisation and Embryology Authority direct observation of the human embryo in vitro has provided and additional source of information on the preimplantation phase of human embryogenesis. Figures I refer to are produced at "JM1"
13. **Carnegie Stage 1** At ovulation the oocyte has a diameter of 100 um and is enclosed by the zona pellucida, a non-cellular envelope the thickness of which is reduced as the woman ages. The zona pellucida is produced by the follicular cells and it possesses species-specific spermatozoal receptors. After fertilisation the zona pellucida protects the integrity of the preimplantation embryo during its early development. Each female gamete begins its first meiotic division during intrauterine life and completes it at ovulation, while its second meiotic division is only completed if fertilization occurs. Carnegie stage 1 of embryogenesis begins with the entry of the fertilizing spermatozoon into the oocyte and ends with the first mitotic division of the zygote (Fig. 1.1). The female gamete's protracted reduction division delivers 23 X chromosomes to the newly formed zygote which also receives 23 X or 23 Y chromosomes from the male gamete. The resulting chromosomal complement of karyotype of the zygote is either 46,XX or 46,XY and thus its genetic or chromosomal sex is established. With successful fertilisation the single cell zygote acquires the capacity to initiate, sustain, control and direct the subsequent events of embryogenesis. The importance of the first cleavage division is that it heralds the onset of Carnegie stage 2 of human embryogenesis. After in vivo fertilization the first cleavage division takes place some time between 24 and 30 hours after fertilization, whereas after in vitro fertilization it occurs some 22-24 hours after insemination.
14. After fertilization in the distal third of the uterine tube, various mechanisms are involved in the movement of the zygote towards the uterine cavity which it enters some 80 hours after fertilization. During that period mitotic activity generates an increasing number of cells called blastomeres, within which the total volume of cytoplasm decreases as cell numbers increase. The age of the conceptus and its cell content and organization on entry to the uterine cavity were thought to be critical to its subsequent successful implantation and development. However, the birth of normal infants following external fertilization (IVF) of human gametes and subsequent embryo transfer to the uterine cavity has shown that the tubal phase of development is not essential to normal embryogenesis. Nevertheless, zygotes cultured in vitro differ significantly from those developed in vivo. For example, mouse zygotes developed in vitro show altered glycogen storage patterns, elevated free radical production and altered patterns of both gene expression and genomic imprinting.
15. **Carnegie Stage 2** The duration of Carnegie stage 2 is considered to be about 48 hours and extends from the two-cell embryo to the appearance of the fluid-filled segmentation cavity which identifies the blastocyst. The central cells of the morula (Fig. 1.2) are thought to be embryonic and the

peripheral cells trophoblastic. The segmentation cavity begins to form when the conceptus has 32 cells although it has been observed in 8 cell embryos after external fertilization.

