THE VICISSITUDES OF SPUTUM CYTOLOGY

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'THE state of the secretions whether by the bladder, the intestines, or the skin, or by any other passage, when unnatural, ought to be examined; if they be little changed, the disease is slight; if much, it is considerable; but if entirely altered, the disease will be fatal' (*The Aphorisms of Hippocrates*, trans. Coar, 1822, p. 231). Although secretions from the lungs are not specifically mentioned in this aphorism, there is evidence both in *The Prognostics* and *The Aphorisms* that Hippocrates frequently examined and tested sputum from cases of pulmonary disease, and that he considered that such studies could be of prognostic significance. *The Aphorisms* tell us that 'dark, bloody, fetid and bilious expectorations are unfavourable appearances in continued fever; but if easily expelled they are favourable'; that 'expectoration of pus after spitting of blood is a bad omen' (Coar, 1822, pp. 93 and 195), and that 'in persons affected with phthisis, if the sputa which they cough up have a heavy smell when poured upon coals, and if the hairs of the head fall off, the case will prove fatal' (*The Genuine Works of Hippocrates*, trans. Adams, 1849, II, 739), or in the more pungent translation by Coar (1822, p. 119): 'If the fluid expectorated by the phthisical yield, when exposed to heat, a fetid odour, and the hairs fall off, death is denoted.'

The best known of the sputum tests usually ascribed to Hippocrates, but probably of earlier origin, is that taken from the *Coacae Praenotiones*, which states that if expectorated matter sinks in sea-water, the disease will shortly be fatal. Celsus confirmed that if tuberculous sputum was thrown upon the fire there was a bad smell and 'those who are in doubt as to the disease employ this as a test', but Aretaeus, whose descriptions of disease, according to Adams (1856, p. xii), have been universally admitted to be unsurpassed for elegance and accuracy, did not agree that the Hippocratic sputum tests, either with fire or water, were of diagnostic or prognostic value. Nevertheless, these tests were still performed by some physicians in relatively recent times. Adams (1849) cites a report by the seventeenth-century physician Heurnius, who found the heat test for phthisis of value, and the nineteenth-century physician and physicist Thomas Young (1815) considered that the Mediterranean sea-water used by Hippocrates was better than 'common water' for distinguishing pus from mucus, but that 'the additional precaution of employing a vessel of copper, which is defended by a friend of Morgagni, can only have been dictated by some fanciful theory or founded on some inaccurate observation'. Although somewhat of an anachronism in an historical review, it is of interest to note that the flotation test was still being used when a twentieth-century American chest physician was a medical student (Webb, 1936).

Christopher Bennet, who was awarded a Doctorate of Medicine at Cambridge University in 1644, stressed the importance of sputum examination. In his *Theatrum tabidorum*, published posthumously in 1656 and anonymously translated into English in 1720, he castigated those physicians 'although in other respects the most sagacious, who slightly examined the Nature of what is expectorated'. He described the various kinds of sputa in considerable detail: 'the white and frothy', 'of what is a yellow colour', 'blackish, bluish or rust coloured', 'of a dirty ash-coloured and purulent spittle', 'of a salt spittle' and 'the sweetish spittle', the latter being commonly expectorated by consumptives. There is no reference to microscopy in Bennet's detailed work, but this is hardly surprising since the bilenticular microscope had only been invented at the end of the sixteenth century in Holland, and independently constructed by Galileo in Italy in the first decade of the seventeenth century (Singer, 1914).

According to Dobell (1932) the first 'micrography' was *The Century of Microscopic Observations* by Pierre Borel, published in Latin at The Hague in 1656: soon followed by the similar work of Henry Power (1663–4) and the more celebrated *Micrographia* of Robert Hooke (1665), both written in English and published in London. No reference was made to microscopic study of sputum or saliva in either of the two later works, and the first observations were probably those of Leeuwenhoeck reported in the *Philosophical Transactions* in 1674. In a paper entitled 'Microscopic Observations Concerning Blood, Milk, Bones, Brain, Spitle and Cuticula', Leeuwenhoeck (1674) recorded that he had found in the fluid matter of fasting spittle very many small globules, and looking upon the spittle in the afternoon globules and odd corpuscles in great number. Although the descriptions were brief and unillustrated, there is little doubt that Leeuwenhoeck had observed squamous epithelial cells, macrophages and possibly leucocytes in his preparations.

