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Intraoperative Histology or Cytology?

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Summary. 500 parallel histological and cytological intraoperative examinations were carried out. In cancerological problems false positive and false negative results are more common with the cytological than with the histological method, for methodic reasons. For many non-cancerological questions the cytological method is not suitable. Quick cytological diagnosis therefore cannot generally replace intraoperative histological examination. Malignant lymphomas are diagnosed more reliably by the quick cytological specimen than by histological quick section. Supplementary cytological quick diagnosis is also advisable in larger tumours that cannot be covered completely histologically, in neoplasms with extensive regressive changes and in uncertain histological quick section results.

1. Introduction

Material obtained during operation by classical biopsy (excision, incision, punch or thicker needle) can be examined histologically by the quick section method or cytologically after imprint or smear. Lately material obtained during operation by fine needle biopsy is also being used for immediate cytological diagnosis.

Histological intraoperative examination dates back to W. H. Welch (1891), intraoperative imprint and smear cytology to van Walsem (1923) and Dudgeon and Patrick (1927). In the thirties cytological intraoperative diagnosis was used above all in neurosurgery (cerebral tumour diagnosis). In the last 2 decades intraoperative cytological examination has been recommended increasingly. Most clinics or institutes however prefer intraoperative histological quick section methods.

With the introduction of modern cryostat microtomy the quality of sections and thus the reliability of histological diagnoses increased considerably and the required time was distinctly reduced. Previously adduced arguments in favour of the cytological method (morphological details assessable only in this way, quicker results) have therefore lost some significance (Hermanek and Bünte, 1972). We therefore thought it appropriate to compare the usefulness of the two methods by our own parallel investigations. The purpose was not polarisation or confrontation of the methods but to show their limitations and advantages and to settle the question to what extent the two methods supplement each other meaningfully.

2. Material and Method

During the period 30.9.1972 to 5.4.1973 500 out of 538 intraoperative morphological examinations were compared histologically and cytologically. In 38 cases the cytological examination was omitted because the material had been fixed (27 cases) or by error (11 cases).

The fresh unfixed material received, except in very small biopsies, was first cut to the required size. From the cut surface, later to be cut by microtome, 2 imprint and 2 smear specimens were taken in each case.

Histological examinations (Hermanek and Bünte, 1972): Freezing in CO_2 quick-freeze device, cryostat microtome, thickness of section 6–8 μm, staining in polychrome methylene-blue solution, residual tissue in paraffin blocks, examination in step sections.

Quick cytological examination (Mavec, 1967): Fresh imprint and smear specimens left to dry in the air for 30 sec, staining with Mayer's haemalum solution (Merck, article No. 9249) for 3 min, short and vigorous rinsing with Aq. demin. (wash bottle), ethanol 100% 4 sec, xylol, mounting in water-free medium (Eukitt).

In 28 examinations we carried out additional phase contrast microscopical examinations of the unstained imprint and smear specimens.

Cytological and histological diagnosis was made separately by investigators of long experience and with no knowledge of other findings in each case.

3. Results

Our 500 combined examinations cover 419 cancerological (malignant or benign), 77 non-cancerological and 4 combined problems (such as malignancy or specific inflammation of lymphnode).

a) Cancerological Examinations

In 423 examinations with a question of cancer the quick cytological and histological findings and the final histological findings agreed in 361 cases (85.3%). In 2 cases the quick cytological and histological findings agreed (benign) but the final paraffin method showed malignancy. In 60 examinations (14.2%) the quick cytological and histological findings differed. The cytological diagnosis was malignant in 18 of these cases but the quick section findings and examination of paraffin step sections showed no sign of malignancy. In these cases it has to be established whether the cytology was misinterpreted or whether there was circumscribed malignancy which was detected only in cytology and not in histology. These cases were further analysed, taking account of the type of change (possibility of malignant change only focally), clinical data, any additional histological results (further specimen) and clinical progress. The cytological and histological specimens were re-examined. This showed that 15 cases were in fact benign but in 3 cases a final definite distinction between malignant and benign was not possible. These cases are first discussed separately (Table 1a).

