The emergence of pathology in gynaecology¹

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In this address I propose to recount some gleanings I have made whilst probing the literature and the ideas that were held in past years in the context of pathology and gynaecology. Inevitably, people have to be considered alongside the work for which they are noted in order to do justice to my purpose, and it is advantageous to try to bring together present-day knowledge and those elements from former times that have stood the test of experience.

Pathology of a Surgical Speciality

In the early days, as specialist surgeons began to be identified, one supposes that it was only to be expected that the pathology of particular specialities was to be developed by those surgeons and clinicians who concerned themselves mainly with one region or system of the body; knowledge was not available otherwise because hospital pathologists, or even less likely, pathologists working closely with surgeons were few and in most cases did not exist. Thus, a great deal of the pathology in the past was done by gynaecologists themselves; this was the pattern in many countries and the custom has continued almost to the present day in a few centres in England and Scotland.

Hydatidiform Mole

Anomalies of conception in woman have been the occasion of wonder and study from ancient times to the present day. One anomaly or disorder of the conceptus that has claimed a major part of this study is hydatidiform or vesicular mole as it is sometimes called.

The essay by Alan Brews of The London Hospital, published in 1939, is worth consulting by the reader interested in the earlier writings, which are freely interleaved with folklore.

Hydatidiform mole is a disorder in which the placenta does not form but the chorion with its villi changes into a fast growing mass of branched, bloated vesicles, resembling hydatids or grapes.

The embryo does not develop; the gestation sac, if it be found in the mass, may contain a shrivelled stalk and rarely a stunted embryo.

Formerly, the aetiology of hydatidiform mole was held to lie in the ovum itself, or that it was simply a myxomatous degeneration of the stroma (Virchow, 1853). Felix Marchand, born in 1846, who worked as a pathologist in Leipzig, is now generally held to have been responsible for shifting the emphasis, to regard it as a disorder of trophoblast, hyperplasia being a leading feature. The vesicles were designated hydatidiform to distinguish them from other hydatids—those now known to result from *Echinococcus* infestation.

The work of Marchand was taken up and confirmed in Glasgow by Teacher (1903) who contributed much to the study of mole and of chorionic carcinoma.

Teacher also studied the occurrence and spontaneous disappearance of metastases. It has long been known that elements of trophoblast are deported through the blood stream. Recent studies of nodules excised from the lungs at thoracotomy or from the vagina have revealed them to be molar rather than carcinomatous (Haines and Taylor, 1962) in some patients in whom embolizing chorionic carcinoma was thought to be present.

Molar lesions that are accompanied by embolic happenings or that permeate the uterine wall were considered by Ewing (1910) to be a distinct variety of hydatidiform mole and he called them 'chorio-adenoma destruens'.

Such cases by whatever designation is used form a middle group between vesicular mole and chorionic carcinoma and their outcome is generally favourable, as indicated by Ewing and by later authors.

Ovaries in Hydatidiform Mole

For a great many years certain changes in the ovaries have been observed in patients with hydatidiform mole and usually also in chorionic carcinoma but to a lesser extent. The ovaries are cystic, with several luteal cysts; sometimes they become

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large with clear yellow fluid which may be blood-stained.

Knowledge concerning the chorionic gonadotrophins when it became available, largely due to Aschheim's work, provided some explanation for this phenomenon. There is usually a correlation between the hormone level in the blood and the amount of luteal change in the ovaries which far exceeds in amount the comparable change in the ovaries of normal pregnancy. In this context it should be widely known that such ovarian cystic development is also a recognized side effect arising from the use of the new substances—human gonadotrophin and clomiphene—prescribed to induce ovulation in patients who fail to ovulate spontaneously. Unless this possibility is known to those in clinical charge of such patients, surgical intervention may take place with disastrous consequences for the luckless woman if the cystic ovaries be removed mistakenly.

Pregnancy Diagnosis Tests

Further study of vesicular mole and the spectrum of trophoblastic tumours received a new impetus from the discovery of gonadotrophins in urine and blood and the introduction of tests, using biological reactions, in female laboratory animals. The first of these, which came to be known as the Aschheim-Zondek test, was based on experiments carried out by Aschheim in Germany.

Selmar Aschheim's early years in medicine were devoted to both laboratory and clinical work in Berlin, and in 1912 he became Director of the Laboratory of Pathological Histology at the Charité Hospital in that city. He described his new pregnancy test at a congress in Bonn and thereafter the test achieved universal acceptance (1928). This event marked his debut in a long career of scientific achievement whose importance far outvalued the number of written pages. In an address acknowledging Aschheim's 75th birthday, Hughuer (1965) commented on the fine simplicity of demeanour which in Aschheim was combined with so much scientific glory, to which Aschheim replied that chance had favoured him by allowing France to become his second fatherland. (Aschheim had gone to live in France and became a French citizen in 1937.) In 1951 I visited this fascinating man in his laboratory at the ancient Maternité of Port Royal in Paris and he allowed me to see him conduct his then current method of pregnancy testing using immature rats (Aschheim and Varangot, 1949). The novelty to me was that he chose to kill the animals with town gas; it was effective, and, by reason of carboxyhaemoglobin, the diagnostic spots on the

ovaries were cherry red. I tried to get his views on the then new male toad test for pregnancy; he smiled and said he preferred the rats because he thought toads and (male) frogs might be too agile for him—he was then well over 70.

