FROZEN-SECTION DIAGNOSIS*

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[WITH SPECIAL PLATE]

Rapid histological diagnosis by frozen section is a classical method that is not widely used in this country, although the demand would appear to be increasing. The late Dr. Ernest Shaw, of the Royal Northern Hospital, did pioneer work of the first importance in this field from the end of the last century onwards (see Shaw, 1910, 1923). Most of the literature, however, comes from the U.S.A. There the method has been generally favoured and was formally recommended by the American College of Surgeons (cited by Hellwig, 1935). Rather surprisingly, there have not been many analyses of results. The purpose of this paper is to attempt such an analysis, mainly from the point of view of validity of reporting and value, if any, to the surgeon.

Routine Method

The pathologist receives the biopsy specimen in the theatre and selects the block and surface to be cut. The section is cut from the fresh unfixed tissue by an expert technician, but the pathologist should be able to do this himself if necessary. The finished section is 5–10 μ thick, is stained by haematoxylin and eosin, is permanent, and takes from 7 to 10 minutes (per block) to prepare. A few special stains can be used—for example, for free iron—but are not often necessary. The quality of the routine frozen section may be judged by the accompanying low- and high-power photomicrographs (Special Plate, Figs. 1–10), all of which, except Fig. 10, are from cases of the present series. The use of the phase contrast microscope to plumb the depths of the section, as suggested by Fisher (1958), can be seen to be totally unnecessary. The apparatus for the frozen technique is easily transportable and the process can be done in any room close to the theatre; running water and electricity are advantages but are not indispensable.

*Received for publication on February 4, 1959.

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FIG. 1.—Fat necrosis of breast. Foreign-body giant cell in focus of inflammatory cell infiltration and active fibrosis. Macroscopically this lesion closely simulated carcinoma. (H. and E. $\times 550$.)

FIG. 2.—Carcinoma of breast. Common type. (H. and E. $\times 125$.)

FIG. 3.—Large pleomorphic-celled carcinoma of breast invading fat. (H. and E. $\times 125$.)

FIG. 4.—Meningioma with psammoma bodies, incidentally demonstrating origin of such bodies from blood vessels. (H. and E. $\times 125$.)

FIG. 5.—Cellular glioma. Area of gemistocytic astrocytes. (H. and E. $\times 550$.)

FIG. 6.—Malignant melanoma of skin. (H. and E. $\times 125$.)

FIG. 7.—Secondary adenocarcinoma in peritoneal fat. Macroscopically a milium cyst on root of mesentery. (H. and E. $\times 125$.)

FIG. 8.—Secondary adenocarcinoma in bone (vertebra). (H. and E. $\times 125$.)

FIG. 9.—Secondary squamous-celled carcinoma in lymph node. (H. and E. $\times 125$.)

FIG. 10.—Aschoff body in myocardium. Sudden death in infant. (H. and E. $\times 125$ enlarged $1\frac{1}{2}$.)

After the frozen section is reported verbally in the theatre, the tissue is processed by the paraffin method as a routine and the final written report is issued as follows:

Frozen section reported in theatre as
Specimen (macro.)
Histology (paraffin)

In every case, therefore, accurate comparison of the frozen and paraffin reports is available for both the surgeon and the pathologist.

Present Series

Material.—This consists of slides, blocks, and reports of 188 consecutive cases in which histological diagnosis by frozen section was given in the theatre (whole series). In 147 cases the clinical diagnosis and macroscopic tissue diagnosis were also recorded at the time (fully recorded series).

The work began in September, 1952, and continues; the last entry, however, to be included in the present analysed series is dated May 9, 1957. Thus the annual totals for comparison extend over four complete years: 1953 to 1956, the totals being 9, 18, 55, and 75 respectively.

This increase may be compared with the figures from the Presbyterian Hospital, New York, where there were 28 frozen sections in 1929 and 923, in 1954, the operations with specimens for these two years totalling 2,066 and 6,511 respectively (Stout, 1956).

Whole Series (188 Cases) Validity of Reporting

In 175 cases (93.1%) the frozen and the paraffin reports have been identical. In 7 cases (3.7%) there has been an unimportant difference between the two reports. In 6 cases (3.2%) the frozen report has been wrong; in one of these the diagnosis was given in the theatre as essentially uncertain and the various possibilities were mentioned. The subsequent paraffin sections of this case were so difficult that they were referred to the consultant panel in morbid histology, who gave only a majority opinion. For the purposes of this analysis this case and the unimportant difference group may reasonably be added to the first group to represent working or practical validity. These figures are shown in Table I for comparison.