Table 1. Results of cytological and histological quick examination

Diagnosis	Cytology	Histology
a) Cancerological questions		
Correct	381 (90,1%)	394 (93,1%)
False negative	17 (4,0%)	7 (1,7%)
False positive	16 (3,8%)	1 (0,2%)
Uncertain	6 (1,4%)	18 (4,3%)
of which actually benign	3 (0,7%)	6 (1,4%)
of which actually malignant	3 (0,7%)	12 (2,8%)
Undiagnosable[a]	3 (0,7%)	
b) Non-cancerological questions		
Correct	48 (59,3%)	80 (98,8%)
False	26 (32,1%)	—
Uncertain	7 (8,6%)	1 (1,2%)

[a] Actual character of the changes not established.

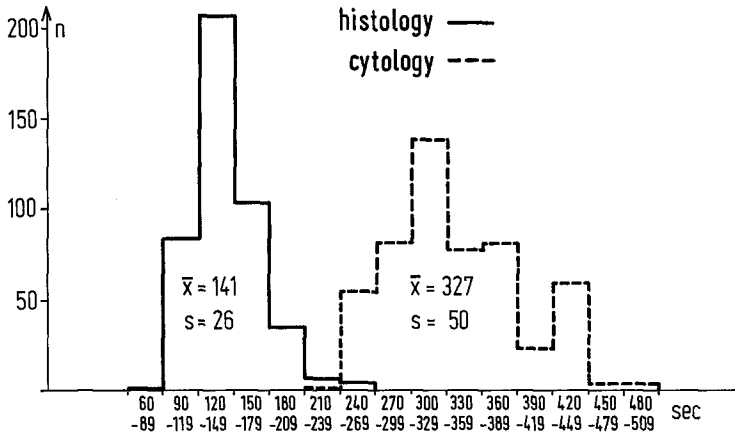

Fig. 1. Duration of histological and cytological quick examination

Table 1a shows a division of the quick cytological and histological examinations into correct, false negative, false positive and uncertain diagnoses. More informative from the clinical aspect for the assessment of diagnostic oncological methods are the parameters of effectivity and specificity shown in Table 2.

b) Non-cancerological Examinations

A summary of the results of the non-cancerological examinations is show in Table 1b.

c) Duration

Fig. 1 shows the times between arrival of the material at the laboratory and issue of the result of the quick histological and cytological examination. The mean value with histological examinations was $\bar{x}$ 141 sec, the standard deviation s 26 sec, with cytology 327 sec and 50 sec.

d) Unstained Phase Contrast Cytology

In 28 cancerological examinations we additionally carried out a phase contrast microscopical examination of the unstained specimens. Whereas in the stained specimens the cytological diagnosis was correct in all 28 cases, we saw one false negative result in phase contrast microscopy. In 7 cases we did not want to make a final diagnosis before seeing the stained specimens. Phase contrast microscopic cytological examination requires special experience. It is quicker than the quick section examination and cytological examination of stained specimens. The average values for phase contrast microscopy were 114 sec, for quick section examination 138 sec and for cytological examination of stained specimens 304 sec.

4. Discussion

a) Introduction

Intraoperative morphological diagnosis must be reliable and quick. It must quickly give clear and correct answers to the surgeon's special questions. It was

the purpose of this study to make it clear to what extent the histological and cytological methods of intraoperative examination of biopsies and operation specimens fulfil these requirements. So which method is more advantageous in general and in what circumstances is the combined use of the 2 methods advisable? To answer these questions we must first analyse the "faults" of both methods. Clinically the most important standards of reliability of a diagnostic method are the proportion of false positive and false negative results. An additional measure of effectivity is the proportion of correct positive results in malignant tumours. In the analysis of the results it is also necessary to distinguish between the examination of cancerological problems and that of non-cancerological problems.

b) False Positive Results in Cancerological Problems

By the proportion of false positive results we (Hermanek and Schricker, 1973) mean the number of false positive results in all positive diagnoses issued. Thus the clinician can see clearly what value he can attach to a positive result and what is the probability of the positive result being false. In our material the proportion of false positive results in the quick histological examination was 0.8%, in the quick cytological method 11.4% (Table 2). A histologically positive diagnosis is therefore more reliable.