Several tests have been devised based on the Aschheim-Zondek principle, employing females of various animal species, but an innovation was introduced in 1947; Galli Mainini used male toads and frogs (Haines, 1948). A species of male toad had long been the animal used in Buenos Aires by Bernardo Houssay in his fundamental endocrine researches on the hypophysis, and it became known that spermatogenesis could be elicited by chorionic gonadotrophins. This effect Galli Mainini found could be achieved by injecting the animals with pregnancy urine, but spermatogenesis did not occur after other substances were injected (1947). In this animal, following swelling of Sertoli cells spermatozoa are detached almost immediately and escape by the vasa deferentia to the kidney, to be excreted in the urine within 20 to 30 minutes of the injection.

By these tests and other methods it was soon found that high values of gonadotrophin were obtained in hydatidiform mole and chorionic carcinoma and the test could be useful in detecting the onset of malignant change. But in this regard it was further determined that high values could be measured towards the 60th day of a normal pregnancy without fear of malignant change.

More recently other tests have been developed based on immunological techniques using prepared reagents (Wide and Gemzell, 1960; Wilde *et al*, 1965). However, such test materials are not universally available or practicable, and in many laboratories some variety of animal test is the method of choice, not least because of the degree of accuracy which can be achieved with a well tried test.

In diagnosis, using biological and other pregnancy tests, it is fundamental constantly to appreciate that none is infallible. Doubts should always be checked by repetition of tests.

Endometrium

It seems scarcely necessary to remind anyone that the complaint of uterine bleeding has been the subject of inquiry for centuries past.

However, as and when it became practicable to examine tissues by the naked eye and later by histology, some hopes of finding an answer were created and in fact certain reasons for the bleeding have been revealed.

Search for a cause in the uterus disclosed polyps and tumours as well as hyperplasia of the endo-

metrium. First, however, physiological proliferation has to be considered.

Beliefs were held for many years that some form of inflammation of the endometrium caused the bleeding, becoming identified with a condition of the endometrium known then as endometritis glandularis. This view was abandoned following the publication of the epoch-making paper of Hitschmann and Adler (1908). They clarified the relationship of the ovarian cycle to the endometrium showing that this went through a series of changes controlled by maturation of an ovarian Graafian follicle and corpus luteum formation.

Nevertheless, bleeding can occur in a patient with endometritis but that is not to say that bleeding is caused by endometritis. Often there is a different cause. We see no reason to disagree with the view expressed originally by Teacher concerning non-specific endometritis: if we exclude cases clearly related to conception and foreign body, endometritis is rarely encountered by the pathologist (Teacher, 1935).

The endometrium observed in the uterus during the late luteal or premenstrual phase is sometimes remarkably thick and polypoid, and microscopy is needed to distinguish between a physiological bulky secretory endometrium and simple hyperplasia. Furthermore, failure to appreciate the significance of different histological pictures that accompany the phases of the cycle can still lead to misdiagnosis by the inexperienced observer. Attention to the menstrual dates and thoughtfulness are required. The pattern of endometrial glands in early pregnancy can be confusing too. Teacher (1935), speaking of observations he made many years before, pointed this out, and in this context also awareness of the menstrual dates and the physiological patterns of pregnancy endometrium serve to avoid errors in diagnosis.

Hyperplasia of Endometrium

Hyperplasia of the endometrium is today one of the principal features to be considered in the study of uterine bleeding.

Simple overgrowth often showing small cysts has long been a recognizable entity, usually being accompanied by some hyperplasia of the myometrium. However, another line of thought arose from the observations of Schröder (1914; 1915) who suggested that there was a link between the hyperplasia and the simple cysts of the ovaries which were present also. This observation came at a significant time, following the recognition of different patterns in the endometrium during the menstrual cycle.

The cystic follicles in the ovary of these patients suggested to Schröder that persistence of one or

more follicles associated with only occasional formation of a corpus luteum allowed the endometrium to proliferate for several days or weeks longer than the normal preovulatory phase. Thus amenorrhoea was prolonged and was often ended by severe uterine bleeding. This disorder came to be known as metropathia haemorrhagica. A somewhat comparable oestrogen linkage was put forward some time later, noting that feminizing ovarian tumours also appeared with endometrial and myometrial hyperplasia.

Schröder had a long experience as a pathologist, beginning at Rostock a few years before the publications mentioned earlier, and subsequently he worked at Kiel and at Leipzig. His views on the endometrium were highly regarded and we find him in 1954 writing a commissioned article in the *American Journal of Obstetrics and Gynecology*. He spoke of more than 3,000 cases of endometrial hyperplasia he had observed in the course of 40 years. He stated that his experience showed no special risk of cancer supervening in patients with simple hyperplasia. He distinguished clearly between this and the much less common atypical hyperplasia. These views were reinforced in the writings of Novak who was his contemporary.

Schröder's work on hyperplasia was almost unknown in Britain up to 1920 and until it was confirmed by Shaw (1929). Wilfred Shaw had begun his task under the stimulus of his chief Herbert Williamson, whose name was attached to the laboratory, where for many years a lively tradition of gynaecological pathology was maintained at St Bartholomew's Hospital, London.

There were other pathological lines that Shaw investigated personally in the laboratory, notably chocolate cysts of the ovary and ovarian tumours, re-examining the views of Walter Schiller; Shaw wrote two successful textbooks which bore the stamp of originality, and the appropriate pathology was usually accorded a leading place in his description of a lesion.

Meanwhile, Novak and others in America studied and wrote extensively about endometrial hyperplasia. There seemed little disagreement in the views held in Europe and America, but the recognition of atypical forms and a possible relationship to carcinoma created a problem which remains largely unsolved at the present time.

In summarizing investigations that have been made to explain the causes of uterine bleeding, it can be concluded that certain lesions have been revealed by anatomical and histological examination, certain other entities have been clarified but there remain many cases of the malady that have not been explained on observed pathological lesions.

