

Methods for obtaining specimens from the nasal mucosa for morphological and biochemical analysis

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ABSTRACT: The nose is the part of the airway system which is most easily accessible for morphological and pathophysiological evaluation of changes occurring as a response to various stimuli. During recent years several new atraumatic techniques for harvesting cells for morphological and biochemical analysis have been introduced, in addition to the more well known surgical biopsy procedures and nasal smears. Such techniques include nasal lavage, scrapings from the nasal mucosa, brush techniques and imprints. Several of these techniques allow repeated samplings, obtaining quantitative as well as qualitative information as to the cells present on the surface of, as well as within, the epithelial lining of the nasal mucosa. Some techniques provide the investigator with a method for obtaining information on the cellular content of certain biochemical markers such as histamine. The present review describes the merits and disadvantages of the old and new methods and provides guidelines as to when each method should be considered.

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The nose is the part of the airway system which is most easily accessible for morphological and pathophysiological evaluation. Morphological changes in the nasal part of the airway mucosa may be of interest not only in the routine clinical histopathological work-up of lesions, but also for research-oriented studies of the cellular aspects of immunological reactions taking place in the airway mucosa [1-6]. Such reactions may be part of a naturally occurring disease [7, 8] or may be intentionally induced, as in airway challenge studies [9, 10]. The information gathered may be valid not only for the actual site of the study, but may in certain aspects reflect basic cellular immunological reactions which are also valid for other parts of the airways such as the bronchial mucosa.

In order to study processes in the nose there is a need not only for biopsy procedures but also for methods which permit repeated atraumatic sampling of cells from the mucous membrane. The smear technique [11, 12], whereby cells are taken from the nasal mucosa with a cotton swab and then smeared onto glass slides, is easy to perform, but is hampered by its poor reproducibility and the lack of quantitative information [13]. With this in mind, new methods, such as lavage, imprint, scrapings and brush sampling have recently been developed [13-17]. The aim of the present review is to assess the merits and disadvantages of the old and new methods and provide guidelines as to when each method should be considered (see also table 1).

Table 1. - Cytological methods for cell harvesting

Method	Quantitative	Secretions included	EM	Biochemistry
Smears	no	yes	no	no
Blown secretion	no	yes	no	no
Imprints	yes	yes	no	no
Lavage + cytocentrifuge	yes	no	yes	yes
Brush + cytocentrifuge	yes	no	yes	yes

EM: electron microscopy.

Methodological considerations

Preparations before sampling

Regardless of the final choice of the method for harvesting cells, one should be familiar with the anatomy of the nasal cavities, have a good light-source (headlight) and a nasal speculum to examine the nose prior to the sampling procedure.

Purpose

Before selecting any specific morphological method it is important that the purpose of the cell sample has been clarified. Thus, if the aim is only to obtain a pathological anatomical diagnosis of a suspected lesion, a single biopsy would be sufficient. On the other hand, if the intention is to look for more discrete changes in the mucous membrane, the need for control specimens for comparison cannot be underestimated [18, 19]. This aspect might become even more important in the light of the increased use of the nasal mucous membrane as a drug target not only for the treatment of nasal diseases but also as a convenient way of administering drugs which act systemically, such as various peptide drugs [20–22]. Monitoring changes in specific cell elements over a shorter time span may, on the other hand, call for methods which permit repeated atraumatic cell samples. Other factors should also be considered when selecting a method. Is there a concurrent monitoring of other parameters, such as the level of putative biochemical mediators [10, 23, 24], which would suggest the selection of a method where the cells are sampled in a suspension? Is the main thrust only to study a single cell type, such as mast cells? Is a single method sufficient or are repeated samples called for? More than two or three samples will rule out any biopsy procedure.

Which level of the nasal mucosa is of major interest, the cells on the surface, within the epithelial lining or in the subepithelial structures? Is there any specific cell type which is of major interest and would require specific handling? Are the cells of interest numerous so that only small samples are sufficient or are the cells scarce thus necessitating a larger sample? Are the cells of interest tissue cells, or blood cells like eosinophils? Do you want to do other morphological work in addition to light microscopy, such as transmission or scanning electron microscopy or simultaneous biochemical studies? Is any logistic problem involved? How fast do the cells have to be processed in order to obtain optimum results? It is important that these factors are borne in mind since no single method is the best for all purposes.