Table 2. Effectivity and specificity of cytological and histological quick examination in cancerological questions

Parameter	Cytology	Histology
Effectivity		
Proportion of correct positive findings (correct positive findings/all malignant cases)	121 / 141 (85,8%)	122 / 141 (86,5%)
Proportion of uncertain findings in malignant cases	3 / 141 (2,1%)	12 / 141 (8,5%)
Specificity		
Proportion of false positive findings (false positive findings/all positive results issued)	16 / 140 (11,4%)	1 / 123 (0,8%)
Proportion of false negative findings (false negative findings/all negative findings)	17 / 277 (6,1%)	7 / 282 (2,5%)

In the literature the rate of false positive quick cytological diagnoses is between 0% and 7.7%, average 1.6% (Dudgeon and Patrick, 1927; Wrigley, 1932; Dudgeon and Barrett, 1934; Roth, 1951; Dearing, 1952; Castelain and Castelain, 1953; Mouriquand and Dargent, 1957; Marsan and Bertini, 1960; Tribe, 1965; Sakai and Lauslahti, 1969; Tokai and Szombathelyi, 1969; Aust and co-workers, 1971, Dolff and Weißenfels, 1973; Szczepanik, 1973). It also depends on the material. The authors who make a comparison with the histological quick section examination find the proportion of false positive results with the cytological method to be higher than with the histological method (Castelain and Castelain, 1953; Tribe, 1965; Sakai and Lauslahti, 1969). Only Dolff and Weißenfels (1973) observed neither cytological nor histological false positive results.

Every false positive finding in quick section diagnosis is due to misinterpretation by the examiner.

The only histological false positive quick section result was in a case of a foreign body reaction in the abdominal wall with nodular proliferation of a relatively large number of large histiocytary elements which in the quick section were mistakenly regarded as true epithelial and therefore as metastatic carcinoma formations.

In contrast to the histological quick section diagnosis, in the quick cytological examination by no means every false positive result is a misinterpretation by the examiner. 6 out of 16 false positive cytological results were due to the method insofar as cytology gives no information on infiltrative growth. Any highly atypical epithelium in situ therefore cannot with certainty be distinguished cytologically from an infiltrative malignant tumour.

The atypical changes of circumscribed preblastomatous melanosis Dubreuilh, limited to the basal epidermis, therefore cannot with certainty be distinguished cytologically from an infiltrative malignant melanoma. For the same reasons a distinction between an adenomatous or villous polypus from the colon or rectum with superficial markedly atypical epithelium and an infiltrative well-differentiated adenocarcinoma is cytologically hardly possible. The false positive diagnosis in a case of chronic peptic gastric ulcer is also explained by atypical epithelium at the margin of the ulcer.

Similar possible errors should be mentioned for the sake of completeness: proliferative papillomas and papillary carcinomas, especially of the urinary tract, carcinoma in situ and infiltrative carcinoma in the region of the oral cavity, the larynx and the female genital organs.

False positive cytological diagnoses must also be expected in the so-called pseudomalignant tumours (Zollinger, 1968; Hermanek and Bünte, 1972).

c) False Negative Results in Cancerological Problems

By the proportion of false negative results we mean the proportion of false negative results among all negative diagnoses issued. With the cytological method it was 6.1%, with the histological method 2.5% (Table 2). The discrepancy between histology and cytology is thus considerably smaller than in the false positive results.

Statements in the literature vary from 0% to 8.7%, average 1.9% (authors as in section 4b). It should be pointed out however that studies are included here which report 100% correct cytological results (no false and no doubtful diagnoses!) (Wrigley, 1932; Aust and co-workers, 1971; Dolff and Weißenfels, 1973; Szczepanik, 1973). This must be viewed with some scepticism to say the least.