Adenomyosis

Study of adenomyosis and the pathology of certain other lesions of the uterus was prominent in the work of two obstetricians of earlier times. Cuthbert Lockyer (1867-1957) worked in London, and T. S. Cullen (1868-1953), Canadian by birth, spent most of his professional life in Baltimore starting there with a short spell in the laboratory of W. H. Welch, Professor of Pathology at the Johns Hopkins School.

Lockyer was one of many obstetricians active in an era when much attention was given to descriptive pathology. He was in the van of this company in England; he published a great deal and it is generally recognized that his book 'Fibroids and allied tumours' (1918) was a landmark among books on the subject, not least because of the variety and meticulous care given to the illustrations. One of these is of particular interest to pathologists because it appears to portray very well a lesion which today we know as stromal endometriosis but at that time was called 'periendothelioma of the uterus'. The case and its pathology were described by Lockyer's chief, Alban Doran, at the Royal Society of Medicine in 1909. The lesion with its extensions from the uterus along the Fallopian tube, into the mesosalpinx, ovary, and broad ligament received scant attention until many years had elapsed (Dougal, 1926; Hunter, 1953).

Lockyer collected a great amount of material from his own practice, the Samaritan and Charing Cross Hospitals, and from numerous surgical friends. He examined the specimens and prepared them for preservation, ultimately presenting the Lockyer collection to the museum of Charing Cross Hospital Medical School in 1912. The exhibits were most carefully catalogued and Lockyer himself published the descriptions in book form (1930). Most of them still remain and at the time of the catalogue there were 1,150 mounted specimens and 1,828 microscopic sections.

Another notable contribution came from Lockyer when, jointly with T. W. Eden, he brought out their textbook 'Gynaecology for students and practitioners' which appeared first in 1916. The book embodied much of the content of Lockyer's other book. It remained a standard work for more than 30 years; not only was it amongst the leaders in textbooks of gynaecology, but in addition it dealt extensively with the morbid anatomy of tumours and with the histopathology of most of the recognized gynaecological conditions as far as was possible 45 years ago.

Beckwith Whitehouse, of Birmingham, took on the fourth edition which appeared in 1935. He it was who distinguished the types of carcinoma of the female urethra (1911) and made a detailed study of

the material voided from the uterus in patients with severe dysmenorrhoea—a study which included careful histological examinations. In his Hunterian lectures to the Royal College of Surgeons (1914), Whitehouse advocated a coordinated clinical, pathological, and experimental attack on the problems of the aetiology of irregular uterine bleeding, a theme taken up by Wilfred Shaw some years later.

In 'Fibroids and allied tumours' almost one third of the text concerns adenomyosis and this topic provided a subject of common interest and discussion for the two contemporaries, Lockyer and Cullen in America. Their books and papers contain many exchanges of illustrations and comments about individual cases which they discussed with mutual agreement. In fact their correspondence continued for most of their active lives.

Use or misuse of terms is often a cause of misunderstanding and I venture to repeat that lack of precision in terminology has done much to impede the interchange of medical knowledge. The disorder I have just mentioned was called 'adenomyoma' by Cullen and his contemporary writers; nowadays we use adenomyosis for the lesion in the uterus, and for that on the outside of the uterus, and elsewhere endometriosis is the term generally in use. A further variation in this context was championed by Blair Bell in 1922; he pleaded that endometrioma be adopted. He further stated that his specimen of chocolate cyst in which endometrium was found microscopically was the first of the kind to be reported in Britain, though Sampson (1921) in America had already published such cases. With the exception of a few gynaecologists who do not choose to change, the designation endometriosis is now preferred to endometrioma.

William Blair Bell (1871-1936) the first President of the Royal College of Obstetricians and Gynaecologists, a graduate of the University of London (1896) who made his professional career in Liverpool, was a born investigator, writer, and lecturer, and was no doubt a successful gynaecologist. He devoted much of his time to cancer research. His writings included many with pathological titles such as 'Sarcoma of the vulva', 'The nature of the obstructing membrane in haematocolpos', 'Rhabdomyosarcoma of the uterus' (Glynn and Bell, 1914), and 'Ovarian neoplasms'. An attractive biography of the man and his many-sided capabilities can be found in Sir Stanford Cade's inaugural Florence Blair Bell lecture (1951). Bell, in common with most gynaecologists of his day, examined the slides from his own operations, and another in Liverpool, H. Leith Murray, published thought-provoking views (1910) on the mechanism of necrobiosis, red degeneration of uterine fibroids; maybe we are no closer to a clue in 1970.

Cullen's early years in Baltimore were spent under the guidance and influence of Welch and of Kelly, the gynaecologist. This short epoch ended with Cullen being put in charge of the laboratory of gynecological pathology at the hospital, the first laboratory of its kind in America, and he joined Kelly's surgical staff about 1896, thus filling a dual role, providing the foundations for the important publications that were to come. Following his paper on adenomyosis, which became his abiding interest, his first book 'Carcinoma of the uterus', appeared in 1900. It remains a classic comprehensive treatise on the pathology of carcinoma at this site (Willis, 1960); the number and variety of specimens are unsurpassed.

Not long after his arrival in Baltimore Cullen published his description (1908) of adenomyosis of the uterus based on a remarkable series of examinations of excised specimens, remarkable having regard to the very limited facilities and laboratory aid at that time, because he carefully scrutinized upwards of 50 uteri by a multiple block or even step section technique; the thought of the labour this must have entailed will surely daunt many histopathologists of today. He concluded that the glands and stroma diffusely dotted throughout the myometrium were derived by extension from the lining of the uterus—a view that brought him into conflict with von Recklinghausen, who stood for a Wolffian origin. The conflict was sometimes fierce but eventually Cullen's view prevailed and the two protagonists corresponded for many years.