Procedure standardization

In order to make a fair evaluation of the findings any method for obtaining specimens for morphological analysis should be standardized, at least as far as the investigator is concerned. The properties of biopsy specimens, which can be regarded as being taken during standardized conditions, may actually vary to a great extent, due for example to tissue oedema. Therefore, differences found in a cell counting procedure on light microscopy slides should be related not only to the counting area or the visual high power field but preferably also to a biochemical parameter, such as protein content, since tissue oedema could be a crucial factor [25].

For the other methods such as smears, imprints, lavage and brush sampling there are several points that are

important when it comes to standardization. These factors involve not only the sampling technique but also the steps which are performed prior to the final evaluation on glass slides or otherwise. Several attempts have been made to standardize the smear technique, but they appear to have had only limited success so far [26]. The smear technique is currently used only for demonstrating the presence or absence of eosinophils [27–29]. The other techniques mentioned above have mainly been applied as research tools and used by a limited number of investigators. They should, nevertheless, be considered since they are easy to perform and could be more informative than the smear procedure.

At present there are very few studies which compare the results obtained using different methods applied simultaneously in the same patients. It is therefore not known whether changes in one fraction of cells harvested in a lavage procedure, for example, parallel those found in a biopsy specimen from the same patient.

Biopsy procedures

Biopsy site

The morphology of the nasal epithelial lining changes from a squamous epithelium in the anterior parts to a ciliated, columnar, respiratory epithelium in the posterior parts of the nasal cavities [30]. Consequently, it is important to select the site of biopsy carefully no matter whether the aim is to compare specimens from different subjects or to compare repeat samples from the same patient. The most common site for biopsy is the lower edge of the inferior turbinate. The reason for this is mainly practical as this is the most accessible part of the nasal cavity, with a comparably lower risk of per- and post-operative bleeding. Furthermore, the inferior turbinate is the part of the nasal mucosa which is most exposed to the influence of the inspired air with its content of putative noxious or allergenic agents [31]. Concerning the differences in morphology, it is obvious that the selection of biopsy site is totally dependent on the aim of the planned study. A light microscopic specimen of the nasal mucosa taken in such a manner is shown in figure 1.

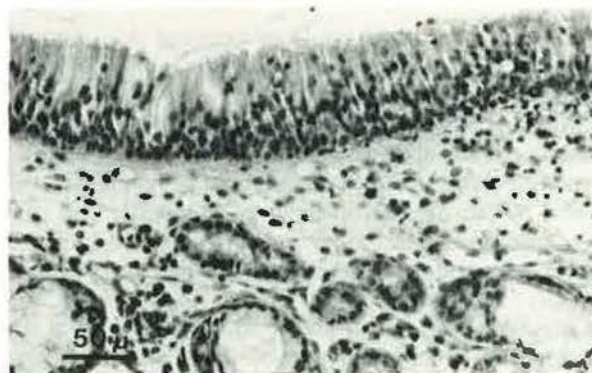


Fig. 1. – A light microscopic section of a nasal mucosa stained with haematoxylin-eosin. A normal nasal epithelium consisting of ciliated cells, goblet cells and brush border cells. Below the basement membrane are glands and vessels.

Anaesthesia

The use of anaesthesia is essential when taking biopsy specimens with enough tissue to permit good morphological studies. Anaesthesia can be applied either topically with the agent soaked in a piece of cotton wool, which is put into place some time ahead of the intended procedure, or injected into the mucosa through a thin needle. The latter approach produces a deeper anaesthesia which might be useful. Since the nasal mucosa is one of the best perfused organs in the body [32, 33], a vasoconstrictor is usually required in order to reduce the risk of per- and post-operative bleeding. Nevertheless, the risk of profuse bleeding is obvious and one has to be prepared to use suction to clear the nasal cavity and to be able to perform a nasal packing or cauterization. It is reasonable to assume that the administration of the vasoconstrictor does not alter the blood vessel morphology and that topically applied anaesthetics do not alter the composition of the epithelial lining, although studies comparing results with and without drug application have not been performed.