16. **Carnegie Stage 3** This stage of development begins with the formation of the blastocyst which enables embryonic and trophoblastic cells to be specifically identified. Carnegie Stage 3, about 48 hours in duration, embraces the period of development during which the blastocyst (Fig. 1.2) normally lies free within the female reproductive tract. The embryonic cells of the blastocyst are referred to as the embryonic pole or the inner cell mass. A prerequisite for further development and implantation is the dissolution of the zona pellucida and it is estimated that this occurs during the fifth day as the result of both embryonic and maternal factors. Since 87% of embryos transferred to the uterus following in vitro fertilisation fail to establish a clinical pregnancy (Human Fertilisation and Embryology Authority 1999) it has been suggested that problems associated with zona pellucida dissolution may contribute to implantation failure. Such reasoning has persuaded some IVF practitioners to assist zona pellucida prior to embryo transfer in various procedures described, somewhat infelicitously, as “assisted hatching”. There is as yet no evidence that such assisted hatching procedures achieve an improved outcome following embryo transfer.
17. **Carnegie Stage 4** On day 6 of embryogenesis. The blastocyst, orientated correctly to allow the trophoblast immediately overlying the inner cell mass to make contact with the maternal endometrium, begins its attachment to and subsequent invasion of the endometrium.
18. **Carnegie Stage 5** The stage extends from the seventh to the twelfth postovulatory day. During this period the outer envelope of cytotrophoblast, forming the wall of the blastocyst, generates syncytiotrophoblast on its external surface and extraembryonic mesoderm from its internal surface. The syncytiotrophoblast, cytotrophoblast and extraembryonic mesoderm together form the chorion (Fig. 1.3a). The invasive and endocrine properties of the syncytiotrophoblast are crucial to the survival of the embryo as is the appropriate preparation of the endometrium to receive the implanting embryo. Both maternal and embryonic tissues are mutually interactive in this process of implantation and neither can be regarded as chiefly responsible for its success.
19. The interaction of the embryonic and maternal tissues allows the embryonic chorion to erode through the surface layer of the maternal endometrium to make contact with the endometrial connective tissue or supporting tissue. This connective tissue is then displaced and the chorionic tissue makes contact with the maternal endometrial blood vessels which themselves are eventually breached, about the ninth or tenth postovulatory day, to allow maternal blood to flow through the chorionic spaces and establish the primitive placenta. Thereafter, this maternal embryonic interface serves the respiratory and excretory needs of the embryo. At the end of Carnegie Stage 5 the embryo is completely enclosed within the endometrium.
20. During Carnegie Stage 5 the primitive amniotic cavity develops by cavitation within the inner cell mass (Fig. 1.3b) some seven and a half days after fertilization. The floor of the amniotic cavity is the primary ectoderm. A second layer, the primary endoderm, is formed from the cells between the blastocyst cavity and the floor of the amniotic cavity. The opposed layers of primary ectoderm and primary endoderm, which are structurally quite different from one another, form the bilaminar embryonic disc. The blastocyst cavity is subsequently enclosed by the exocoelomic membrane which is continuous with the primary endoderm at the margins of the embryonic disc. The exocoelomic membrane and the primary endoderm of the embryonic disc enclose the yolk sac (Fig. 1.3c).
21. **Carnegie Stage 6** During this stage, which extends from the thirteenth to the fifteenth postovulatory day, several significant events occur within the conceptus. The chorionic cavity, or extraembryonic coelom (Fig. 1.4), which has been forming by resorption of extraembryonic mesoderm, is now readily identified. The amniotic cavity and yolk sac remain enclosed by extraembryonic mesoderm which extends from the caudal end of the embryonic disc to the chorion proper, thereby forming the primitive body stalk. Blood vessel primordia are present within this primitive body stalk and indicate the future umbilical vessels. In addition a recess of the yolk sac penetrates into the primitive body

stalk as a narrowing diverticulum (Fig. 1.4) and forms the allantois or allantoic diverticulum. The precursor cells of oocytes and spermatozoa arise from the endoderm of the allantois and subsequently migrate to the future gonads. The primitive streak or groove is also observed during this stage as a proliferation of cells lying in the median plane of the caudal region of the embryonic disc. The primitive streak may be observed in the floor of the amniotic cavity (Fig. 1.5a). During this stage of development the bilaminar embryonic disc begins to be converted into a trilaminar disc. This is achieved by the primitive streak generating intraembryonic mesoderm which migrates through the embryonic disc in the plane between ectoderm and endoderm (Fig. 1.5b). The ectoderm fives origin to the central nervous system and skin, the endoderm to the gastrointestinal system and the respiratory system and the other tissues of the body develop from the intraembryonic mesoderm.