One hundred and thirty-five years elapsed before the Royal Society published, in 1809, another paper containing some observations on the microscopic appearances of expectorated matter. Somewhat earlier Home (1788) had shown by microscopy that pus consisted of white globules and a transparent colourless fluid, but it was left to Pearson (1809) first to record that puriform expectorated matter contained thousands of globules similar to the indestructible globules seen in blood. Pearson's report was concerned largely with the physical and chemical properties of the various macroscopic types of expectorate, but mention was made of the paucity of spherical microscopic particles in jelly-like transparent sputum and of numerous spherical particles, not unlike those seen in blood but larger, in the opaque ropy forms of expectorate. The indestructibility of these globules, except by such agents as destroy charcoal, was stressed by Pearson, who concluded that the particles consisted mainly of organized carbonaceous matter. In a later dissertation Pearson (1813) conclusively demonstrated that the black pigment in the lungs and bronchial glands was derived from inhaled charcoal, but unfortunately no further reference was made to microscopic studies of the sputum globules.

Although remarkable progress was made during the first quarter of the

nineteenth century in medical diagnosis and in the correlation between clinical and morbid anatomical findings in pulmonary disorders, it was not until the revolutionary concept of the cellular nature of all animal tissues enunciated by Schleiden and Schwann and the application of this theory to pathology by Virchow had been established, that the value of microscopy in the study of disease became apparent.

Early reports on the microscopic appearances of sputum included those by Henle (1838a, 1838b), Vogel (1838) and Gruby (1840), and culminated in the first monograph on sputum examination, *Die Lehre vom Auswurf* by Biermer, published in 1855. Detailed descriptions were given in this work of the various types of cells that might be seen in sputum: epithelial cells, including small, round alveolar epithelial cells, larger cylinder cells from glandular epithelium and numerous, very large pavement epithelial elements; blood corpuscles, pus cells and pigment epithelial cells found in tuberculous and catarrhal sputum. Golden-yellow pigment cells were described in pneumonic sputum and giant cells, with five to twelve nuclei, were seen in some tuberculous specimens.

The number of monographs devoted to sputum examination is small. Biermer's work was followed by two British books on sputum, both published in Edinburgh in 1886; one by Troup (1886) entitled *Sputum: Its Microscopy and Diagnostic and Prognostic Significations*, and the other by Mackenzie (1886) with the title *A Practical Treatise on the Sputum*. Next came the extensive *Traité de l'examen des Crachats* by Bezançon and de Jong, published in Paris in 1912, followed a few years later by the even more comprehensive monograph *Das Sputum* by von Hoesslin, first published in 1921 and re-edited in 1926. A short work, claimed by the author to be the only monograph on sputum in the English language, entitled *The Sputum. Its Examination and Clinical Significance* written by Clifford was published in New York in 1932. It is admittedly the last monograph on this subject, if one excludes the more specialized works of Farber *et al.* (1950) on *The Cytologic Diagnosis of Lung Cancer*, and of Hartmann (1955) on *Die Cytologie des Bronchialsekretes*.

Francis Troup (1886), who commented that the bronchial secretions of persons in good health very seldom have any residuum to be expectorated, defined sputum as 'All the stuff which coughing and hawking mechanically eject from the respiratory passages'. The formed elements in sputum, including epithelial cells, mucus, pus and blood corpuscles, were described in some detail. Normal squamous epithelial cells derived from the respiratory and upper digestive tract were said to be a constant constituent of sputum, while epithelium from the lung alveoli was frequently seen, and cylindrical cells, with or without cilia, seldom seen, but more commonly than was generally supposed. Troup commented that some of the ciliated cells may have originated from nasal epithelium, and that the alveolar epithelial cells of adults were almost always more or less replete with black pigment, and in brown induration of the lung, consecutive to cardiac mischief, the same cells were saturated with a golden-brown or yellow pigment, derived from imbibition of altered blood. The variation in size and shape of alveolar cells, ranging from flattened cells to large,

spherical forms, pigmented more or less deeply, and showing in some instances fatty and myelin degenerative changes, were also noted. Early in his studies Troup considered that some forms of alveolar epithelial cells were indicative of phthisis, but further experience modified his views and he concluded that although such cells were abundant in phthisis they were common enough in many other respiratory affections. Little reference was made to the presence of tumour cells in sputum, except for the statement that patients with malignant disease of the tongue, tonsils, fauces and larynx often expectorate certain morsels of exfoliated tissues in which the cell formations distinctive of their disease can frequently be detected, and a lithograph of what appears to be a fragment of a laryngeal papilloma recovered from sputum is shown. The monograph included a chapter on elastic tissue, with especial reference to its value in the diagnosis of pulmonary tuberculosis, which Troup held 'was much underestimated in the present day (1886) when the tubercle bacillus, like Aaron's rod, swallows up everything else'.