Procedure and handling

Specimens can be taken using a pair of forceps with a grip large enough to reduce the risk of crushing. A punch biopsy may also be considered [5]. If crushing could severely jeopardize the quality of the specimen, such as in immunohistochemical studies, it is advisable to use a small knife and cut out the specimen [34]. The latter procedure is more time-consuming and the risk of bleeding is higher, but it makes it possible to handle the specimens more gently. The biopsy specimen should be placed in the fixative immediately in order to avoid artifacts. Some methods require the specimen to be placed in an ice-cold fixative or other solution. It is a good idea to have such facilities beside the patient in order to avoid proteolytic degradation and other problems which may have a negative effect on the evaluation of the specimen.

Nasal scrapings

Using a curette, which could be a normal steel surgical curette size 3 or a plastic version (Rhinoprobe™), small specimens can easily be scraped from the nasal mucosa [8, 16]. The cell harvest which is obtained consists mainly of chunks of the epithelial lining that are well preserved and which permit differential counting of epithelial cells as well as the detailed evaluation of specific cell elements like mast cells and goblet cells as shown in figure 2. One advantage of this method is that it is known precisely from which part of the nasal cavity the specimen has been taken. Other advantages are that the scraping can be repeated several times and that it requires no anaesthesia. The main disadvantage is that the specimen only includes the epithelium and consequently does not permit evaluation of changes in deeper layers of the mucosa.

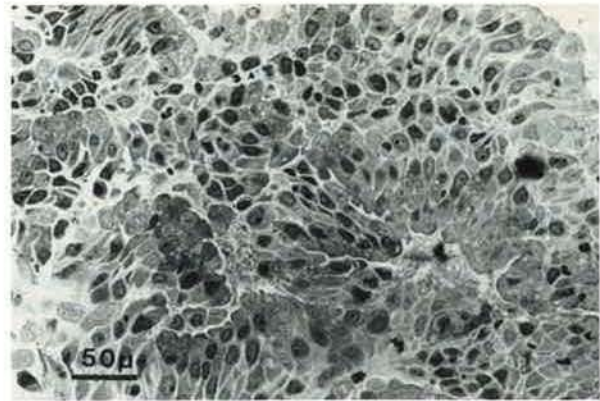


Fig. 2. — Section of a nasal scraping showing chunks of nasal epithelial cells which can be used for evaluating different cell elements.

Cytology

Smears

Smears from the nasal mucosa have long been used for morphological analysis. A cotton wool swab is moved over the nasal mucosa from the anterior to the posterior part of the nasal cavity. The swab is then smeared over a standard glass slide, fixed and stained. This is a simple procedure to perform but a very small sample of cells is usually obtained from the secretion or from the superficial part of the mucosa in particular. Although attempts have been made to standardize this procedure, the cell yield varies considerably and any results obtained should, therefore, be interpreted with great care [25].

Nevertheless, this method can be used to determine the presence or absence of a specific cell population in terms of a relative proportion, but does not permit the safe quantification of the number of cells.

Blown secretions

In this method secretions in the nasal cavities are blown onto a plastic film and later fixed on glass slides [35]. The cells are only those which are contained in the secretion proper and thus reflect a different cell population to that collected in the smearing procedure. A disadvantage is that the area from which these cells originate is unknown. Furthermore, the cell yield, like that obtained using the smearing procedure, is highly variable and may only contain cells which are discarded from the mucosa. Another disadvantage of this method is that conditions with limited quantities of nasal secretions do not make any cell yield possible.

Imprints

Efforts have been made to standardize the area from which the cytological specimen is being taken using the imprint technique. This can be performed with small

rounded glass slides [36] which do, however, have the disadvantage of having a completely flat surface so that only a limited number of cells can be collected. Consequently, an improvement in this method has been introduced and involves the use of small, thin, plastic strips [14]. These are painted with 1% albumin to produce a sticky surface and are then introduced into the nose and gently pressed onto the mucosal surface, usually the nasal septum. The plastic strip is then fixed, stained and finally examined under a coverslip. As a result the handling of the cells is very gentle and they stay on the plastic strip. A reasonably good cell yield is obtained and the number of different cells can be enumerated. This method is especially useful in the evaluation of cells which are less numerous *e.g.* mast cells [4], as shown in figure 3. A disadvantage of this method, like smears and blown secretions, is that a considerable amount of the mucus in the nasal secretions remains on the slide. In the ordinary Giemsa stain the mucopolysaccharides in the mucus are stained and this hampers the microscopic evaluation of the cell elements.