22. The well documented events of early human embryogenesis which transform the single cell zygote, brought into being by fertilisation, into the complex organisms that it is at the end of the second week are initiated and controlled by the embryo within the maternal reproductive tract which itself has a profound influence on the success of these events.
23. After fertilisation the embryonic genome is immediately functional to initiate and direct cell division and induce the sequential cell differentiation necessary for blastocyst formation. The embryo synthesises and secretes specific, biochemically active products which are identified in maternal serum and urine as well as in the supernatant fluid of IVF embryos. These products include early pregnancy factor (EPF), embryo derived platelet activating factor (EDPAF) normally referred to as PAF, immunosuppressive factors and the beta subunit of HCG together with a number of growth factors. Much of this evidence was initially obtained from animal experimentation and subsequently confirmed in humans. Whatever specific roles these products have in determining the success of pregnancy they are undoubtedly embryonic signals to the mother that she is pregnant.
24. EPF was initially detected in maternal mouse serum within six hours of fertile mating (1) and subsequently in human serum within 24-28 hours of coital fertilisation (2) and within three days of embryo transfer (3). More recent work has shown EPF to be secreted into maternal human serum 12-16 hours after fertilisation (4) and its presence, in maternal serum prior to implantation, to be evidence of fertilisation and a viable embryo in women wishing to conceive(5). Animal experimental work has demonstrated that antibodies raised against EPF and administered to pregnant mice during the immediate post-fertilisation period retard embryonic development and during the peri-implantation stage prevent implantation (6). It has indeed been recognised for some time that the presence of EPF in maternal serum can signify the occurrence of fertilisation, continuation of pregnancy and the existence of a viable embryo (7).
25. PAF is functional within 24 hours of embryo transfer in women undergoing IVF and its production has been used as a marker for embryo quality (8). Its role in early embryogenesis is to assist in the preparation of the endometrium for implantation.
26. The secretion of immunosuppressive factors is associated with the requirement that the early embryo be protected from the maternal immune response directed against the foreign antigens of the father whose genome forms 50% of the embryonic genome.
27. Precursors of the beta subunit of HCG have been identified in IVF 8-cell human embryos, 2 days post fertilisation (9) and its presence in maternal serum and/or urine, prior to expected menstruation, is routinely used as a pregnancy test. The specific role of HCG is to prevent the degeneration of the corpus luteum that occurs at the end of an infertile ovarian cycle to herald the onset of menstruation.
28. Other embryos products, together with maternal products, are involved in the dissolution of the zona pellucida, which is a prerequisite for implantation.
29. As indicated in paragraph 9 the ovarian cycle is controlled by a complex series of hormonal interactions designed to prepare the endometrium for the possibility of embryo implantation. Numerous morphological changes occur in the endometrium during a normal 28-day ovarian cycle and those associated with the preparation for implantation are evident from day 16 and are more

marked between days 19 and 21. These structural changes are accompanied by changes in the expression of molecules on the endometrial cell surface, which convert it from a non-receptive to a receptive state thus identifying a brief period of time known as the "window of implantation". During IVF treatment embryos replaced before day 20 may implant; those replaced after day 24 do not (10). As stated in this recent BMJ editorial "It is therefore not surprising that the coordination of the process of human embryo attachment has been attributed to oestrogen and progesterone and to "quality embryos". The embryo is not passive but is an active orchestrator of its attachment and fate. The spatiotemporal expression of embryonic proteins and their influence on the endometrium may prove critical". It is therefore obvious that any disturbance of the finely balanced hormonal interactions of a fertile ovarian cycle, which influence both the maturation and metabolic activity of the early embryo and the preparation of the endometrium for implantation, will disrupt and prevent the progress of a pregnancy already begun.

References

1 Morton H et al 1976; Proceedings of the Royal Society, Series B, 193: 413-419
2 Rolfe B E 1982; Fertility and Sterility, 37: 655-660
3 Chen C 1985; In: Early Pregnancy Factors, eds. F Ellendorf and E Koch, Perinatology Press, New York, 215-226
4 Haq A et al 2001; European Journal of Medical Research, 6: 209-214
5 Fan X G, Zheng Z Q 1997; American Journal of Reproductive Immunology, 37: 359-364
6 Athanasius-Platsis S et al 2000; American Journal of Reproductive Immunology, 43: 223-233
7 Shahani S K et al 1994; Gynecological and Obstetrical Investigation, 37: 73-76
8 O'Neill C et al 1985; Journal of In Vitro Fertilisation and Embryology Transactions 2: 87-93
9 Bonduelle M L et al 1988; Human Reproduction, 3: 909-914
10 Horne A W et al 2000; British Medical Journal, 321: 1301-1302