TABLE I.—Frozen-section Validity Compared with Paraffin

	Frozen and Paraffin identical or similar	Unimportant Difference	Frozen Wrong
Absolute validity	175 (93.1%)	7 (3.7%)	6 (3.2%)
Working	183 (97.3%)	—	5 (2.66%)

The wrong group of five cases is further broken down in Table II and compared with Sjölin's (1955) results in a much larger series of frozen sections (1,467 blocks: 504 patients).

TABLE II.—Error Analysis

Total	5 (2.66%) (Sjölin, 3.2%)
Faulty sampling by pathologist	3 (1.6%) (" 2.5%)
Histological misinterpretation	2 (1.06%) (" 0.7%)

The two misinterpreted cases were: (1) atypical duct papilloma of breast, doubtful malignancy (paraffin); frozen section reported as early carcinoma (false positive); and (2) carcinoma of thyroid (paraffin); frozen section reported as benign (false negative). The surgeon remained sufficiently suspicious of this lesion, however, to operate as for carcinoma.

It should be noted that sampling errors also occur in paraffin work, as the experienced histologist

recognizes by taking deeper cuts in the block or selecting more tissue when a negative surprise turns up in a section.

When it is remembered that most cases are selected for their diagnostic difficulty, it is safe to assume that the correspondence between frozen and paraffin reporting is high enough for the method to be used with confidence.

Sampling errors by the surgeon have not been included, as irrelevant to an analysis of validity of reporting; in practice they have been very infrequent.

There are very few normal or pathological tissues which are quite unsuitable for the method, though some are technically more difficult than others. Even tissue containing light spicules of bone can be cut (Special Plate, Fig. 8). Excellent preparations can be made from post-mortem tissues if fresh, and a frozen section may be very useful on occasion, particularly in a forensic case. For example, a 3-year-old infant died suddenly and unexpectedly, the only history being of rather vague joint pains. Gross changes at necropsy suggested rheumatic carditis, but were not definite. Frozen section of myocardium showed a typical Aschoff body (Special Plate, Fig. 10), and it was therefore possible to give an immediate explanation to the coroner and so to the bereaved parents. Special studies of frozen-section work on particular tissues have been made by some workers. They include prostate (Culp and McDonald, 1954), stomach (Jones and Bullock, 1954), skin (Mescon *et al.*, 1951), joints (Swift, 1936), and a recent analysis of breast lesions (Sandison, 1958). The type of tissue or anatomical site of the present material is given in Table III.

TABLE III.—*Tissue and Organs Examined in 188 Cases*

Breast	122	Ovary, uterus, and vagina ..	3
C.N.S.	17	Testis	3
Skin and subcutis ..	16	Stomach	2
Thyroid	6	Rectum	2
Lymph nodes	5	Bronchus	2
Peritoneum	4	Urinary bladder	1
Bone and joint	4	Parathyroid	1

Fully Recorded Series (147 Cases)

It would appear from Table IV that in 22.4% of 147 cases the frozen section was of some direct use (cf. Dockerty's (1952) estimate of approximately 20%). Apart from straight pathological diagnosis, this group includes special information such as limits of spread of a malignant tumour and tissue identification—for example, testicular tissue in a ? hermaphrodite ? cryptorchid.

TABLE IV.—*Macroscopic Tissue Diagnosis Compared with Frozen-section Diagnosis*

	Cases
Macro. and frozen the same	112 (76.2%)
„ doubtful or wrong, frozen diagnostic ..	33 (22.4%)
„ right, frozen wrong	2 (1.3%)

Some value in the fact of confirmation may be claimed for 76.2% of the group. It may, for example, be helpful with a very anxious patient or relative.

Brief Notes of Selected Cases

1. 1004/54. Lump in breast. Frozen section typical fibroadenoma with a small contiguous and partly enveloping carcinoma; very difficult combination to detect macroscopically.

2. 2522/55. Pigmented skin tumour, macroscopically ? malignant melanoma, ? sclerosing angioma. Frozen section, cellular tumour loaded with pigment. Iron stain on frozen section showed massive deposits of haemosiderin, distribution approximately similar to that in the H. and E. Diagnosis of sclerosing angioma given, confirmed in the paraffin section.