Cullen published other outstanding books: 'Adenomyoma of the uterus' and with Kelly, 'Myomata of the uterus'. Each was written with the same care as his first. His last title was 'Embryology, anatomy and diseases of the umbilicus' in 1916; here we can find extensive detail of adenomyoma/endometriosis in this region, and he pointed further to the fact that many carcinomas at the umbilicus are in fact metastatic. Cullen kept up his work in the laboratory until about 1915 when it passed to the hands of Novak and this centre of dissemination of knowledge flourished thereafter.

Surgeons and Pathologists

I have already referred to some work of Teacher of Glasgow, but there are certain other pathologists and surgeons to mention.

Matthew Stewart of Leeds is one who is probably well known to many present, both as a pathologist and a distinguished Editor—he too was a Glasgow graduate. He published articles on uterine tuberculosis (1912), and contributed two important chapters to 'A manual of obstetrical and gynaecological pathology' (1935). Teacher had written about

half this book before his death; it was completed with the help of other contributors but for a variety of reasons it missed becoming a standard book.

In looking back one can reflect that in preparing his own book Teacher must have been somewhat daunted by the remarkable book on gynaecological pathology from Oskar Frankl of Vienna (1914) which reached England after the war. The volume was enriched by exquisite illustrations, according to Teacher, which comprised 34 plates in bright colours made from histological slides. Incidentally sets of plates were obtained by the numerous foreign gynaecologists who made the trip to Vienna after World War I, and doubtless pathology was brought to many gynaecologists by this method. Frankl was a frequent contributor to the *Journal of Obstetrics and Gynaecology*, the *American Journal of Obstetrics and Gynecology*, as well as to the German literature.

Nicholson's era at Guy's Hospital preceded Stewart. I should imagine his interests were quite different as can be learnt from his 'Studies in tumour formation' recently bound together (1950). Certain of these studies contributed to our current views on mesodermal mixed tumours of the uterus (Taylor, 1958); the rather rare teratoma of the uterus was the subject of another paper (Nicholson, 1956).

It may be said that Nicholson's most effective role in gynaecology concerns ovarian teratoma, including goitre. He demolished the older and established the current views on pathogenesis. He was also concerned with the nature of squamous cells found in sections of endometrial carcinoma. It is still not sufficiently widely known that such squamous change is often observed in histological specimens and that this has no significance in assessing the prognosis of the patient suffering from uterine carcinoma (Haines and Taylor, 1962).

Walter Schiller of Vienna and later of Chicago is one whose many contributions to pathology are overlooked. His description of one variety of ovarian carcinoma as 'mesonephroma ovarii' attracted a somewhat unmerited notoriety and many consider his view of a histogenesis to be ill founded.

Schiller's worthwhile studies concerned the pathology of the different types of ovarian tumours and the less obvious stages in the course of carcinoma of the cervix. For the clinicians he provided the iodine test (1928) which can help in the selection of areas for biopsy of the cervix uteri.

Lawson Tait, born in 1845 in Edinburgh, was one of Birmingham's notable surgeons, who made significant additions to pathology; for such a man the critical examination of an operation specimen was a natural 'next thing' to the surgical intervention (Taylor, 1965). He was among the first to consider that inflammation of the Fallopian tubes and, more

particularly, pyosalpinx, were due to ascending infection. Included in his published books was one on 'The pathology and treatment of diseases of the ovaries' and, as cited by Meigs (1954), he described a 36-year-old patient with pleural effusion and benign ovarian tumour who recovered after removal of the fibroma (Tait, 1892).

John Bland Sutton was one of the several outstanding surgeons in the early part of this century. Not only was he a pioneer in surgical techniques, specially of hysterectomy, but he studied and wrote extensively on a wide range of subjects in comparative anatomy and pathology, often of gynaecological disorders. Like many of his generation his titles included 'uterine fibroids' and 'diseases of the ovaries'; his Hunterian lectures were about dermoid tumours. He was gynaecological surgeon to Chelsea Hospital for Women from 1892, and he left a lasting memorial at the Middlesex Hospital, where he was also a surgeon, by presenting money to found the Bland-Sutton Institute of Pathology in 1914.

It was due to the efforts of Dan Dougal that a pathology laboratory was inaugurated at St Mary's Hospital, Manchester, whose staff he joined in 1919. He strongly supported a place for pathology in the practice and teaching of gynaecology—a move which was spreading also in Germany and America. He was interested in a variety of pathological topics, including notable studies of endometriosis (Dougal, 1926; 1938).

Robert Meyer—Emil Novak

No review of pathology in gynaecology would be worthy of the title without paying due regard to the work of Robert Meyer in Germany (1864-1947) and that of Emil Novak (1884-1957) in America. Both men spent their early professional life as family doctors only to begin their pathological work in their early thirties, though Novak went on to practise gynaecology as well. I am bound to say that to attempt more than to indicate guide lines to each man's considerable and informative achievements is neither justifiable nor proper here. Each would need a separate address and besides tributes to the life and work of each have been done well already (Novak, 1946 or 1947; Martzloff, 1954; 1957).

Meyer began his work in gynaecology and pathology under Veit in Berlin; he later came under the influence of Stoeckel but it was Ruge who appears to have been Meyer's principal guide. Together these obstetricians became world leaders in gynaecological pathology, campaigning successfully to have microscopical examination of tissues established as a diagnostic method in gynaecology.