Early Embryo Loss

30. Early embryo loss within 14 days of conception is probably unrecognised by most women since menstruation occurs at or about the expected time. Surveillance of early embryo loss therefore requires the co-operation of a representative sample of couples and a reliable assay to establish the presence of an embryo within the reproductive tract.
31. The first report concerning early embryo loss was published in 1959 and involved 210 fertile women, aged 42 or younger, undergoing therapeutic hysterectomy (1). 107 women fulfilled the criteria for possible conception i.e. no abnormality likely to prevent conception was present in the upper reproductive tract and coitus had occurred within 24 hours of known ovulation. In these 107 hysterectomy specimens 34 early embryos were identified, ranging from a 2-cell tubal embryo to a 17-day villous embryo. Of these 34 embryos, 10 were considered to be incapable of survival and the authors interpreted these findings as indicating a 29% early embryo loss. Some doubt must exist as to whether women undergoing therapeutic hysterectomy 50 years ago constitute a truly representative sample of the normal population. Other authors have subsequently reinterpreted these findings without access to the original specimens, to give estimates of early embryo loss of 35% and 78% respectively (2, 3).
32. The chorionic membrane of the human embryo begins to secrete human chorionic gonadotrophin (HCG) from day 6 of embryogenesis (4) and an embryo within the reproductive tract may be detected by a positive HCG assay in maternal serum or urine from that time. Assays of urinary HCG, extending over 198 cycles in a normal population of 82 women, of whom 41 were nulliparous, demonstrated increases of HCG in 118 cycles when compared with control values of urinary HCG from a group of

sterilised women. 51of these cycles (43%) resulted in clinical pregnancy ie a 57% loss of early embryos (5). The same group of investigators had previously assayed urinary HCG in 197 women over 623 ovarian cycles; 152 conceptions were detected of which 50 were lost at the next menstrual cycle ie a 33% loss of early embryos (6). Another study used assays of serum HCG over 226 ovarian cycles in 91normal healthy women who wished to conceive (7). These women during the three months prior to the study, when barrier contraceptives were being used, provided their own control values for the hormones being assayed. During the investigation proper, serum samples in the week before expected menstruation, revealed increased levels of HCG in 92 cycles, of which 7 ended in normal menstruation. In the remaining 85 cycles menstruation did not occur and a diagnosis of clinical pregnancy was made, of which 11 (13%) ended in spontaneous miscarriage. The incidence of unrecognised early embryo loss was therefore only 8%. Since the figure for spontaneous miscarriage in this study was within the range (10-15%) normally quoted the figure for early embryo loss may be more reliable than others that have been quoted.

33. However, any estimate of early embryo loss derived from HCG assays cannot include embryos failing to reach the stage of HCG secretion. Surveillance of embryo loss during the period from conception to blastocyst formation requires some other means of identifying the presence of a viable embryo within the reproductive tract. In the mouse, conception is followed by maternal thrombocytopenia which is sustained until implantation (8). This effect is caused by the embryo since it is observed after the transfer of early embryos to surrogate mothers. Early pregnancy associated thrombocytopenia has been observed in women within 24 hours of embryo transfer following IVF (9). The conceptual product responsible for causing maternal thrombocytopenia has been termed embryo derived platelet activating factor of EDPAF. Assays of PAF in the immediate postovulatory phase of the ovarian cycle in women trying to conceive would identify the presence of a viable early conceptus. Subsequent assays of HCG would identify the proportion of embryos surviving the first week of embryogenesis. See also item 24 in the previous section of this statement.
34. Early embryo loss is of great biological interest but over the last two decades it has acquired political significance with regard to legislation on human embryo experimentation and the use of emergency hormonal contraception. It is therefore important to obtain as accurate an estimate as is possible for the occurrence of early human embryo loss. A critical analysis of the methodology involved in these quoted studies suggests that unsuspected early embryo loss may have been substantially overestimated (10).