Mackenzie (1886) laid more emphasis on the characteristics of sputum in the various pulmonary diseases, and in his preface stated that his work did not affect to be of the nature of an exhaustive microscopical and chemical analysis of all the constituents of sputum. The sputum preparations were examined mainly as unstained, wet films, although picrocarmine or logwood was used in the study of neoplastic fragments expectorated by some patients with epithelioma of the larynx and pharynx. The various types of epithelial cells (pavement, columnar, pulmonary alveolar and ciliated), together with pus and blood cells, mucous corpuscles and fat cells were listed, but Mackenzie considered that none of those cells was of special diagnostic significance, except that an abundance of pulmonary alveolar epithelium indicated alveolar catarrh and a probable tendency to phthisis. Tuberculous sputum showed no pathognomonic macroscopic or cytological features; and elastic fibres, though almost universally met with in phthisis, were not diagnostic since they indicated little more than pharyngeal or laryngeal ulceration from various causes. Mackenzie described in detail the macroscopic and microscopic appearances of the sputum in catarrh; in bronchitis, in which the sputum was mucoid, mucopurulent, or purulent according to the intensity, extent and duration of the disease; in bronchiectasis and putrid bronchitis in which the sputum had a characteristic foetid odour; in lung abscess; catarrhal pneumonia; empyema; pulmonary congestion and oedema; asthma; croupous bronchitis and pneumonia. Mackenzie concluded that in these conditions the sputum showed no specific features, except for the characteristic macroscopic and microscopic changes that occurred in the sputum during the course of an attack of croupous pneumonia.

The early cytologists mainly used unstained wet films of sputum for microscopic examination, but with the application of some of the improved histological methods of fixation and staining of tissues to sputum cytology, previously unrecognized cells such as eosinophils, mast cells and plasma cells were identified in some sputum specimens. The occasional presence of mast cells in sputum, recorded by Schmidt (1892), Mandybur (1892) and Hildebrandt (1904), and

of the more frequent plasma cells has occasioned little interest. The presence of eosinophils in sputum was first recorded by Gollasch (1889), who credited Müller with having previously detected such cells in sputum from cases of asthma and bronchitis. Gabritschewsky (1891), Aronson (1892) and Mandybur (1892) noted an abundance of these cells in the sputa of asthmatics, and during the following decade exaggerated reports on the occurrence of such cells in sputa from a variety of pulmonary diseases were made. For instance, Teichmüller (1898) claimed to have found eosinophils in more or less large numbers in the majority of his cases of bronchitis, bronchopneumonia and pulmonary tuberculosis, and Carrière and Bourneville (1898a, 1898b) also mentioned that eosinophils were frequently found in tuberculous specimens. A detailed study of eosinophils in sputum was made by Bezançon and de Jong (1912). These authors criticized the results of several previous workers who, they stated, had confused other leucocytes with true eosinophils as a result of using unreliable staining procedures. Bezançon and de Jong recommended haematoxylin-eosin staining of smears fixed in either alcohol-ether or 1 per cent chromic acid. They stated that one never found eosinophils in appreciable numbers in tuberculous sputum and concluded that 'Ces vraies cellules eosinophiles se voient presque exclusivement dans les crachats des malades presentant des crises d'asthme'. Modern views on the significance of eosinophils in the sputum are expressed by Unger (1945), who states that eosinophilia in the sputum is strong evidence of allergic asthma, but small numbers may be found in other pulmonary conditions such as chronic bronchitis, tuberculosis, whooping-cough and carcinoma of the lung.

Following the discoveries of Koch, Fränkel, Friedländer, Pfeiffer and others in the last quarter of the nineteenth century, bacteriological examination of the sputum became all important and the cytological studies lapsed, except for a protracted discussion on the diagnostic significance of sputum eosinophilia. The residual emphasis on these cells is epitomized by the space given to them in the sections on sputum cytology in the monographs of Bezançon and de Jong (1912) and von Hoesslin (1921, 1926). Hoesslin's comprehensive work included detailed descriptions of the macroscopic and microscopic features of sputum together with its chemistry, bacteriology, protozoology and parasitology. Exhaustive details were given of the various types of cells that might be found in sputum. These were described and reviewed under nine main headings: red blood cells, white blood cells, epithelial cells, pigment cells, myelin cells, fat cells, giant cells, liver cells and tumour cells. The extensive bibliography given by Hoesslin is invaluable, but comparison of the first and second editions of his work clearly shows that few were interested in sputum cytology at that time, and it was with justification that Gloyne, in 1937, wrote that the cytology of sputum was a much neglected subject.

