History of cytodiagnosis

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The place, Oxford; the time, around 1845-50. Henry Acland lectured on medicine in a room furnished with ‘little railroads on which ran microscopes charged with illustrations of the lecture, alternately with trays of coffee’. ‘Dr Ogle, applying his eye to the microscope, screwed a quarter-inch right through the object; and Dr Kidd, after examining some delicate morphological preparation, while his young colleague explained its meaning, made answer first, that he did not believe in it, and secondly, that if it were true he did not think God meant us to know it’ (Tuckwell, 1907). However apocryphal the story, the setting is authentic. Microscopy in the service of medicine had been long delayed, but within the following 20 years most of the diseases then known had been classified in terms of their histological features.

The father of medical microscopy was the physiologist Johannes Müller. Under his influence Virchow became its greatest exponent. In the first volume of Virchows Archiv (1847), which also contains one of the earliest descriptions of chronic granulocytic leukaemia, he published an extremely long article on the nature of cancer illustrated with two plates full of drawings of tumour tissue and cancer cells. In those days microscopists studying soft tissues had to tease out or spread the material in order to show the component cells. By the seventies medical students knew that the ‘tissues’ are not primarily tissues at all, in the original sense of fabrics made of woven fibres, but rather colonies of cells which may live in a fibrous framework; Virchow’s contention was also accepted, that cells originate only from pre-existing cells.

Malignant cells from solid tumours were described and illustrated by a number of other mid-19th-century authors; Müller himself published some, but he was more concerned to demonstrate that tumours contain cells at all than to show any difference between benign and malignant ones (Müller, 1840). Illustrations can be found in the works of Donné (1844), Lebert (1851), Donaldson (1853), and Beale (1854). Figure 1 shows a small part of one of the plates in Lebert’s (1857-61) magnificent Atlas, representing the best quality of drawings made from unstained microscopic preparations. Most of the illustrations of that period, purporting to show that cancer cells are different from normal ones, could never really have been of much practical help, but this can be said equally of some of the half-tone photographs of cells which get printed in medical books and journals today.

The idea of tumour puncture was referred to by Lebert (1851) but it did not develop as a diagnostic method at that time. He also performed measurements on the nuclei and nucleoli and noted the increased nucleo-cytoplasmic ratio in many cancer cells. Measurements of this type were not repeated for many years and are only now having a renewed importance in connection with attempts at automation of cytodiagnosis.

A major technical advance was the use of stains to display the details of nucleus and cytoplasm (see Castiglioni, 1947; Bamforth and Osborn, 1958). Paul Ehrlich used stained air-dried films to identify the cells not only of blood but also of serous effusions. He described (Ehrlich, 1882) the features of adenocarcinoma cells in three pleural effusions, two due to carcinoma of the ovary and one to carcinoma of the breast, but unfortunately provided no illustrations and did not develop this theme any further.

In spite of the introduction of staining methods, unstained wet preparations have continued to be used right up to our own time, especially for the routine examination of urine. Also certain advances in the identification of malignant cells were made without stains, even in the 20th century—for instance, Mariní’s (1909) remarkable study of gastric washings. Some workers preferred supravital methods or stains applied to cells in suspension, as in Quensel’s (1928a, b) beautiful studies of the cytology of serous fluids.

Microscopists have used thin slices ever since the time of Leeuwenhoek, but the staining of sections constituted the breakthrough for histology as we
know it. It is obvious that a pathologist who never used stained sections but relied on smears and imprints would lose the greater part of his essential visual data. But the converse is also true, that by examining sections only, and not seeing the cells displayed to full advantage, histopathologists lose information which would improve diagnostic precision. The simultaneous use of both types of preparation unfortunately became difficult as soon as the histopathologist began to receive material fixed at the time of collection, since what was necessary for good sections was ruinous for cell preparations. From the introduction of paraffin embedding in about 1880, cytological methods were gradually abandoned for all solid tissues and finally retained only in the domains of haematology, parasitology, and bacteriology. Even so, textbooks of pathology continued almost up to the end of the 19th century to print line drawings showing cells teased or scraped from solid tissues (including tumours); they were copied, for instance, from Billroth's 'Lectures on Surgical Pathology and Therapeutics', which went into many editions from 1863 onwards.