3. 885/46. ? diffuse carcinoma in lactating breast, the macroscopic appearances of the tissue at exploration tending to support this diagnosis. On frozen-section report of very inflamed lactating breast, a deeper incision was made into the mass and a large "artesian well" of an abscess found and drained.

4. 1495/56. Doubtful mass in breast. Macroscopic appearances very difficult to interpret. Frozen section—anaplastic carcinoma 1 cm. diameter, surrounded by zone of inflamed and degenerate breast tissue. Secondaries found in axillary lymph nodes in main specimen.

5. 1758/56. Needle biopsies for ? cerebral tumour. One of the biopsies showed inflamed degenerate brain tissue, as in the vicinity of a tumour. This indicated another burr-hole in a definite direction, and the biopsy through this contained a particle of astrocytoma (Special Plate, Fig. 5).

6. 1977/56. Intracranial tumour, clinically and radiologically; ? suprasellar meningioma, ? craniopharyngioma. Sella turcica normal. At operation the tumour was found to be a spherical dark-red mass which suggested the additional possibility of aneurysm. Frozen section of a needle biopsy showed chromophobe pituitary adenoma. In view of the radiologically normal sella the surgeon was rightly sceptical, but further dissection showed the broad pedicle of the tumour largely replacing the diaphragma sellae, and the growth was removed. Clearly the tumour had arisen very superficially in the pituitary and had grown straight up and out of the fossa.

7. 2584/56. Pigmented tumour of skin; ? angioma, ? malignant melanoma. Macroscopically the cut surface appeared solid and black, and minute streaks of pigment were visible, streaming away through the subcutis at the base and margins. There was no doubt in the minds of all those in the theatre that this was a malignant melanoma. Frozen section showed a cavernous haemangioma welded into a solid mass by gross recent and old haemorrhage, the streaking visible at the base being phagocytosed haemosiderin.

8. 2604/56. A girl of 19 with a tumour in the pituitary region; ? craniopharyngioma, ? pituitary adenoma. At operation the tumour was seen as a dark-red conical mass occupying the sella turcica and projecting straight upward. Frozen section reported as diagnosis uncertain; ? atypical pituitary adenoma, ? angio-endothelioma. The tumour was removed and the paraffin sections were equally difficult to interpret. The blocks were referred to the consultant panel in morbid histology (see above), and by a majority opinion the diagnosis was given as chemodectoma. Local recurrence about six months later, with clinical evidence of invasion of the cavernous sinus. Some improvement followed radiotherapy.

9. 825/56. Small lump in breast, clinically and macroscopically probably carcinoma. Frozen section—focal fat necrosis (Special Plate, Fig. 1).

Other Rapid Methods

Cytological methods are sometimes used on organized tissue by scrape, smear, or wet impress techniques. Personally I have found these methods inferior to the frozen section. Tumour diagnosis and classification is and will remain histological; that is to say that architecture, micro-anatomical relationships, and assessment of the biological property of invasiveness carry as much or more weight than cytological detail. If, therefore, a histological preparation is possible, it seems clearly wrong to use a method that disrupts these aspects of a lesion; and one that may have as much or more artifactual disadvantage (thick smears, distortion, and bursting of cells), and, if the specimen be small, may leave no material for paraffin histology. It is perhaps not widely appreciated that a specimen as unpromising as a needle biopsy of pathologically softened brain measuring 2 by 1 mm. can be adequately sectioned (fresh) by the frozen method and still leave

something to process at leisure. Without bearing in any way on the value of exfoliative or smear cytology in general, it is my view that, if a macroscopic piece of true organized tissue, however small, is available, the frozen section should have pride of place in the immediate diagnosis of tumours or other lesions (see also Carleton and Drury, 1957), although supplementary information on cell detail may be given by cytological methods (cf. Bamforth and Osborn, 1958).

Terry's method (Terry, 1928, 1929; Hellwig, 1935) consists in cutting a thin slice of tissue by razor, free-hand staining with neutralized polychrome methylene blue on one surface only, and relying on translucency to reveal a recognizable picture. In my view, again, it has only speed and ingenuity to recommend it; the preparations are inevitably far below the standard required for critical diagnosis.