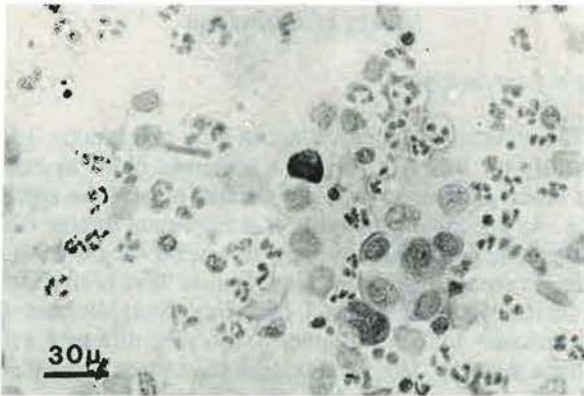


Fig. 3. — Cells from the nasal mucosa obtained in an imprint utilizing a small plastic strip for carriage of the cell elements. A toluidine blue stained preparation of epithelial cells with an interspersed mast cell and granulocytes.

Brush

Small brushes made of plastic coated steel wire with nylon strings are used for the cell harvest. The brush is introduced into the nasal cavity under direct visual guidance and is placed between the nasal septum and the inferior turbinate (fig. 4). No anaesthesia is used. The brush is removed, whilst being slightly rotated, and is immediately placed in a small tube containing a small amount of physiological buffer solution and then carefully shaken and brushed off [15]. The cell harvest which is separated from the secretions can be used for morphological work, light or electron microscopy (figs 5 and 6), and biochemical evaluation.

As the total volume in which the cells are suspended is known the total number of cells can be estimated through a cell count of a small proportion using a Bürker chamber or by counting the total number of cells on the cytospin preparation when the volume that was loaded is known. The coefficient of variation for repeated sam-

plings from the same individual for the major cell types harvested has been reported to be 40%.

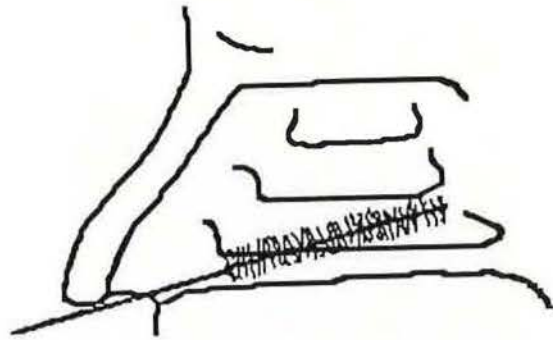


Fig. 4. — Schematic figure illustrating the usage of a brush for harvesting cells from the nasal mucosa.

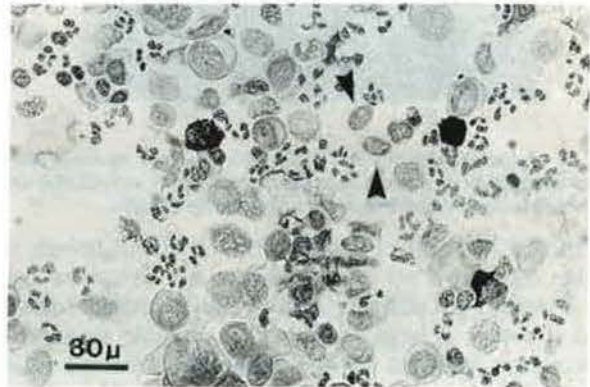


Fig. 5. — A light microscopic cytospin slide from a brush specimen obtained from a normal subject. Shown is a variety of cells, including epithelial cells, macrophages (arrow heads), mast cells (filled with dark granules) and granulocytes.

Light microscopy preparations are best made using cytocentrifugation. Several specimens can be made from each sample and stained differently depending on the cell type which is of major interest. Specimens obtained in this way are preserved with excellent morphological details [15] due to the very gentle handling of the cells and also to the lack of secretions that might be stained and interfere with the evaluation of the specimen. The cells obtained include the cells floating in the nasal secretions and a significant proportion of epithelial cells (up to 40%), thus reflecting a cell pool involved in the barrier function of the mucous membrane as shown in figures 5 and 6.