Until the 1930s, the occasional medical micros-
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copist reported his experiences with the examination of serous fluid, sputum, urine, and so on, but these studies did not serve as bridgeheads from which advances were subsequently made; it seems that each discovery was forgotten and never added to the corpus of knowledge handed down to successive generations of pathologists. Probably, as a result of many (unpublished) false positive diagnoses made by inexperienced pathologists using inadequate cytological methods, the tradition handed down was one of scepticism. In the words of Roodhouse Gloyne (1919), speaking of malignant cells, 'it is practically impossible to identify these cells, in film preparations'.

Vaginal and cervical smears

The cytology of vaginal secretion was described by Donné (1844) and Pouchet (1847), but not in connection with the diagnosis of cancer. Pouchet's monograph is remarkable in that it describes the findings at different stages of the human menstrual cycle. In clinically suspected cervical carcinoma, cytological examination was recommended by Richardson (1871) in the United States, who wrote: 'In suspected cancer of the womb...a small portion of the secretion from the os uteri, or from the ulcerated surface of the growth itself, should such exist, must therefore be removed by means of a probe or pair of forceps introduced through a speculum, and on examination with a power of 200 diameters will probably disclose at least a few cells on each slide, which will indicate with more or less certainty the character of the morbid formation.' Friedlaender (1886) also used this method but warned against diagnosing carcinoma from the cytology alone; he recommended also a histological examination of a little piece of excised tissue, a procedure which about 10 years later became known as 'biopsy'.

The vaginal smear was first systematically used by Papanicolaou and has rightly become known by his name. Recently his biography has been written by Carmichael (1973). George N. Papanicolaou qualified in medicine in Athens in 1904. He then specialised in zoology, especially the experimental study of reproduction. In 1913 he emigrated to New York, and from then onwards for many years he studied the oestrous cycle in animals and the menstrual cycle in the human female as revealed by vaginal smear.

In the course of studies on patients in the Women's Hospital, New York, Papanicolaou saw malignant cells in vaginal smears, and in 1928 he gave his first paper on this subject at a conference, entitling it 'New cancer diagnosis'. Figure 2 shows one of his photographs with the accompanying text. He thought that the mononuclears reacted to the cancerous toxins in such a way as to make them cytologically recognisable so that the diagnosis could be made without finding actual cancer cells. There were no case-histories or statistics nor any cytohistological correlation. Moreover, the paper as published was badly marred by errors of transcription which were not corrected in proof; this, coupled with the prevailing climate of opinion, prevented any widespread interest from being aroused at that time.

Simultaneously and independently, cancer cells were recognised in cervical smears by Aurel Babeş of Bucharest. Babeş was a pathologist, who collaborated with his uncle Victor Babeş in writing a four-volume textbook of pathological anatomy, and who also published research on the pathogenesis of pellagra and of typhus and other infectious diseases, and later on endocrinology and cancer research, altogether publishing 283 scientific papers. In 1927, with C. Daniel, he presented to the Bucharest Gynaecological Society (Fig. 3) a new method for the diagnosis of carcinoma of the cervix, using a platinum loop to transfer material from the affected area to the slides. They were then air-dried and stained with Giemsa.

The results were published, with clear and informative drawings, in the Presse Médicale of 11 April 1928, and cervical smears continued to be used in the gynaecological clinics of Professor Daniel from that time onwards. (A translation of the 1928 article has been published with the illustrations (Douglass, 1967.).

In an article on carcinoma in situ of the cervix uteri in 1931, Babeş said that the smear method had been used on a large scale by Kermauener and Schiller; however, it does not appear to have taken root, and Babeş's contribution was practically forgotten. Before he died in 1962 he was given credit in Europe (Zinser, 1957; Boddington et al., 1960), and J. E. Ayre referred to him in the atlas Cancer Cytology of the Uterus (1952), though he made him come from Budapest instead of Bucharest; but his work was probably unknown to Papanicolaou, who died in the same year, and Babeş modestly refrained from ever raising the question of priority.