Macrophages, albeit under a variety of names, have been described by numerous observers. Since they are always found in sputum specimens their presence, as such, is of no diagnostic significance, but numerous attempts have been made to evaluate the importance of quantitative and qualitative changes

in these cells. For instance, Buhl (1873) considered that nuclear proliferation, cytoplasmic pigmentation and fatty myelin degeneration of 'epithelial cells' were characteristic of the sputum in pulmonary tuberculosis. Aufrecht (1873) held similar views, but these erroneous concepts were later refuted by Heitler (1877). An abundance of macrophages has been noted in various pulmonary disorders, including pulmonary tuberculosis, pneumonia, chronic pulmonary congestion and oedema, chronic bronchitis and emphysema, and in dust diseases such as silicosis and asbestosis (Clifford, 1932; Gloyne, 1937). A paucity of macrophages, except in those conditions associated with a grossly purulent sputum, has occasioned little comment, although Herbut and Clerf (1946a), in one of their earlier papers on the cytological studies of bronchoscopically removed secretions, have stated that macrophages are rare in what they termed 'cancerous flora', and that when such cells are abundant then cancer cells are not found. Wihman and Bergström (1952), on the other hand, comment that groups of macrophages, lying close together, are a very common finding in cases of lung cancer. The limited diagnostic significance of finding haemosiderin-laden phagocytes in sputum has been appreciated for many years despite the persistence of such richly descriptive terms as 'herzfehlercellen' and 'cellules cardiaques' or our own more mundane 'heart-failure cells'. Bezançon and de Jong (1912) emphasized that such cells might be found in a variety of pulmonary diseases and that they were indicative only of a reabsorption of an intra-alveolar extravasation of blood.

Cells containing fat and so-called myelin droplets, formerly regarded as degenerate forms of epithelial cells, are now mainly considered to be alveolar phagocytes (macrophages) and such terms as myelin cells and fat cells, as used by earlier sputum cytologists, have tended to become obsolete. Schuster (1943) and others have commented that fatty cells are often seen in the sputa from cases of resolving pneumonia and broncho-pneumonia and, according to some observers, in early pulmonary tuberculosis. However, in general, little attention has been paid in recent years to the significance of true lipoid and fat-laden phagocytes in the sputum, except by some American workers. Papanicolaou (1954) uses the term lipophages to describe histiocytes showing a 'characteristic bubble-like vacuolation' of the cytoplasm and states that such cells are diagnostic of lipoid pneumonia. Losner *et al.* (1950) also considered that the examination of sputum for characteristic vacuolated macrophages (lipophages), staining an orange-brown when treated with Sudan IV, is of diagnostic value in suspected cases of lipoid pneumonia. Such cells were found in the sputa of nineteen out of twenty patients in whom the clinical history, physical examination and X-ray findings were said to suggest a diagnosis of lipoid pneumonia, and in only two sputa from a 'control group' of forty-five patients. Since nineteen out of twenty of the lipoid pneumonia cases gave a history of having used oily droplets for nasal irrigation, either intermittently or continuously over a period ranging from two to thirty years, it would appear that the authors have used the term 'lipoid pneumonia' in its restricted sense (i.e. 'pneumonia secondary to inhalation of oily droplets'). It was not stated whether or not similar

lipoid-laden macrophages were found in those cases of so-called lipoid pneumonia in which there was no antecedent history of exuberant nasal irrigation.

Several observers have recorded the presence of epithelioid cells and Langhans-type giant cells in sputum and bronchial secretions from cases of pulmonary tuberculosis; but the incidence of Langhans-type giant cells in sputum would appear to be relatively low, and Gloyne (1937), in his classical paper on the cytology of sputum, stated that he had never seen these cells in sputum, and he suggested that the cells were probably broken up on the preparation of the smears. Pealtz and Probst (1953) have commented that whether or not epithelioid and Langhans-type giant cells are found in bronchial secretions depends on the type of the tuberculous lesion. The cells were absent in cases of so-called productive tuberculosis, but were found in twelve out of sixteen cases of exudative tuberculosis in which there was usually tuberculous cavitation and tuberculous bronchitis. The authors suggested that cytological studies might be of value in the diagnosis of pulmonary tuberculosis, but admitted that bacteriological examination is of greater importance. Herbut and Clerf (1946b) have also considered that a presumptive diagnosis of pulmonary tuberculosis can be made from the cytological examination of bronchial secretions.