Nasal lavage

Nasal lavage can be performed in several different ways. It is important to avoid the insertion of any mechanical device such as rubber catheters into the nasal cavities; these might be helpful under other conditions [37, 38] but they could scrape off cells and thereby influence the number and kind of cells harvested. A better way of performing the lavage is with the patient's head bent backwards during closure of the soft palate as

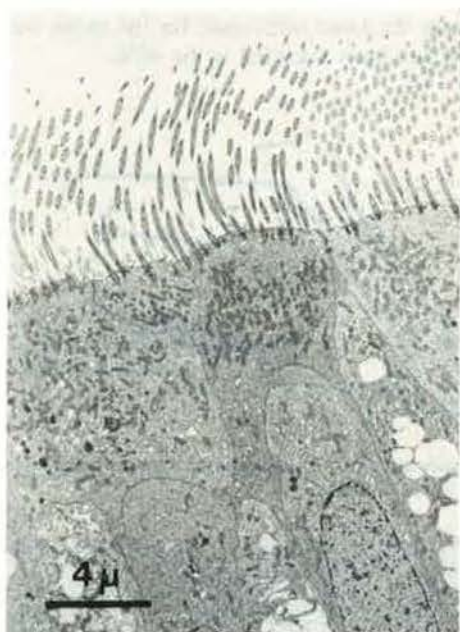


Fig. 6. — A transmission electron micrograph of a brush specimen taken from a normal nasal mucosa. The micrograph shows an epithelial cell with well preserved ultrastructure which includes the cilia.

described in detail elsewhere [22]. A 10 ml lavage of saline solution, 5 ml in each cavity, is then carried out. As a result, by utilizing a fairly large lavage volume which covers a large surface it is possible to harvest somewhere between 10^5 – 10^6 cells. The returned nasal lavage fluid is immediately chilled on ice and its volume measured. The total number of cells can be counted using a Bürker chamber. As the volume of the returned lavage fluid is known, the total number of cells harvested can be calculated. The lavage fluid is then centrifuged at 1200 rpm for 10 min and the supernatant collected. The cell pellet from the lavage is resuspended and the cytospin preparations are made [8, 13]. The slides obtained are handled in the routine way for cell preparations with fixation and staining procedures. Such a slide is shown in figure 7. All or part of the cell pellet can also be used for different biochemical determinations [39], such as histamine, protein or DNA analysis. It is thus possible to calculate the amount of a biochemical marker per cell. Another way of handling the cells when a specific count of cells such as polymorphonuclear leucocytes is of interest, is to perform a direct count on the haematocytometer as suggested by FARR *et al.* [18].

Several methods simultaneously

In order to capture events in different parts of the mucous membrane it may be worth utilizing several methods simultaneously. This might include one method which captures only the cells floating on the surface, one which captures mainly the cells associated with the epithelial lining and one which captures events taking place beneath the epithelial lining. The advantage of this approach is shown in a recent study where it was pos-

sible to evaluate events taking place in relation to time and natural allergen exposure [8].

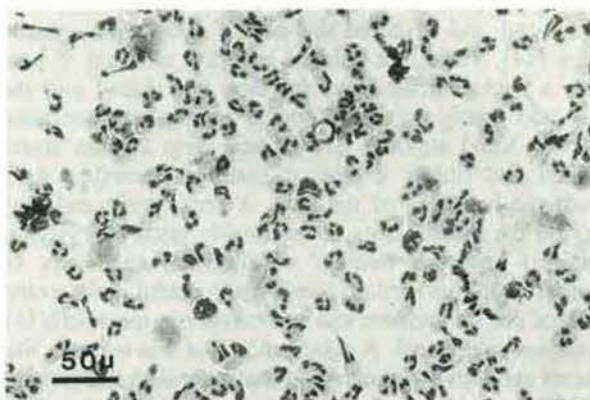


Fig. 7. — Cells obtained in a nasal lavage from an allergic individual during allergen exposure. A cytospin slide stained with toluidine blue at pH 0.5. A thin film of mainly granulocytes is shown.