Conclusions

Immediate histological diagnosis by frozen section is an old-established method of considerable value in surgically doubtful lesions. A good permanent haematoxylin-and-eosin-stained section 5–10 μ thick can be produced in from 7 to 10 minutes. In the present series of 188 consecutive cases reported in the theatre, the working validity of reporting as compared with the subsequent paraffin section has been about 97%. In five cases (2.7%) wrong diagnoses were made; of these, three (1.6%) were due to faulty sampling by the pathologist and only two (1.06%) were histologically misinterpreted. In addition there was one case in which the diagnosis was uncertain and the paraffin sections were equally baffling.

From full data recorded in 147 cases at the time, the information given to the surgeon has been of some direct use in one way or another in about 22% of cases. In about 76% of cases the frozen section may be said to have had confirmatory value.

The traditional criticisms of the method have not therefore been supported by the present analysis. These are that: (1) if the tissue diagnosis is difficult for the surgeon it will be as difficult for the microscopist; and (2) the risks in reporting in a hurry on an imperfect section are too high.

On the contrary, by settling the diagnosis in doubtful cases at the first operation, (1) the risk of metastasis is diminished, (2) the patient is spared the anxiety of waiting for a paraffin biopsy report, (3) the patient has one anaesthetic only, (4) the rare unnecessary radical operation is prevented, and (5) in brain tumour cases the amount of needling is reduced to a minimum and unnecessary craniotomy may be avoided in rapidly declining patients.

Few tissues, normal or pathological, are unsuitable for the method, and tiny fragments—for example, needle biopsies—can be reported on and still leave a residue for paraffin confirmation. Even tissue containing spicules of bone can be cut (Special Plate, Fig. 8). Where a piece of organized tissue could be produced, the method was found to be superior to other rapid methods of diagnosis.

In Dr. Shaw's days the time taken by the method was counted something of a disadvantage, but this is not so with modern anaesthesia. To-day, the average of 7 to 10 minutes required to produce a permanent section of good quality stained in the way that the pathologist sees daily adds nothing to the patient's risk.

Naturally, if the tissue diagnosis is obvious macroscopically, the surgeon will proceed straight away; it may, however, still be worth cutting a frozen section to give the grade of a tumour or to define the limits of spread.

Summary

The classical method of rapid histological diagnosis by frozen section of tissue from the theatre is reviewed and the data from 188 cases are analysed.

The method is found to be reliable, and useful in selected cases.

It is a pleasure to record my indebtedness to Mr. Hayward Cox, A.I.M.L.T., who cut the sections, took the photomicrographs, and also read the manuscript. I thank Dr. M. Hynes, Mr. R. S. Murley, Mr. L. C. Oliver, and Mr. A. Small for reading the draft and for many valuable suggestions; and Dr. H. Caplan, who, in addition to this, reported five of the cases. My thanks are due to Sir Bentley Purchase for permission to include one case. I am obliged to Mrs. H. M. Page for secretarial help.

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THE CYANOTIC (SYNCOPIAL) ATTACK IN FALLOT'S TETRALOGY

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Patients with Fallot's tetralogy are prone to attacks of increased cyanosis, with associated loss of consciousness ("cyanotic or syncopal attacks"; "anoxic spells"). These patients may recover spontaneously from the attacks, but fatalities are known to occur. A history of syncopal attacks makes corrective surgery, or if this is not feasible systemic-pulmonary arterial anastomosis, an urgent necessity.

The mechanism of the attack was not definitely known until recently. Wood (1958) has shown that it may be precipitated by increased obstruction to the flow of blood through the right ventricular outflow tract into the pulmonary artery, with increased shunting of deoxygenated blood into the aorta.

We have recently had the opportunity of studying a cyanotic attack occurring during the course of cardiac catheterization. The mechanism of production of the attack as described by Wood was confirmed. The problem of management of the attack gave rise to anxiety, and several forms of therapy were tried, with varying success.

G. W. WATSON AND R. L. TURNER: BREAST CANCER

FIG. 1.—Metastasis in humerus before (left) and after (right) treatment.

FIG. 2.—Ulcerated skin metastasis before (left) and after (right) treatment.

FIG. 3.—Early (left) and late (right) cytological effects of treatment.

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FIG. 1

FIG. 2

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FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIG. 9

FIG. 10