Meyer's views concerning cervical erosion and

non-specific cervicitis gained popular acceptance at the time (Meyer, 1910; 1911). Perhaps more important was his attitude towards the histological differentiation of carcinoma from epidermization and there seems no doubt that this and the interpretation of epidermization which came later were inspired starting points for current ideas about changes in the epithelium of the cervix uteri. He contributed much to standard textbooks of the day, including the Veit-Stoeckel Handbuch, and later several sections of the Hencke-Lubarsch work on 'Speziellen pathologie'; he was also a successful editor of journals. Of the more than 200 publications listed I can choose only a few topics.

Meyer had taken a course in practical embryology, and he put to good use knowledge thereby acquired in papers and demonstrations of a variety of developmental and anomalous defects, culminating in his mammoth study of the development of the human vagina.

He was a critical reviewer in debates concerning adenomyosis and later of endometriosis. One of Meyer's most outstanding presentations was to review almost collectively what he called special tumours of the ovary (1931). I will not list them: they are well known to most histologists and gynaecologists, and to many of us they remain as interesting as no doubt they were 40 years ago. Soon after his 70th birthday Meyer left Berlin for the USA to continue his work at the University of Minnesota until the age of 80.

No doubt Robert Meyer is to be remembered amongst the great—a tireless original worker, a prolific writer, and a devoted and enthusiastic teacher as testified by many who went to his classes (Traut, 1946).

Emil Novak began his long association with the Johns Hopkins Medical School in 1915 as an instructor assisting in the course in gynaecological pathology given by Cullen, who by that time had attained international recognition as an authority. Novak combined this role with the practice of gynaecology at other hospitals in Baltimore but he was never able to have patients in the Johns Hopkins Hospital. He was to assume direction of the laboratory where in due course, according to Martzloff his chronicler, he strove single handed to keep the laboratory orientated in the rapidly changing discoveries of new knowledge.

Novak repeatedly maintained that pathology for him was a hobby, and it is clear from a study of his early years that this hobby had two chief components. From childhood he had been an omnivorous reader and this advantage facilitated his ready acquisition of the essentials of much new work that was being published during the years after his graduation. His

other source of knowledge stemmed from careful and critical study of the large volume of well documented pathological material that Cullen had already stored in the laboratory.

Once again, I feel bound to say as I did concerning Meyer, that it is beyond the scope of this essay to consider Novak's work in detail but I may recall certain topics that were never far from his thoughts or his pen. The corpus luteum, for example; various aspects of menstruation; hyperplasia of the endometrium; and the special ovarian tumours to which as a group he had been introduced by Meyer. Furthermore it was Martzloff who said 'probably no one in America besides Cullen has done so much to help clarify and establish a sound anatomical basis for the diagnosis of uterine cancer'. Martzloff, I believe, was speaking of the uterine body, but I feel that Novak's firm principles applied equally to the histological diagnosis of carcinoma of the cervix. There can be no doubt that Novak was the outstanding expositor of gynaecological pathology of his generation (Martzloff, 1957). This exposition was badly needed by the gynaecologists and pathologists of the time. Novak pursued his programme, using not only knowledge published in Britain and America, but also he was able to impart an interpretation of the contents of European publications, coming mostly from the German school, as he often called it.

Of the books that Novak wrote, his 'Gynaecological and obstetrical pathology' (1940) is the one that concerns us. Martzloff considered it to be Novak's magnum opus, and he continues: 'the book is written in an easy, engaging, narrative style' and 'carries the indelible stamp of authenticity'. It was an instant success, sought after and consulted all over the world. Some years later (1946) Novak brought out a new venture called *Obstetrical and Gynecological Survey*, with N. J. Eastman as Editor in Chief for obstetrics. This journal, several numbers appearing annually, was a huge success according to the chairman of the publishing company (Gill, 1954); it continues to flourish, under its current editors. The gynaecological section in this journal of abstracts was enriched by the informative and often pungent comments by Novak who effectively used this further avenue for dissemination of his acquired knowledge for the benefit of the reader.

I would have found it difficult not to consider Novak, the man and his work, partly because of his outstanding prowess as a writer, lecturer, and teacher, and especially because of the strong personal impact he made. One soon came to sense that 'underneath all his actions there was a quiet restraint and undercurrent of kindness' (Martzloff, 1957), qualities possessed by few men.

Genital Tuberculosis

In talking to pathologists and gynaecologists, I find that first-hand experience of the disorder varies considerably, and it seems certain that this experience will continue to dwindle because of the health trends and general improvement in socio-economic status in most countries. Thus it is that tuberculosis affecting the female genital organs is less frequently encountered than in former times but therefore its possible occurrence must not be overlooked in diagnosis. The pattern of the lesion has changed but the disease remains.

In Britain and America up to the early part of this century genital tuberculosis was usually noted only at necropsy. In this era deaths from a generalized infection were common in girls and young women, and often extensive caseating lesions of the uterus were observed. Such specimens can be seen illustrated in Cullen's books mentioned earlier, and examples were published by Matthew Stewart in 1912. It is pertinent to remember that such destructive caseous lesions of the uterus are still to be found in women living in impoverished communities (Rewell, 1958) and in our experience occasionally in older women. A fresh trend in gynaecological practice 30 years ago provided a new approach to the incidence and later to the aetiology of genital tuberculosis, more particularly in European countries. Attention was drawn (Schockaert and Férin, 1939) to the finding of focal tuberculosis lesions in biopsy specimens or curettings of the endometrium taken from symptomless women. Two reasons were given for the apparent increasing incidence: (1) the more frequent use of curettage and histological examination as a means of investigation, and (2) the growing number of married women seeking advice at fertility clinics, the only complaint being that the marriage was infertile. In this selected group of patients tuberculous endometrial lesions were recorded in from 2 to 10%.