Modes of evaluation

Light microscopy

The most common procedure in light microscopy is to quantify the different cells in a specimen either as cells per visual field or as cells per defined area of the specimen. As indicated previously it is important to note that changes in tissue volume may be crucial for the evaluation. In recent years several techniques have been added to the routine stainings used, including the application of monoclonal antibodies directed towards different cell surface markers. These techniques have made it possible to further characterize different cell populations in the specimens, *e.g.* subsets of lymphocytes, and have also been applied to nasal specimens [6].

Electron microscopy

The use of scanning and transmission electron microscopy has added a new dimension to the evaluation of the normal morphology as well as pathological changes in the nasal mucosa [2, 3, 40–42]. When evaluating any changes induced one should be aware of the fact that only a very small part of the mucosa is examined.

Quantitative evaluations are extremely difficult to perform unless a very large number of specimens are examined. Thus, electron microscopy is most suitable for the illustration of cellular events which are also studied by other parameters such as microscopy or biochemical analysis.

Biochemical analysis

Specimens obtained from the nasal mucosa as well as cells obtained in lavage and brush experiments have been subjected to biochemical analysis. These have been

performed as plain measurements without any correlation to the cellular content of the specimens investigated but also with direct correlations between a biochemical marker and a specific cellular component.

In such studies [24, 42] strong correlations have been found between the number of mast cells and histamine content in nasal mucosal specimens as illustrated in figure 8. From cell suspensions harvested with lavage or brush techniques direct correlations between, for example, histamine and mast cell/basophils can be made [15]. It is thus possible to calculate the amount of histamine per cell and also to demonstrate changes in histamine content per cell after challenge experiments [43]. In a biopsy specimen the actual cellular content can be estimated. The amount of protein or DNA should be measured in order to calculate the content per cell and not only in relation to the weight of the specimen.

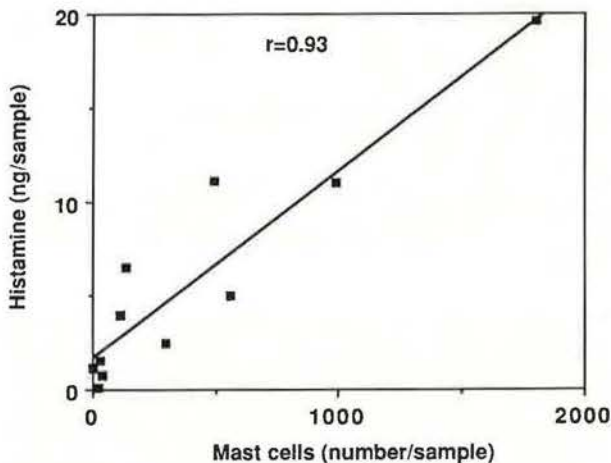


Fig. 8. - Correlation between mast cells obtained in a brush specimen and the number of mast cells in the same specimen (redrawn from Pipkorn, Karlsson & Enerbäck, 1988). An excellent correlation was obtained ($r=0.93$) which can also be used for estimation of the histamine content per mast cell.

Conclusions

At present there are several old and new methods for the harvesting of cells from the nasal mucosa. Each method has inherent advantages and disadvantages and it is important to know these in order to select the right method in relation to the aim of a proposed study. Furthermore, the introduction of several new methods for harvesting and evaluation will leave us with a spectrum of methods which will give considerable new insights into the complicated features of immunological reactions of the nasal mucosa.

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RÉSUMÉ: Le nez est la partie la plus accessible du système des voies aériennes pour l'évaluation morphologique et physiopathologique des modifications survenant comme réponse à divers stimuli. Au cours des dernières années, différentes techniques nouvelles et non traumatiques pour le recueil de cellules pour analyse morphologique et biochimique ont été introduites, à côté de méthodes bien connues comme la biopsie chirurgicale et les frottis nasaux. Ces techniques récentes comportent des lavages nasaux, des abrasions de la muqueuse nasale, des techniques de brosse et d'empreinte. Plusieurs de ces techniques permettront des prélèvements répétés, assurant une information qualitative et quantitative concernant les cellules présentes à la surface, ainsi qu'à l'intérieur du revêtement épithélial de la muqueuse nasale. Plusieurs de ces techniques permettront en outre d'offrir à l'examineur une information concernant le contenu cellulaire en marqueurs biochimiques comme l'histamine. Cette revue décrit les avantages et inconvénients des méthodes anciennes et nouvelles, et indique quelques orientations quant aux indications de chacune d'elles.