Only one of the 7 histologically false negative results was a true misinterpretation. In the 6 other cases they were due to the histotopographic situation (see below). This was also responsible for 6 of the total of 17 cytologically false negative findings. In the other 11 cases the cause was the specific limitations of the cytological method. These lie on 2 planes:

α) highly differentiated malignant tumours show only slight atypias,

β) if only little or no cellular material is obtained, a cytological diagnosis of malignancy is impossible. This is true in very stroma-rich cancers (scirrhus ca. of stomach, breast or pancreas), in very discrete tumour formations in preexisting tissue (e.g. dissociated growth of gastric cancer in the muscularis propria, circumscribed cell associations of malignant lymphoma in coarse-fibrous connective tissue) and in mesenchymal malignant tumours with much interstitial substance

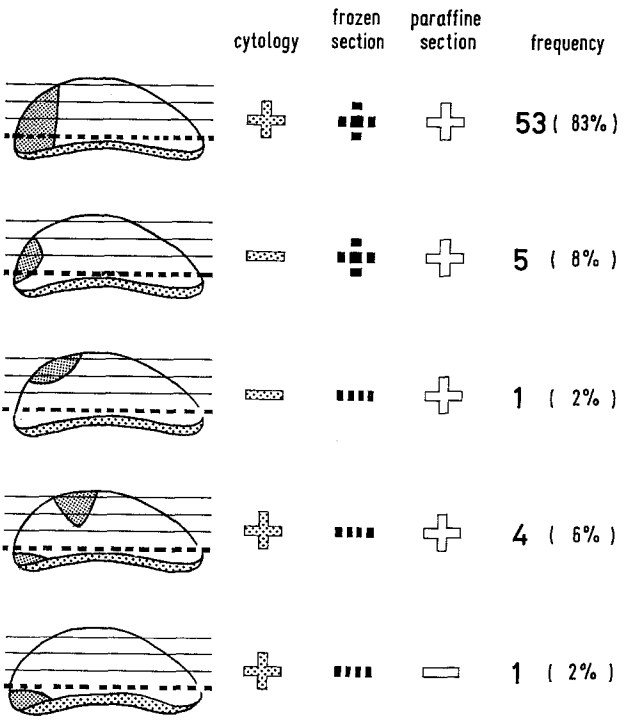

Fig. 2. Demonstration of metastases by intraoperative diagnosis and histological paraffin section examination (46 lymphnode, 14 peritoneal, 4 pleural metastases)

(well-differentiated fibrosarcoma, myosarcoma, chondrosarcoma, osteosarcoma with much bone and osteoid formation).

d) Histotopographic Aspects

What is seen in quick cytological and histological specimens cover only a small part of the material and a different part in each case. The later examination of paraffin step sections covers other parts of the biopsy (Fig. 2). "Mistakes" may occur with any method if the malignant changes are only focal. (Metastases in lymphnodes and serous membranes, so-called micrometastases).

Fig. 2 shows a summary of the different results in 64 such examinations where finally metastases were confirmed in 63 cases and were very probable in 1 case (Fig. 3).

The problems posed by the presence of focal malignant changes are the same as in the case of normal histological examinations of biopsies, for instance. In the cutting of the material tumour formations may in certain circumstances escape histological demonstration but may be detected by parallel cytological examination. This was already pointed out by Ultmann and co-workers in 1957 on the basis of their examinations of lymphnode imprint specimens.