Returning to New York between the wars, we find Papanicolaou patiently studying endocrinological problems until the appointment of Joseph Hinsey to

1 For reproductions of his drawings, see Bamforth and Osborn (1958).
the Department of Anatomy at Cornell. With Hinsey's support, Papanicolaou returned to the question of cancer diagnosis and in 1941, with Herbert Traut, he published 'The diagnostic value of vaginal smears in carcinoma of the uterus'. This was followed in 1943 by the monograph, *Diagnosis of Uterine Cancer by the Vaginal Smear*, beautifully illustrated with coloured drawings by Murayama. This time medical opinion was less antagonistic. In particular, many gynaecologists became enthusiastic about the possibility, mentioned by Papanicolaou, of identifying cancer of the cervix at an early and curable stage. Very soon, with an increased awareness of the possibility that very early or even precancerous stages of the disease are histologically recognisable.
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Societatea de Gynecologie

Președinte Prof. C. DANIEL

Ședința din 23 Ianuarie 1927

1

Posibilitatea diagnosticului cancerului uterin cu ajutorul frotiului

de Prof. C. Daniel și A. Babeș

Având în vedere dificultățile în unele cazuri de a practica o biopsie în cazuri suspecte de cancer uterin este de dorit a se putea în aceste cazuri să se stabilească diagnosticul anatomo patologic prin alte metode.

În acest scop s-a încercat în un număr de 10 cazuri în parte cu leziuni cancer, în parte fără cancer, a se stabili diagnosticul pe baza unor frotiuri de la nivelul leziunilor. Acest nou procedeu cu rezultatele care le-a dat până în prezent, promite cu adevăr a deveni un procedeu de utilitate practică.

Acest procedeu e b țat pe prezentă în frotiurile făcute în cazurile de cancer a unei atiști celulare, precum și a prezentă de placarde epiteliale mai mari, pe lângă atiști celulare. Se poate constata o mai mare variabilitate în caracterul celulelor epiteliale.

Aceste caractere lipsind în afară de cazurile fără leziuni canceroase, credem că vor putea servi la diferențierea acestor 2 fe luri de leziuni.

and can be found by the ‘Pap smear’, clinicians (and interested laymen too) began to demand that these tests should become available. This meant training programmes, and the unassuming Dr Papanicolaou found himself in 1947 running a course in cytological diagnosis with an initial intake of 70. He also continued investigating the identification of cancer cells in many other sites, particularly in urine, sputum, gastric washings, and breast secretions. Every application was quickly taken up and confirmed by other cytodiagnosticians, who became known as ‘exfoliative cytologists’. Although Papanicolaou’s counterstains were devised to show the stages of maturation of squamous epithelial cells, the same method was applied to every other material. Where a body of expertise existed already, using some other technique (for instance, the haematological practice of air-drying before fixation and staining with Romanowsky dyes), an uncomfortable conflict developed and continues to this day.

By 1954 Papanicolaou had produced his comprehensive Atlas of Exfoliative Cytology. His activity continued undiminished until his death in 1962 at the age of 78 years.

During the fifties there was a deluge of literature on this subject. Almost everyone who used Papanicolaou’s methods apparently felt the need to publish. Suddenly there appeared a new body of literature with a new jargon and concepts which at first were unsupported by properly controlled observations. To many pathologists these concepts seemed unacceptable at the time, though they have become more respectable now. In particular, many pathologists distrusted the evangelism with which converts to the new discipline sought to press on with the conquest of uterine cancer. These facts of history serve to explain why clinical cytology was only slowly accepted as part of the normal training of a pathologist, though Shields Warren wrote in the preface to Gates and Warren’s illustrated Handbook (1947): ‘It is on the practising pathologist that the onus of this task will fall.’

The emergence of a body of trained exfoliative cytologists made possible the rapid development of population screening, first by the vaginal smear and soon after by the cervical scraping introduced by Ayre (1947, 1952). In the event this timetable proved to be a misfortune, because population screening
became an accepted practice before the general introduction of randomised controlled trials. A proper trial could have given a clear indication of the extent of benefit to be expected from defined screening strategies, and services could have been rationally planned instead of becoming a football between Public Health authorities, epidemiologists, lay pressure groups, politicians, and clinical cytologists. There are very strong reasons for supposing that cervical cancer can, in principle, be prevented by this means (Spriggs, 1972), but the application of it to most of the women at highest risk is still only a hope for the future.