References

1 Hertig A T et al 1959; Pediatrics, 23: 202-211
2 James W H 1970; Population Studies, 24: 241-245
3 Roberts C J, Lowe C R 1975; Lancet, 1: 498-499
4 Simpson E R, MacDonald P C 1981; In: Textbook of Endocrinology ed. Williams R H 6th edition. Philadelphia: W B Saunders. 412-422
5 Edmonds D K et al 1982; Fertility and Sterility, 38: 447-453
6 Miller J F et al 1980; Lancet, 2: 554-556
7 Whittaker et al 1983; Lancet, 1: 1126-1127
8 O'Neill C 1985; Journal of Reproduction and Fertility, 73: 559-566
9 O'Neill et al 1985; Journal of In Vitro Fertilisation and Embryology Transactions, 2: 87-93
10 Walker E M 1988; British Journal of Obstetrics and Gynaecology, 95: 659-663

Social Implications

35. I understand that the Family Planning Association is concerned at the social consequences of restricting the supply of Levonelle. I comment below on emergency hormonal contraception and on the consequences of removing medical oversight on the administration of this medicine.
36. There are two forms of emergency hormonal contraception available in the UK: Schering PC4 and Levonelle. The Committee on Safety of Medicines approved the use of Schering PC4 in 1984 as a prescription only drug . (Yuzpe introduced this method in 1977 using the high dose oestrogen OC) Each of the 4 pills contains 50 micrograms of ethinyloestradiol and 500 micrograms of norgestrel (equivalent to 250 micrograms of levonorgestrel). Two of the pills must be taken within 72 hours of sexual intercourse and the remaining two 12 hours later. The 1998 WHO trial (1) found that given within 24 hours of sexual intercourse it prevented 77% of expected pregnancies, within 25-48 hours 36% and within 49-72 hours 31%. The WHO trial found that 50.5% of women experienced nausea and 18.8% reported vomiting after the administration of Schering PC4. Ovran, a high dose oestrogen OC with the same formulation as PC4, is used by many family planning clinics since 4 of these pills cost 8 pence while the price of PC4 as quoted in the National Formulary is £1.60.
    Levonelle-2, also marketed by Schering Health Care Ltd, was approved by the CSM in 1999 as a prescription only drug. As Levonelle it is no longer a prescription only drug and is now available from Pharmacists. The 1998 WHO trial (1) found that given within 24 hours Levonelle prevented 95% of expected pregnancies, within 25-48 hours 85% and within 49-72 hours 58%. 23.1% of the women experienced nausea and 5.6% reported vomiting after the administration of Levonelle 2. The price of Levonelle-2 quoted in the National Formulary is £5 while at a pharmacy the price of Levonelle is £20.
37. Levonelle-2 or Levonelle has a number of undesirable side effects:

Effect	Percent of women with the effect N ==977 women
Nausea	23.1
Low abdominal pain	17.6
Fatigue	16.9
Headache	16.8
Dizziness	11.2
Breast tenderness	10.8
Vomiting	5.6
All others (diarrhoea, bleeding and spotting)	13.5

38. O'Brien (2) claims that the UK has been a leader in the provision of emergency hormonal contraception with exponential growth in prescriptions since the mid 1980s. In 1998 O'Brien states that there were 800,000 prescriptions for Schering PCs; this figure must now be approaching 1,000,000 per annum. These figures do not include the provision of emergency contraception in the form of high dose oestrogen OCs by family planning clinics.
39. Some Health Authorities have stated that there is to be no lower age limit and girls aged 12 or younger may have access to Levonelle. In the UK the average age of menarche is 13.0 years with a standard deviation of approximately 1 year. Thus 95% of the adolescent female population have the menarche between their eleventh and fifteenth birthdays (3). Garden (4) quotes 12.8 years as the age at which menstruation typically begins. Many ovarian cycles in young women, even when associated with menstruation, are anovulatory (i.e. no oocyte is released); 85% during the first year after menarche, 59% during the third year and 26% during the sixth year (5).
40. Schering in its data sheet for Levonelle-2 state that it is not recommended in children and there is very limited data available from women under 16 years of age. Conditions which the manufacturer states as being possible relative contraindications to the use of Levonelle-2 include acute porphyria,

severe hypertension, diabetes mellitus with associated complications, ischaemic heart disease, stroke or a history of breast cancer.