These considerations have led Japanese authors (Furuya *et al.*, 1968; Yamakawa, 1969, 1971; Yoshii *et al.*, 1970; Shida, 1971) and, in Germany, Georgii's study group (Georgii, 1972; Atay and Preussler, 1973; Ostertag *et al.*, 1973) to

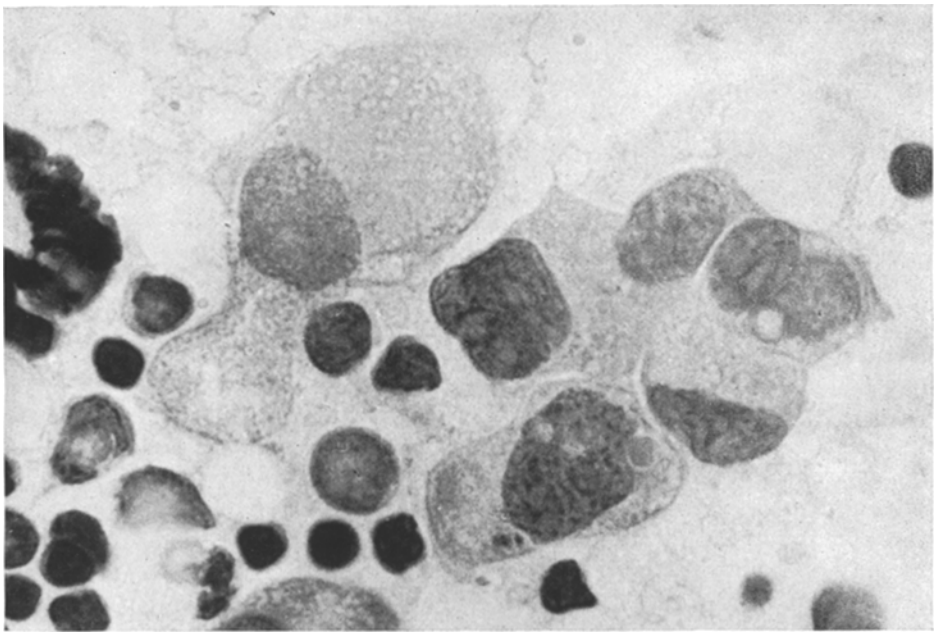

Fig. 3. Cytological specimen of lymphnode (removed with tumour of testicle). Malignancy in cytological smear only, histologically neither in quick section nor in paraffin step and serial sections. Very probable a micrometastasis

examine biopsy material from endoscopies not only histologically but also cytologically as a matter of principle.

Smear specimens of biopsies, made from the surface of smaller specimens instead of from a cutting surface prepared at the laboratory, may include tumour cells present in secretions from operation wounds and fluids and thus give the impression that tumour tissue is present in the biopsy itself.

This kind of "contamination" is of different importance according to the type of material and the question at issue. In incision biopsies for the purpose of confirming malignancy of a suspect focus such cytologically positive findings will assist our diagnostic efforts. This is not so in the examination of marginal specimens to determine the need of radical removal. Here a positive cytological result due to contamination with secretion from the operation wound actually would be misleading and lead to an unjustifiable and possibly dangerous extension of the operation. The number of tumour cells visible in the cytological specimens is some indication. Massive findings of tumour cells exclude contamination but if only sparse tumour cells are found, contamination is possible though not proved.

In 42 examined marginal specimens from radical operations cytology and histology gave identical results in 39 cases (33 no tumour, 6 tumour). In 1 case tumour tissue was demonstrable by histology only. In 2 cases (radical prostatectomy) only the cytological examination was positive. In both these cases only very occasional tumour cells were seen. Neither quick section nor a total of

41 paraffin sections showed tumour formation histologically. A control examination 6 months after the operation showed no sign of any local recurrence or distant metastases.

e) Proportion of Correct Diagnoses in Malignant Tumours

Considerable differences in the proportion of positive results between histology and cytology were seen primarily in malignant lymphomas. Out of 11 cases a correct cytological diagnosis was made in 10, a correct histological one in 5. Here we see a true superiority of cytology.

Cytology also offers advantages when tumours are to a large extent destroyed by necrosis and/or inflammation. In such cases the diagnosis of malignancy can be made more easily from cytological specimens on the basis of isolated, still intact, small groups of cells.