Cytodiagnosis from sputum

During the second half of the 19th century there were many medical microscopists who studied the cells of sputum, but their concern was generally with tuberculosis rather than with malignant disease (for references, see Finlayson (1958)). Leaving aside various early records of actual expectorated fragments of carcinoma, the first mention of cancer cells in sputum is a remark in Walsh's *A Practical Treatise on the Diseases of the Lungs* (1860), in which he says that they have 'been occasionally found microscopically'. The first illustration is usually attributed to Beale (1861), though the primary was in the pharynx and the 'sputum' was obtained *post mortem* by Mr Newham (who had permission to examine only the throat but 'ventured as far as the chest'). A number of other early reports can be found, with illustrations, in the review by Grunze (1960). Systematic examination of sputum for the diagnosis of carcinoma of the lung was undertaken by Hampeln of Riga; his first case report appeared in 1887 and his final series in 1918-19, with 13 out of 25 cases correctly diagnosed by microscopy of the sputum.

It must be remembered that, in those days, carcinoma of the lung was quite uncommon. Indeed, it was possible to write a whole book about the microscopy of sputum in 1886 without mentioning cancer of the lung (Mackenzie, 1886).

Hampeln's work was not taken up systematically by others at the time, and the fact that malignant cells can be reliably identified in sputum had to be rediscovered by Leonard Dudgeon and his colleagues at St Thomas's Hospital, London.

Along with extensive studies on the cytology of scrapings from surgical specimens, of which a series of over 1000 were reported in 1934 (Dudgeon and Barrett, 1934), Dudgeon made a careful investigation of the possibility of identifying malignant cells in sputum, using smears wet-fixed with Schaudinn's solution and stained with haemalum and eosin. He had originally developed this method for studying the cytology of human milk (Dudgeon and Jewesbury, 1924). He did not rush into print and, by the time his one paper on the subject appeared (Dudgeon and Wrigley, 1935), he was already expert in making the diagnosis from sputum by this means. This series (which, unlike many much later studies, presented the data in tables) contained 38 cases of lung cancer. Of these, 26 were found to have malignant cells in the sputum, and there was one false positive. The rate of correct detection, 68%, is about the same as that almost universally obtained today. Figure 4 shows one of Dudgeon and Wrigley's drawings illustrating oat-cells in sputum. It was accompanied by the first description of this distinctive cell type in smears. Dudgeon's method was in continuous use at St Thomas's from then onwards. Dudgeon's papers presented his data with a clarity and simplicity which has not always been imitated by his successors. He died in 1938 without having trained a sufficiently large nucleus of disciples in England to create a 'snowball' of pathologists able to apply his methods.

Wandall in Copenhagen pursued the subject, using a similar wet-fixation method, and in 1944 published a series of 100 cases of primary lung carcinoma, 84 of which were correctly diagnosed from the sputum, and in most of which it was possible to state the histological type. His published photomicrographs were good enough to be useful for teaching, unlike most of what had gone before.

Following the cytology explosion in America, resulting from the work of Papanicolaou, the cytological diagnosis of carcinoma of the lung from sputum and bronchial aspirates became a universally applied diagnostic test and, in practised hands, one of the most reliable.

Miscellaneous applications of cytodiagnosis

The examination of urine is as old as medicine, and the microscope added a new dimension to 'uroscopy'. In the various 19th century books on the subject of the urine, many drawings can be found showing different cell types encountered. In 1854, Beale, who for many years was the English protagonist of medical microscopy, illustrated cells from different parts of the urinary tract (Fig. 5). Malignant cells from carcinoma of the bladder were probably first described and illustrated by Lamb (1856) and soon after by Neubauer and Vogel (1863), though emphasis was placed on papillary fragments more than on isolated cells. This application of cytodiagnosis was considered easy, but it was admitted

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1 Some coloured photographs from Dudgeon's slides can be found in the historical note by Bamforth (1963).
that cells from carcinoma of the kidney were much harder to find, as we still agree today. Beale (1878) illustrated cells resembling those of carcinoma found in the urine of a young girl with nephritis and put in some salutary words of caution; this was a most unusual thing to do in a period when any mention of doubts and mistakes was generally avoided in medical writing.