41. The use of certain medications reduces the efficacy of oral contraceptives. These include barbiturates (insomnia), phenytoin (antiepileptic), carbamazepine (antiepileptic), ritonavir (protease inhibitor used in HIV infection), St John's wort (depression) and particularly the rifamycins (antituberculosis). Such drugs might also reduce the efficacy of hormonal emergency contraception when these are taken concurrently; therefore the dose of hormonal emergency contraception should probably be increased by 50% in women taking these drugs. More data is necessary to clarify this position.
42. Hormonal emergency contraception does not protect against sexually transmitted disease. Chlamydia is the most common sexually transmitted bacterial infection in the UK. Of those infected up to 70% of women and 50% of men are asymptomatic, thus a large number of cases are never diagnosed. (6) This has public health significance because Chlamydia can have serious long-term consequences especially in women. It is a well established cause of pelvic inflammatory disease (PID) leading to infertility, ectopic pregnancy and chronic pain which are expensive to treat and have major lifetime consequences for the individual concerned. Chlamydia also causes ophthalmia neonatorum and pneumonitis in children born to infected women (6). Diagnosed Chlamydial infections in women in England and Wales rose from 16,525 in 1995 to 29,283 in 1999, and increase of 77%.During the same period Chlamydial infection in teenagers rose from 5,481 to 11,311 an increase of 106% and for those under the age of 16 the comparable figures 762 and 1,346, an increase of 76%. (Source: Public Health Laboratories Service quoted in the FYC family Bulletin, Issue 101, Autumn 2000).

    Median prevalences of C trachomatis in different clinical settings(6):

Survey population	Median prevalence (%)	Range
General Practice	4.5	1-12
Antenatal/Obstetric clinics	4.6	2-7
Gynaecology clinics	4.8	3-6
Family Planning clinics	5.1	3-7
Women seeking abortion	8.0	7-12
STD clinics	16.4	7-29

43. In experimental work progesterone is used to establish chlamydial infections in rodents (7), and other workers have shown (8) that progesterone treated chlamydial infected animals do not mount a chlamydia-specific immune response while untreated animals demonstrate a protective enhanced lymph node cell proliferation. In humans chlamydial infections are more likely to be diagnosed in the fourth week of a regular menstrual cycle (9)
44. The provision of Levonelle without prescription is an attempt to reduce the number of abortions in England and Wales. However, as O'Brien (2) stated the provision of emergency hormonal contraception has been available for many years and has been used extensively, yet the number of abortions per annum continue to rise even when standard forms of contraception are provided free and have never been more readily available.
45. Any act of sexual intercourse that is potentially fertile is also capable of transmitting infection. Unless the possibility of such an infection is considered any woman receiving emergency hormonal contraception is being ill-served by its provision. All doctors have a duty to elicit the information necessary to make an assessment of the risk of infection. It will be difficult if not impossible to ask questions appropriate to such an assessment outside of a medical consultation ie how many sexual partners have you had in the last three months?

46. The presence of an untreated sexually transmitted infection in a female patient implies that there is at least one male partner who also has the infection. Previous sexual partners of either of these two individuals may be infected and any subsequent partners will be infected. The need for contact tracing after the diagnosis and treatment of a sexually transmitted disease is essential.
47. Smoking is recognised by the medical profession and the general population as a hazard to health and individuals have been encouraged to stop of reduce their intake of nicotine. The availability of emergency hormonal contraception on prescription seems to have had little effect on the number of unintended pregnancies and its availability without prescription may increase the number of individuals with untreated sexually transmitted disease.