On the other hand, there were better results from the histological examination in gastric carcinomas. Out of 8 cases of gastric carcinoma the cytological diagnosis was correct in only 5 cases, the histological one in all cases. This is due primarily to the difficulty of recognising cytologically scirrhous carcinomas or carcinomas which infiltrate the wall of the stomach diffusely only in discrete formations. Here imprints and smears provide only little cellular material and the diagnostic yield of cytological examination is therefore limited. The same applies to metastases of scirrhous carcinomas.

In all highly differentiated malignant tumours the diagnosis is more often correct histologically because here the recognition of infiltrative growth is helpful.

f) Usefulness in Non-cancerological Problems

On the whole, quick cytological examination for solving non-cancerological questions is distinctly inferior to the histological method. Many questions cannot be answered at all cytologically, e.g. whether in a gastrectomy at the distal resection margin or in a secondary operation after B II there is antral or duodenal mucosa in the duodenal stump. Neither the superficial epithelium nor the mucoid epithelium of the glands are significantly different in the duodenum and antrum. The essential criterion, i.e. whether Brunner's glands are present or not, is a question of topography and not one of cellular difference. For the same reasons it is not possible to distinguish in quick cytological examinations in hyperparathyroidism between normal, hyperplastic or adenomatous parathyroids, or between adrenal adenoma and adrenal hyperplasia. A differentiation between thymus and lymphnodes can be made only if besides the lymphoid cells there are definite cell elements of Hassal's bodies present in the imprint or smear specimen. On examining intestinal biopsies for aganglionosis we find in the cytological specimen frequently no ganglionic cells because they do not separate from the tissue complex. These examples show why many non-cancerological problems cannot be solved cytologically. In the first place a structural analysis is indispensable and cytological analysis is not enough, secondly biopsies do not yield sufficient cellular material for definite cytological diagnoses.

g) Time Factor

In the cytological method employed by us (haematoxylin quick staining based on mavec) the time required was longer than with the quick histological exami-

nation (Fig. 1). The staining time including air drying of the specimens is slightly longer than the time for making and staining histological sections. The time taken for the examination of cytological specimens is very variable. If there are plenty of tumour cells, the examination requires little time. In negative cases the scrutiny of the specimens under high magnification takes longer than that of histological specimens which can be examined under lower magnification.

Instead of the staining we use, other quick cytological staining methods can be employed (review in Hermanek and Bünte, 1972). With regard to the choice of stainings, we are in principle of the same opinion as with regard to different histological quick stainings: all stainings are essentially of equal value, provided the examiner is familiar with the particular staining.

Unstained phase contrast microscopy is desirable for reasons of time. Admittedly this technique requires special experience to get good results.

h) Cytology or Histology?

A complete replacement of histology by cytology cannot be recommended for quick diagnosis. The methodic limitations of cytology to the recognition of cells or the cell population, implying the abandonment of an analysis of tissue structure, represents a disadvantage of cytology, prohibiting the exclusive use of cytology for intraoperative diagnosis. If a histological intraoperative examination is impossible for personal or space reasons while an intraoperative cytological examination is possible, the latter possibility should be utilised. This is what we have done since these investigations were concluded. We have however made it quite clear to our surgeons that all cancerological questions resulting in therapeutically different consequences according to in-situ or infiltrating changes cannot be answered cytologically. Non-cancerological questions, too, are often not answerable cytologically.

i) Regular Combined Histological-cytological Diagnosis?

Regular combined histological-cytological diagnosis increases the required personnel. In order to avoid delays, 2 medical-technical assistants are needed. If the histological and cytological examination is carried out by separate examiners, the cytologist must also be in constant readiness during regular operation times.

Is this increased use of personnel for regular combined histological-cytological intraoperative diagnosis justifiable? Certainly not as far as examinations with non-cancerological problems are concerned. Out of 423 examinations with cancerological problems 363 gave concordant results, 6 doubtful cytological findings, leaving 54 with discordant findings. In 33 of these histology proved superior, cytology in only 21. So the problem remains what is to be done with discordant findings. Various possibilities of evaluating discordant findings and their results were compared with the results of exclusive histological examination. Practically no difference was seen between the evaluation methods. We consider therefore that regular combined cytological-histological intraoperative examination even in cancerological questions does not justify the extra requirements and is not advisable because of the resulting difficulties in the evaluation of discordant findings.