Apart from Quensel's (1918) observations using a new supravital staining technique, there were few advances in the cytology of urine until our own time, even though the microscopy of urine sediments has for long been 'routine'. Bamforth and Osborn (1958) described how the great pathologist James Ewing correctly identified malignant cells in his own urine, coming from a carcinoma of the bladder. This was just before the introduction of Papanicolaou's methods (Papanicolaou and Marshall, 1945). Even the next 30 years have not solved the formidable problem of exact cell identification in this particularly difficult material.

Serous fluids were the subject of numerous scattered observations in the 19th century from the late sixties onwards. Ehrlich's (1882) contribution has already been mentioned. Published drawings of the period tend to be non-informative, but an example of clearly recognisable adenocarcinoma cells can be seen in Spencer Wells's (1882) textbook on gynaecological tumours. Nobody had the idea of presenting the figures showing what proportion of malignant effusions could be correctly diagnosed by cytology, or how many such diagnoses were mistaken.

The first systematic study of the cells of effusions...
THE MICROSCOPE.

298. Epithelium of the Genito-urinary Passages.—The forms of epithelium which may occur in urine are very numerous, as the characters of the cells differ very much in different parts of the genito-urinary mucous membrane.

Fig. 158. 

- Figures 158, 159, 160, 161, a, 162, were taken from specimens of epithelium carefully removed from the mucous membrane of the urinary passages of a male subject.

- Fig. 161 a, c, from specimens found in urine.

Kidney.—Consolidated portion of the tubes.—The epithelium is of the variety termed glandular, or secretory epithelium, and forms a thick layer upon the basement membrane (fig. 158).

Fig. 159. 

- Fig. 159, b, is a portion of a urinary epithelial cell from a female subject.

- Fig. 160, c, is a projection of an epithelial cell, which is much flattened, and which is found near the base of the tubes.

- Fig. 161. 

- Fig. 161 a, c, from specimens found in urine.

- Fig. 158, 159, 160, 161, a, 162, were taken from specimens of epithelium carefully removed from the mucous membrane of the urinary passages of a male subject.

- Fig. 161 a, c, from specimens found in urine.

Peluic of the Kidney.—The epithelium consists of flat, thin scales, which are united together at the edges without overlapping each other. This is termed tessellated epithelium (fig. 159).

Fig. 159. 

- Fig. 159, b, is a portion of a urinary epithelial cell from a female subject.

- Fig. 160, c, is a projection of an epithelial cell, which is much flattened, and which is found near the base of the tubes.

- Fig. 161. 

- Fig. 161 a, c, from specimens found in urine.

- Fig. 158, 159, 160, 161, a, 162, were taken from specimens of epithelium carefully removed from the mucous membrane of the urinary passages of a male subject.

- Fig. 161 a, c, from specimens found in urine.

Ureter.—The epithelium is very abundant, and of the columnar or cylindrical form. The nucleus is usually large and distinct (fig. 160).

Fig. 160. 

- Fig. 160, c, is a projection of an epithelial cell, which is much flattened, and which is found near the base of the tubes.

- Fig. 161. 

- Fig. 161 a, c, from specimens found in urine.

- Fig. 158, 159, 160, 161, a, 162, were taken from specimens of epithelium carefully removed from the mucous membrane of the urinary passages of a male subject.

- Fig. 161 a, c, from specimens found in urine.

Bladder.—The epithelium of the bladder differs much in different parts. In the fundus there is much columnar epithelium mixed with the large oval cells figured in 161; whereas, in that part termed the trigone, the large flattened cells, with a very distinct nucleus and nucleolus are most abundant. The columnar epithelium appears to line the mucous follicles, while the scaly lies on the surface of the mucous membrane between them. In fig. 161 the columnar variety is shown at b.

Fig. 161. 

- Fig. 161 a, c, from specimens found in urine.

- Fig. 158, 159, 160, 161, a, 162, were taken from specimens of epithelium carefully removed from the mucous membrane of the urinary passages of a male subject.

- Fig. 161 a, c, from specimens found in urine.

Urethra.—The epithelial cells of the urethra (fig. 162) are, for the most part, large and oval, and are best seen in the penile portion of the organ (fig. 163). The urethral cells and the cells of the prostate are not very different from one another.