References

1 WHO Task Force on Postovulatory Methods of Fertility Regulation, 1998; Randomised controlled trial of Levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Lancet, 352: 428-433.
2 O'Brien P 2000; Emergency contraception with levonorgestrel: one hormone better than two. The British Journal of Family Planning, 26: 67-69.
3 Marshall W A, Tanner J M 1981; Puberty. In: Scientific Foundations of Paediatrics. eds J A Davis and J Dobbing 2nd edition Heinemann, London, 176-209.
4 Garden A S 1998; Paediatric and Adolescent Gynaecology. Arnold.
5 Apter D 1997; Development of the hypothalamic-pituitary—ovarian axis. Annals of the New York Academy of Sciences, 816: 9-21
6 Chlamydia trachomatis Summary and conclusions of CMO's Expert Advisory Group set up in November 1996
7 Cotter T W, Miranpuri G S, Ramsey K H, Poulsen C E, Byrne G I 1997; Reactivation of chlamydial genital tract infection in mice. Infection and Immunity, 65: 2067-2073.
8 Kaushic C, Murdin A D, Underdown B J, Wira 1998; Chlamydia trachomatis infection in the female reproductive tract of the rat: influence of progesterone on infectivity and immune response. Infection and Immunity, 66: 893-898.
9 Horner et al 1998; Chlamydial trachomatis detection and the menstrual cycle. Lancet, 351: 341-342.

I, Dr John McLean believe that the facts set out above are true and that the opinions I have expressed are correct. I understand that it is my duty to help the Court on matters within my expertise and that this duty overrides any obligation to those who have instructed me in this matter.

(*Signed*: 'John McLean')

Signed……

(*Dated*: '22 October 2001')

Dated……

SECOND WITNESS STATEMENT OF DOCTOR JOHN MCLEAN

I, John McLean, of (*personal address redacted*), will say as follows:

1. I make this witness statement in addition to the first witness statement I signed on 22 October 2001. I have been asked by the Claimant's solicitors to briefly explain how the commencement of pregnancy is dated.
2. The duration of human pregnancy is generally accepted as being 280 days (40 weeks) from the onset of the last menstrual period and the expected date of delivery is determined from that date. The actual duration of human pregnancy is approximately 38 weeks (266 days) since in normal circumstances pregnancy can only begin with fertilisation which follows ovulation about the mid point of the ovarian cycle following the last menstrual period.

I, Dr John McLean believe that the facts set out above are true and that the opinions I have expressed are correct. I understand that it is my duty to help the Court on matters within my expertise and that this duty overrides any obligation to those who have instructed me in this matter.

(*Signed*: 'John McLean')

Signed……

(*Dated*: '4 Feb, 02')

Dated……

WITNESS STATEMENT OF DR CONNIE SMITH

1. [redacted]

[redacted]

[redacted]

2. [redacted]

3. [redacted]

4. [redacted]

[redacted]

5. [redacted]

6. [redacted]

[redacted]

7. [redacted]

8. [redacted]

9. [redacted]

[redacted]

10. [redacted]

11. [redacted]

[redacted]

12. [redacted]

[redacted]

13. [redacted]

14. [redacted]

[redacted]

[redacted]

15. [redacted]

16. [redacted]

17. [redacted]

18. [redacted]

19. [redacted]

20. [redacted]

21. [redacted]

22. [redacted]

23. [redacted]

24. [redacted]

[redacted]

[redacted]

25. [redacted]

[redacted]

26. [redacted]

[redacted]

27. [redacted]

[redacted]

28. [redacted]

[redacted]

29. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

30. [redacted]

[redacted]

31. [redacted]

[redacted]

[redacted]

[redacted]

32. [redacted]

[redacted]

33. [redacted]

[redacted]

34. [redacted]

[redacted]

35. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1. [redacted]

[redacted]

2. [redacted]

3. [redacted]

[redacted]

4. [redacted]

5. [redacted]

6. [redacted]

[redacted]

7. [redacted]

8. [redacted]

[redacted]

9. [redacted]

10. [redacted]

11. [redacted]

12. [redacted]

[redacted]

13. [redacted]

[redacted]

14. [redacted]

15. [redacted]

16. [redacted]

[redacted]

17. [redacted]

18. [redacted]

19. [redacted]

20. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]