Several authors (Pickren *et al.*, 1963; Sakai and Lauslahti, 1969) have suggested that in the case of discordant findings further quick sections be made to clarify the position. We analysed our material from this aspect and found that out of a total of 27 histologically doubtful and false diagnoses possibly a correct, definite histological quick section diagnosis could have been made in this way in a maximum of 8 cases. This does not support regular histological-cytological intraoperative examination either.

j) When Should Supplementary Cytological Examination Be Carried out?

The decision to carry out a supplementary cytological intraoperative examination of small biopsies must be made before the histological specimens are prepared (primary supplementary cytological examination). In the case of larger specimens which are not completely covered by histological quick sections, a cytological examination could follow after the histological quick section diagnosis is available (secondary supplementary cytological examination) if the tissue used for quick section examination is not immediately fixed. A secondary supplementary cytological examination however prolongs the time required for the complete examination.

Primary supplementary cytological examination is advisable in our opinion in the following 4 situations:

α) Suspected malignant lymphoma. In malignant lymphomas the true superiority of the cytological method in intraoperative diagnosis is evident. The diagnosis of individual cells is more reliable in cytological specimens than in histological quick sections. Out of 11 malignant lymphomas a clear intraoperative diagnosis was made histologically only in 5 cases but cytologically in 10.

β) Large tumours, impossible to cover completely histologically. The cytological method can cover larger areas of tumour and therefore makes it easier, with variable appearances in different parts of the tumour, to catch the characteristic structures proving malignancy.

γ) Tumours with macroscopically obvious, extensive necrosis and inflammatory or haemorrhagic destruction (cytologically individual, still intact tumour cells).

δ) Bone tumours which for technical reasons (marked calcification) cannot be dealt with in quick sections without difficulty. This suggestion was made by Zugibe (1970). We ourselves however have always managed to obtain sectionable tissue for quick section diagnosis from biopsies from suspected malignant bone tumours.

Secondary supplementary histological examination is recommended by us when the quick section findings are uncertain or unexpectedly raise the possibility of malignant lymphoma. The cytological diagnosis in cases of doubtful quick section findings is shown in Fig. 4. If the quick section findings are uncertain and the cytological diagnosis is malignancy, it is in our experience very likely that malignancy is indeed present. In isolated cases the possibility of false positive cytological results must be taken into account (see section 4). If with uncertain quick section findings the cytological diagnosis is benign, one should try with further biopsies to get an unequivocal quick section result because the cytological dia-

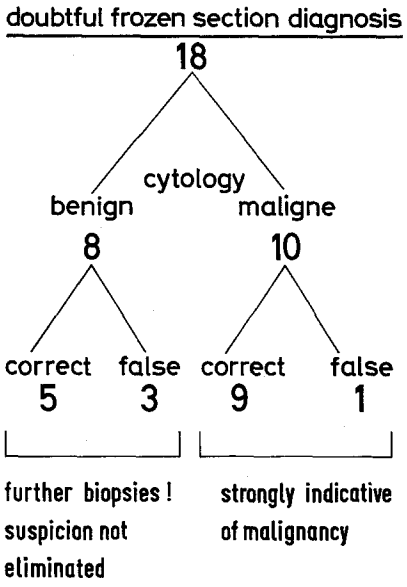

Fig. 4 Quick cytological findings in cases of uncertain histological quick section findings

gnosis of benignity does not exclude actual malignant change with sufficient certainty.

k) Intraoperative Fine Needle Biopsy

The higher risk of false positive findings by cytological examination compared with the histological method tells against a general recommendation of fine needle biopsy. The only point in its favour is the lower rate of complications. This does not seem to us significant in the thoracic region but possibly in the pancreas. We have however, in contrast to other authors, seen no significant complications either with punch or incision biopsies of the pancreas. We therefore see no reason for preferring fine needle biopsy.

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