A predominance of lymphocytic cells in the sputum has been noted in early pulmonary tuberculosis, and an apparent increase of the cells has also been recorded in such conditions as whooping-cough, chronic bronchitis and bronchiectasis (cf. Hoesslin, 1926). Gloyne (1937) commented that lymphocytes were not commonly seen in tuberculous sputum. Clifford (1932) considered that the presence of lymphocytes in the sputum was of no especial diagnostic significance, and the same opinion has been expressed more recently in the Russian literature by Khitrova-Goreva (1951). Lymphocytes, as seen in sputum or bronchial secretions, are briefly mentioned by Wandall (1944), Graham *et al.* (1950) and Farber *et al.* (1950). The cells, as seen in methylene blue stained wet films and haematoxylin-eosin stained smears of sputum, are described in greater detail by Philps (1954). Papanicolaou (1954) comments that large aggregations of lymphocytes are more frequently seen in cases of malignant neoplasms or of leukaemia than in non-malignant conditions, and though not pathognomonic, should not be ignored even in the absence of other indications of malignancy.

It is generally accepted that megakaryocytes may be found in the peripheral blood, and, on occasions, these cells can be identified in the lungs. Their presence in the sputum has, however, been only rarely recorded (Wandall, 1944; Hjelt, 1953). Liver cells originating from a hepatic abscess which has ruptured into the bronchial tree have also been identified in the sputum by a few observers (cf. Hoesslin, 1926; Gloyne, 1937). Other non-neoplastic cellular elements which may be found in 'sputum' specimens received for examination include a variety of animal and vegetable cells of extraneous origin. Striated muscle fibres and botanical curiosities are not infrequently seen, especially in

post-prandial expectorates or in sputa contaminated with vomitus. Recognition of these extraneous cellular elements is usually fairly easy, especially if one has had some experience in the microscopic examination of faeces, although plaques of vegetable cells in sputum smears may, in some instances, simulate groups of neoplastic cells. Rounded corpora amylacea, familiar enough in histological sections of pulmonary tissue, may also be found in sputum. Their non-cellular nature is usually apparent, but as Philps (1954) has recently commented, these bodies may be ingested by macrophages and unless sufficient attention be paid to detail the phagocytic cell with its apparently large, hyperchromatic 'nucleus' may be confused with a carcinoma cell.

The intense interest in the study of sputum for exfoliated tumour elements in suspected cases of lung cancer is of recent origin, though Walshe, in 1851, first recorded that in lung cancer encephaloid detritus, of cognizable physical characters, was in rare instances expectorated, and a similar observation was made by Lancereaux in 1858. Two years later Beale (1860) recorded finding tumour cells in the sputum from a case of advanced cancer of the pharynx, and in the same year Walshe (1860) briefly commented that cancer cells had been occasionally found in the sputa in lung cancer. Hampeln (1887) is commonly accredited with having made the first detailed report on the demonstration of microscopic fragments of growth in a case of primary lung cancer. In this case microscopic examination of unstained wet films revealed numerous large, atypical polymorphous epithelial cells. Hampeln concluded that such cells must have originated from a lung cancer, and his cytological diagnosis was subsequently confirmed at post-mortem. However, in the previous year, Ménétrier (1886) had recorded finding irregular epithelial cells resembling cancer cells in the sputum in a case of lung cancer in which the diagnosis was also later substantiated by histological examination of post-mortem material. The occurrence of macroscopic or microscopic tumour fragments in the sputum of cases of lung cancer was noted by a number of observers over the following forty years, but in most instances these were isolated reports and it was generally held that exfoliated malignant cells were morphologically indistinguishable from other cells and that only the presence of grossly visible particles, which on histological examination showed the structure of neoplastic tissue, justified a diagnosis of carcinoma. Betschart (1895), Hampeln (1897) and Claisse (1899), however, considered that some atypical polymorphic cells found in sputum were diagnostic of malignancy, and in a later communication Hampeln (1918–19) reported that he had examined the sputum in twenty-five out of seventy-five cases of pulmonary cancer and in thirteen of these had observed neoplastic cells.