Bacteriological studies were also carried out not only on this new type of material but on surgical tissues from the pelvis. Results showed that the strain of the infecting mycobacterium was nearly always human, dispelling the long-held view that genital involvement was abdominal in source and consequently of bovine strain. Thus it became inevitable that the mode and time of infection should be reviewed. Clinicians helped by pathologists encouraged by this new source of material were active in this enquiry. It now seems that bacilli infect the genital tract via the blood stream during the active phase of a primary extragenital lesion, eg, in lung, and the consequent genital infection either remains inactive or becomes active after an

interval of eight, 10, or even more years (for references see Haines and Taylor, 1962).

It has been stated (Berkeley, 1903) that it was Morgagni who first recorded a case of bilateral tuberculosis of ovaries and Fallopian tubes and concluded that the peritonitis was secondary to the disease in the organs—a conclusion which can be interpreted as supporting the present view that genital infection is a post-primary lesion, occurring by the blood stream, and indeed Berkeley favoured this view in 1903.

Cytology

Exfoliative cytology remains firmly a part of pathology, although in the early 1950s it looked as if divorce was imminent and especially was this true in the USA.

Of the many important aspects of cytology, the most eye-catching has been the potential role in detection of cancer of the uterus. As pathologists, however, we are aware that cytology plays a part in the study of disorders in other body systems, a theme enunciated in the several writings of Bamforth and recently brought together in a notable book (Bamforth, 1966). Nevertheless it was the published work of Papanicolaou in New York that rapidly drew worldwide critical attention to cytology in the detection of carcinoma, particularly of the uterine cervix.

Papanicolaou followed his earlier work on guinea pigs by the examination of vaginal smears of women as a means of observing the effect of oestrogen therapy. One day he chanced to see what turned out to be cancer cells in a woman's vaginal smear, but the significance of this observation was not realized by clinicians at that time (Cuyler, 1952). Subsequently he collaborated with gynaecologists—initially those on the staff of the New York Lying-in Hospital which is adjacent to the Cornell University Department of Anatomy where Papanicolaou was professor (Papanicolaou and Traut, 1941; 1943). Further developments in vaginal and cervical cytology are recent and known widely enough to merit no further comment here.

However, there are two special points that I consider noteworthy. Histopathologists have long been aware of the appearance of carcinoma *in situ*/intraepithelial carcinoma affecting the epithelia in different parts of the body.

With the increase in number of vaginal smears being examined it was found that this lesion in the cervix also gives rise to abnormal cells in the smear; in fact, to many cytologists these cells may be indistinguishable from those exfoliated or scraped from an invasive carcinoma. The diagnosis is made

only by histological examination. Besides assisting in the detection of invasive carcinoma it soon became apparent that the application of mass screening of women by cytology was discovering a hitherto unthought of number of cases of carcinoma *in situ*, thus unexpectedly providing much pathological tissue useful in the study of suspected precursors of carcinoma of the cervix. The screening and the studies still continue but definite conclusions are yet to be found and authenticated.

I have already named Joseph Bamforth in the sphere of cytology. He was an outstanding character amongst pathologists in London, and his many endearing qualities emerged easily on first meeting. He had come from Liverpool to St Thomas's Hospital soon after the first World War and was active for the succeeding 45 years as a renowned clinical pathologist and teacher (Dempster, 1967). His interests in pathology were wide; he had early been attracted to the use of the wet film method of diagnosis of cells in pathological fluids as introduced by Dudgeon (Bamforth, 1950; 1963), and became well practised in gynaecological pathology. His MD thesis in 1914 was on a histological study of cyclical changes in the endometrium, and he published papers on endometrial tuberculosis, endometrial carcinoma, and Brenner tumours of the ovary.

With such a background it was natural that Bamforth should become caught up in the practice of vaginal cytology, for he was already expert in the detection of malignant cells in sputum. For many years he adhered to a method of staining smears using Mayers' haemalum and eosin (Bamforth, 1950), but was greatly pleased that he could recognize the malignant cells in Papanicolaou-stained smears when shown them for the first time.

Bamforth had a strong coordinating influence in the early formative years of the British Society for Clinical Cytology, and the society was fortunate indeed to have him as its first President.

George Papanicolaou was known to a far greater number of people than Bamforth. His writings achieved world-wide popularity, countless visitors came to visit him in New York, and he conducted courses for large numbers of would-be cytologists. He appeared to be the gentlest of men and his quiet charm had to be experienced to be appreciated fully. He approached with great calm a cherished ambition, which was achieved shortly after retiring from Cornell, to return for a visit to his native Greece after an absence of some 40 years. On this journey he was to be seen in London for a brief stay.

The Future

Before I conclude it seems natural to ask what

trends are likely in the future of pathology directed towards gynaecology. To make a forecast, I think might be presumptuous though a few possible lines may be mentioned.

Already, techniques for radioimmunoassay are used not just to detect pregnancy but to measure low levels of human chorionic gonadotrophin in plasma or urine (Bagshawe, 1969). This procedure alone or with arteriography is advancing clinical care of patients with trophoblastic tumours—some are notoriously lethal.

Histochemistry (Pearse, 1951), which has run an interrupted course since the days of Raspail, 140 years ago, though revealing the metabolic changes, for example, in the endometrium, has not yet brought us information about the antecedents of carcinoma in the uterus (as had been hoped for 25 years ago).