Fig. 162. 

- Fig. 162, a, c, from specimens found in urine.

- Fig. 158, 159, 160, 161, a, 162, were taken from specimens of epithelium carefully removed from the mucous membrane of the urinary passages of a male subject.

- Fig. 161 a, c, from specimens found in urine.

The microscopic examination of urine is an important department of medical inspection. The microscopic examination of urine is an important department of medical inspection.
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Fig. 67. Photographs of ovarian carcinoma cells in pleural fluid, from Quensel (1928b). The cells are stained with methylene-blue-Cd + Sudan-Cd and examined in suspension.

Fig. 68. Quensel: Ergüsse der Brust- und Bauchhöhlen.

Arinkin (1929). Cytological study by lymph-node puncture has been in use rather longer (Guthrie, 1921). The main development of these methods was during and after the 1939-45 war.

Puncture cytology of the lung and liver has been used on a much smaller scale (for literature, see Lüdin (1955)), and fine-needle puncture of tumours, with diagnosis from smears rather than sections, has only recently and locally become popular, but its use is increasing, especially for the breast and prostate (Zajicek, 1974).

These methods are the logical development from earlier studies of smears made from open biopsies, such as those of Dudgeon (Dudgeon and Patrick, 1927; Dudgeon and Barrett, 1934). The most consistent use of the latter method has been made by the neurosurgeons, and in Britain this application has been routine for over 30 years (Russell et al., 1937).
Note on the word ‘cytology’

Librarians and booksellers are apt to be confused because the word ‘cytology’ has taken on two different meanings. The general study of cell biology has been called ‘cytology’ for at least 85 years and the word is still used in that sense; examples are the periodical *International Review of Cytology*, of Bourne and Danielli, and *A History of Cytology* by Arthur Hughes. Darlington’s *Recent Advances in Cytology* (1st edition, 1932) had a more restricted subject, that of the chromosomes, particularly those of plants! With the widespread development of cytodiagnostic laboratories in hospitals, the name ‘cytology’ has been generally adopted for that specialty. (The adjective ‘exfoliative’ was dropped because in many cases the cells examined have not been exfoliated.) Accordingly, we have *Acta Cytologica* as the principal journal of the specialty, begun as the official journal of the International Academy of Gynaecological Cytology (1958), which has since changed its name to the International Academy of Cytology.

Now that the word has become ambiguous, the best that can be done is to qualify it or use another. The study of chromosomes has become ‘cytogenetics’, while the expression ‘cell biology’ has been adopted by the scientists who previously called themselves ‘cytologists’. Medical cytodiagnosticians should speak of ‘cytopathology’, ‘clinical cytology’, ‘diagnostic cytology’, or ‘cytodiagnosis’.

Books and articles on which I have drawn particularly heavily are Bamforth and Osborn (1958), Hughes (1959), Grunze (1960), and Carmichael (1973). I am indebted to the late Dr Lucia-Maria Babes for the information concerning her husband. I am also very grateful to Dr A. H. T. Robb-Smith, the use of whose library was indispensable, and this article is dedicated to him on his retirement.

References


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The November 1977 Issue

THE NOVEMBER 1977 ISSUE CONTAINS THE FOLLOWING PAPERS


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Human papovavirus in Papanicolaou smears of urinary sediment detected by transmission electron microscopy D. V. COLEMAN, W. J. I. RUSSELL, J. HODGSON, TUN PE, AND J. F. MOWBRAY

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Serum protein changes in breast cancer: a prospective study K. W. PETTINGALE AND D. E. H. TEE

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A new histochemical technique of use in the interpretation and diagnosis of adenocarcinoma and villous lesions in the large intestine C. F. A. CULLING, P. E. REID, ANN J. WORTH, AND W. L. DUNN

Histochemical comparison of the epithelial mucins in the ileum in Crohn’s disease and in normal controls C. F. A. CULLING, P. E. REID, W. L. DUNN, AND M. G. CLAY

Technique for microdissection and measurement in biopsies of human small intestine ANNE FERGUSON, A. SUTHERLAND, T. T. MACDONALD, AND FRANCES ALLAN

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