Several subsequent workers, however, considered that the investigation was of little or no practical value. They contended that tumour cells were rarely identified in sputum because of cell autolysis, that distinction between tumour cells and other cells was difficult or impossible, and that the tumour cells only appeared in the sputum in cases of advanced cancer. The first systematic investigation on the cytological diagnosis of lung cancer by the examination of sputum for exfoliated neoplastic cells was made by Dudgeon and his colleagues

at St. Thomas's Hospital (Dudgeon and Wrigley, 1935; Dudgeon, 1936; Barrett, 1938; Bamforth, 1946). In two earlier papers Dudgeon and Patrick (1927) and Dudgeon and Barrett (1934) had reported a successful method for the rapid microscopic diagnosis of tumours removed at operation, which consisted of preparing smears from scrapings of the growth, fixing the smears while still wet in Schaudinn's fluid and staining with Mayer's haemalum and eosin. Later the technique was applied to the demonstration of tumour cells in sputum, and in 1935 Dudgeon and Wrigley reported finding malignant cells in the sputum of twenty-six out of thirty-eight cases of pulmonary cancer. Using essentially the same technique, Gowar (1943) found malignant cells in the sputum in thirty-six out of sixty-three cases of lung cancer, and Wandall (1944) in Denmark recorded 84 per cent positive results in one hundred histologically confirmed cases. A little earlier, several South American workers had commented on the value of the cytological examination of sputum in the diagnosis of lung cancer (cf. Palacio and Mazzei, 1940). Mosto and Polak (1937), for instance, detected tumour cells in the sputum in eleven out of sixteen cases of pulmonary cancer; and in Russia, Althausen (1939) using unstained wet preparations found cancer cells in the sputum in 70 per cent of 120 cases of bronchial carcinoma.

During the past decade a formidable literature has appeared on the cytological diagnosis of lung cancer and of other potential exfoliative tumours. The intense interest in this subject was triggered by the publication, in 1943 of the monograph on the *Diagnosis of Uterine Cancer by the Vaginal Smear* by Papanicolaou and Traut, and since 1946 at least one hundred articles have been written on the cytology of sputum and/or bronchial secretions in lung cancer alone. Considerable differences of opinion have been expressed on the value of examining the secretions for neoplastic cells, and the degree of esteem in which the investigation has been held has closely paralleled the success rate of the investigator. Although the cytodiagnosis of lung cancer by sputum examination is neither absolutely sensitive nor absolutely reliable, and the cytologist may be caught between the Scylla of a false negative and the Charybdis of a false positive, the results obtained by experienced workers indicate that the investigation is nevertheless a valuable diagnostic procedure if used in conjunction with other methods of diagnosis. Several techniques for preparing the sputum or bronchial secretions for examination for tumour cells have been described. It is probable that familiarity and experience with almost any one technique is of greater importance than any particular method.

During recent years the cytological study of sputum has been concentrated almost entirely on the malignant cells that may be present in such specimens. Non-neoplastic cells, except as a possible source of error in differentiating them from neoplastic cells, have received little attention, although the recent comments on epithelioid cells and Langhans-type giant cells in tuberculous sputum by Pealtz and Probst (1953), on eosinophils in asthma and bronchitis by Bachmann and Ruiz Moreno (1953), Rawlins (1955) and Enger (1955), on heart-failure cells (siderophages) by Zipp *et al.* (1955) and on inclusion bodies

in bronchial epithelial cells in cases of measles by Tompkins and Macaulay (1955) and Finlayson (1956) indicate that the study of these cells has not been completely abandoned.

From a review of the literature it is apparent that the cytological examination of sputum as an aid to clinical diagnosis is divisible, historically, into three periods. The early cytologists of the nineteenth century submitted sputum to microscopic examination with the hope of discovering reliable clues to substantiate the clinical diagnosis of phthisis and of other, as then unknown, bacterial infections of the lungs. The various cellular elements were described in considerable detail, but from a diagnostic viewpoint, the studies were mainly unrewarding, and some of the supposed pathognomonic findings, such as the presence of elastic fibres in sputum as being diagnostic of tuberculosis, were later disproved. The second phase was heralded by the great discoveries in bacteriology in the latter part of the last century, and was sustained by the application of these findings to the diagnosis of pulmonary infections. Bacteriological investigations superseded cytological studies, and except for the protracted discussion on the significance of eosinophilia, little interest was taken in the cells of sputum. Microscopic examination of sputum is still dominated by the bacteriologists, but during the past twenty years there has been a recrudescence of interest, focal in Europe, but disseminate in the United States, in the cytology of sputum, more especially as applied to the diagnosis of lung cancer.

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