Electron microscopy is being applied today to many problems but it is not yet clear whether the method will advance pathology in gynaecology. It has been useful in correlating function with morphology, for instance indicating the site or source of gonadotrophin formation.

Lastly, we look with confidence for interesting developments in the field of chromosome studies in connexion with certain disorders of the uterine cervical epithelium and with patients with dysgenetic gonads with or without ovarian tumours.

I venture to suggest that this essay may prove of interest or even value to clinical pathologists, particularly as it seems true in many hospital histopathology laboratories that around 25% of the surgical specimens come from gynaecology.

My gleanings are understandably incomplete; they comprise the topics that interest me and some personalities about whom I have learnt a little. I have sought to show that foundations of pathology in gynaecology have been built largely by gynaecologists and obstetricians whilst fewer pathologists have taken part. My omission of contemporary authors is deliberate. I freely acknowledge with gratitude the ready response from colleagues I have consulted on a number of occasions. In particular I declare my grateful appreciation to C. W. Taylor, for 20 years a friend, collaborator, and educator.

References

- Aschheim, S., and Zondek, B. (1928). Schwangerschaftsdiagnose aus dem Harn (durch Hormonnachweis). *Klin. Wschr.*, 7, 8-9.
- Aschheim, S., and Varangot, J. (1949). La réaction biologique de la grossesse basée sur l'action hyperhémiant des hormones gonadotropes sur l'ovaire de la rate impubère. *Gynéc. et Obstét.*, 48, 17-23.
- Bagshawe, K. D. (1969). *Choriocarcinoma*. Arnold, London.
- Bamforth, J. (1950). The cytology of the vaginal smear. In *Modern Trends in Obstetrics and Gynaecology*, edited by K. Bowes, pp. 454-474. Butterworth, London.
- Bamforth, J. (1963). Pioneer work by Professor Dudgeon in cytological diagnosis. *J. clin. Path.*, 16, 395-398.
- Bamforth, J. (1966). *Cytological Diagnosis in Medical Practice*. Churchill, London.
- Berkeley, C. (1903). Genital tuberculosis in the female. *J. Obstet. Gynaec. Brit. Emp.*, 3, 31-45.
- Brews, A. (1939). Hydatidiform mole and chorion-epithelioma. *J. Obstet. Gynaec. Brit. Emp.*, 46, 813-835.
- Cade, S. (1951). *Chemotherapy of Cancer*. University Press, Liverpool.
- Cullen, T. S. (1900). *Cancer of the Uterus*. Appleton, New York.
- Cullen, T. S. (1908). *Adenomyoma of the Uterus*. Saunders, Philadelphia and London. Kimpton, London.
- Cullen, T. S. (1916). *Embryology, Anatomy and Diseases of the Umbilicus*. Saunders, Philadelphia and London.
- Cuyler, W. K. (1952). The recognition of carcinoma *in situ* of the cervix uteri by Papanicolaou's method. In *Progress in Fundamental Medicine*, edited by J. F. A. McManus, pp. 261-276. Lea and Febiger, Philadelphia. Kimpton, London.
- Dempster, K. R. (1967). Dr. Joseph Bamforth. *Nature (Lond.)*, 214, 218.
- Doran, A. H. G., and Lockyer, C. (1908). Two cases of uterine fibroid showing peritheliomatous changes: long immunity from recurrence after operation. *J. Obstet. Gynaec. Brit. Emp.*, 14, 320-330.
- Dougal, D. (1926). Endometrioma of the ovary and cornual adenomyoma after bilateral salpingectomy. *J. Obstet. Gynaec. Brit. Emp.*, 33, 439-443.
- Dougal, D. (1938). The problem of endometriosis. *Amer. J. Obstet. Gynec.*, 35, 373-386.
- Eden, T. W., and Lockyer, C. H. J. (1916). *Gynaecology for Students and Practitioners*. Churchill, London.
- Ewing, J. (1910). Chorioma: a clinical and pathological study. *Surg. Gynec. Obstet.*, 10, 366-392.
- Frankl, O. (1914). *Kurzgefasstes Handbuch der gesamten Frauenheilkunde*, edited by W. G. Liepmann, vol. II. Vogel, Leipzig.
- Galli-Mainini, C. (1947). Pregnancy test using the male toad. *J. clin. Endocr.*, 7, 653-658.
- Gill, R. S. (1954). About Emil Novak. *Obstet. gynec. Surv.*, 9, 1-40.
- Glynn, E. and Bell, W. B. (1914). Rhabdomyosarcoma of the uterus. *J. Obstet. Gynaec. Brit. Emp.*, 25, 1-12.
- Haines, M. (1948). The male-toad test for pregnancy. *Lancet*, 2, 923-926.
- Haines, M., and Taylor, C. W. (1962). *Gynaecological Pathology*. Churchill, London.
- Hitschmann, F., and Adler, L. (1908). Der Bau der Uterusschleimhaut des geschlechtsreifen Weibes mit besonderer Berücksichtigung der menstruation. *Mschr. Geburtsh. Gynäk.*, 27, 1-82.
- Hughuier, J. (1965). Eloge de M. le Professeur S. Aschheim. *Bull. Féd. Soc. Gynéc. Obstét. franç.*, 17, 119-120.
- Hunter, W. C. (1953). Benign and malignant (sarcoma) stromal endometriosis. *Surgery*, 34, 258-278.
- Lockyer, C. H. J. (1918). *Fibroids and Allied Tumours*. Macmillan, London.
- Lockyer, C. H. J. (1930). *The Lockyer Collection of Obstetric and Gynaecological Specimens*. J. Bale, London.
- Martzfloff, K. H. (1954). The contribution of Dr. Emil Novak to gynecological pathology. *Obstet. gynec. Surv.*, 9, 40-46.
- Martzfloff, K. H. (1957). In memoriam—Emil Novak. *West. J. Surg.*, 65, 107-110.
- Meigs, J. V. (1954). Fibroma of the ovary with ascites and hydrothorax—Meigs' syndrome. *Amer. J. Obstet. Gynec.*, 67, 962-987.
- Meyer, R. (1910). Die Erosion und Pseudoerosion der Erwachsenen. *Arch. Gynäk.*, 91, 658-691.
- Meyer, R. (1911). Zur Genese und Bedeutung der Pseudoerosio congenita et acquisita portiois uteri: ein Beitrag zur Entwicklung und Pathologie der Portio. *Zbl. Gynäk.*, 35, 76-80.
- Meyer, R. (1931). The pathology of some special ovarian tumors and their relation to sex characteristics. *Amer. J. Obstet. Gynec.*, 22, 697-713.
- Murray, H. L. (1910). The haemolytic lipids of degenerating fibroids with special reference to red degeneration. *J. Obstet. Gynaec. Brit. Emp.*, 17, 534-546.
- Nicholson, G. W. de P. (1950). *Studies on Tumour Formation*. Butterworth, London.
- Nicholson, G. W. de P. (1956). Studies on tumour formation. XXI. A polypoid teratoma of the uterus. *Guy's Hosp. Rep.*, 105, 157-188.
- Novak, E. (1940). *Gynecological and Obstetrical Pathology*, Saunders, Philadelphia and London.

- Novak, E. (1946). Life and works of Robert Meyer. *Trans. Amer. gynec. Soc.*, **69**, 98-132. (Also 1947, abridged, *Amer. J. Obstet. Gynec.*, **53**, 50-64.)
- Papanicolaou, G. N., and Traut, H. F. (1941). The diagnostic value of vaginal smears in carcinoma of the uterus. *Amer. J. Obstet. Gynec.*, **42**, 193-206.
- Papanicolaou, G. N., and Traut, H. F. (1943). *Diagnosis of Uterine Cancer by the Vaginal Smear*. Commonwealth Fund. New York.
- Pearse, A. G. E. (1951). A review of modern methods in histochemistry. *J. clin. Path.*, **4**, 1-36.
- Rewell, R. E. (1958). Tuberculosis in the female genital tract in South India. *J. Obstet. Gynaec. Brit. Emp.*, **65**, 28-32.
- Sampson, J. A. (1921). Perforating hemorrhagic (chocolate) cysts of the ovary. *Arch. Surg.*, **3**, 245-323.
- Schiller, W. (1928). Zur klinischen Frühdiagnose des Portiokarzinoms. *Zbl. Gynäk.*, **52**, 1886-1892.
- Schockaert, J. A., and Férin, J. (1939). *Bull. Soc. belg. Gynec. Obstet.*, **15**, 407.
- Schröder, R. (1914). Ueber das Verhalten der Uterusschleimhaut um die Zeit der menstruation. *Mschr. Geburtsh. Gynäk.*, **39**, 3-21.
- Schröder, R. (1915). Anatomische studien zur normalen und pathologischen Physiologie des menstruationszyklus. *Arch. Gynäk.*, **104**, 27-102.
- Schröder, R. (1954). Endometrial hyperplasia in relation to genital function. *Amer. J. Obstet. Gynec.*, **68**, 294-309.
- Shaw, W. (1929). Irregular uterine haemorrhage. *J. Obstet. Gynaec. Brit. Emp.*, **36**, 1-69.
- Stewart, M. J. (1912). Two cases of tuberculosis of the uterus. *Glasg. med. J.*, **77**, 255-260.
- Tait, L. (1892). On the occurrence of pleural effusion in association with disease of the abdomen. *Med.-chir. Trans.*, **75**, 109-118.
- Taylor, C. W. (1958). Mesodermal mixed tumours of the female genital tract. *J. Obstet. Gynaec. Brit. Emp.*, **65**, 177-188.
- Taylor, C. W. (1965). Lawson Tait—a grateful pupil of James Young Simpsom. *J. Obstet. Gynaec. Brit. Cwlth.*, **72**, 165-171.
- Teacher, J. H. (1903). On chorionepithelioma and the occurrence of chorionepitheliomatous and hydatidiform mole-like structures in teratomata: a pathological and clinical study. *J. Obstet. Gynaec. Brit. Emp.*, **4**, 1-64.
- Teacher, J. H. (1935). *A Manual of Obstetrical and Gynaecological Pathology*, edited by A. J. Marshall. Oxford University Press, London.
- Traut, H. F. (1946). In discussion to Novak. (1946 only), pp. 131-132.
- Virchow, R. (1856). *Gesammelte Abhandlungen zur wissenschaftlichen Medicin*. Meidinger, Frankfurt.
- Whitehouse, H. B. (1911). Primary carcinoma of the female urethra. *J. Obstet. Gynaec. Brit. Emp.*, **20**, 269-276.
- Whitehouse, H. B. (1914). The physiology and pathology of uterine haemorrhage. *Lancet*, **1**, 877-885 and 951-957.
- Wide, L., and Gemzell, C. A. (1960). An immunological pregnancy test. *Acta endocr. (Kbh.)*, **35**, 261-267.
- Wilde, C. E., Orr, A. H., and Bagshawe, K. D. (1965) A radioimmunoassay for human chorionic gonadotrophin. *Nature (Lond.)*, **205**, 191-192.
- Willis, R. A. (1960). *Pathology of Tumours*, 3rd ed. Butterworth, London.