THE IDENTIFICATION OF NEOPLASTIC CELLS IN SEROUS EFFUSIONS

CRITICAL ANALYSIS OF SMEARS FROM 2,029 PERSONS*

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The cytologic examination of sediments of serous exudates and effusates is of distinct value in confirming or disproving the presence of cells originating in malignant tumors metastatic to the cavities in which these effusions have formed. Only for mesothelial or synovial tumors could there be any hope of early detection of a primary growth and, since such tumors occur rarely and are seldom if ever recognized as mesothelial by the cytologist, the method is thus limited comparatively to the detection of cells from metastatic tumors. The determination of conditions other than neoplastic (such as cirrhosis or congestive heart failure) is very important, however, in averting unnecessary operative procedures; thus the method is of more value in connection with prognosis than it is with early diagnosis and prevention of further growth.

Methods of Cytologic Examination

There are two techniques for the demonstration of cells for cytologic examination: the conventional Papanicolaou smear and the "cell-block" method. In the former the sample of sediment is smeared over a glass slide and immediately fixed in alcohol and ether in equal proportions; in the latter procedure it is fixed in the centrifuge tube by any desired fixing fluid and forms a button of compacted, fixed cells which may then be removed and embedded in paraffin like any piece of tissue. The resulting block may be sectioned and stained as desired. In many laboratories a portion of the sediment is first removed and used for the preparation of smears while the remainder, if relatively undisturbed, is reserved for blocking. If it has been much disarranged by this manipulation, it may be necessary to repack the cells by further centrifugation.

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Comparison of the Two Methods

In a smear most of the cellular elements are spread out and discretely separated, while in the cell-block they lie closely apposed. Thus, the smear is preferable for detailed cytologic study and the cell-block for rapid evaluation of the cellular population of the sediment. The contrasting appearance of the resulting microscopic pictures is shown in Figures 11 and 13 to 16. While cell-blocks have much to offer and should be employed as a routine procedure, practically all of the diagnoses concerned in the present investigation were made on smears, as it is the policy in the Papanicolaou Laboratory to rely solely upon such examination and cell-blocks are not prepared. From past experience, however, it seems to be generally advisable to use both techniques and to check the results of the examination of one against those of the other. Cell-blocks are particularly valuable in ruling out non-neoplastic conditions like hepatic cirrhosis and congestive heart failure as causative factors in the production of the cells observed. Comparison of each cell with its fellows is all-important and when the cells are closely packed in an optical field, this is more readily accomplished than when they are widely dispersed in the smear. Having thus stated the case for the cell-block, which I have found to be practical and reliable in earlier investigations[1] and therefore wish to commend, it will not be discussed further in this paper, which deals with results obtained wholly from smears.

Recognition of Neoplastic Cells

There is little that is really difficult about recognizing cells from malignant tumors in smears, provided that they are abundant and characteristically abnormal. The classic criteria of malignant change in cells are too well known to require restatement here. The presence in smears of fragments of tumor or of clusters of neoplastic cells is very helpful and may be decisive in arriving at a diagnosis. While non-neoplastic cells also may form clusters, they tend to be closely apposed within the group and not loosely applied and somewhat set off or spaced as are those of neoplastic origin. This feature has been noted and stressed by Koss.[2] When, however, the cells are few and ungrouped, the normal mesothelial lining elements can be very misleading, particularly so if they have undergone metaplasia in response to inflammatory stimuli. These cells and the histiocytes require careful study and familiarity so as to provide the cytologist with normal

standards before he attempts the diagnosis of neoplastic elements. A recent and excellent article by Luse and Reagan[3] will be found to be very helpful in supplementing such a study. Their material represented the examination of sediments from fluids from some 1,000 patients; I have just completed the investigation of smears from 2,029 consecutive cases, taken from the files in our laboratory, and have found that the results of this review compare favorably with theirs.

Report on the Investigation of 2,029 Specimens

The 2,029 cases investigated furnished more than five times that number of smears, each of which was studied with sufficient care to afford definite conclusions as to the presence or absence of cancer. They had all been screened by the laboratory staff, suggestive fields had been marked with ink-dots, and they had been reviewed and reported upon by senior cytologists. While the staff had cognizance of the clinical data on the cases concerned, mostly well documented, I preferred to examine the smears without knowledge of the histories of the patients, believing that subjective reasoning and bias might be eliminated when nothing was known except the serial number of the specimen. Examination of the smears was focussed largely upon the marked fields and entire smears were seldom scanned systematically as were those reported upon in a previous article[4] dealing with the identification of the site of origin and type of tumor.

Sources of the Fluids Examined. The material comprised specimens of sediments of fluids from the pleural (1,301), peritoneal (700), pericardial (28), and articular cavities (17); three taken from hydrocele sacs made up the total of 2,049 which, as it will be seen, exceeds that of the cases examined by 20. This is explained on the basis that specimens of more than one type of fluid (e.g., pleural *and* peritoneal) sometimes were sent in from the same patient. Most of the sets of smears represented a single submittal from a single cavity, but several of them comprised a series of taps made at intervals on several successive dates, often four or more. All of these were examined and compared; oftentimes cells that were noted and suspected in early specimens disappeared from later ones, demonstrating the advisability of submitting several successively obtained specimens whenever possible. It was the pleural and peritoneal fluids that were of chief interest in this investigation; only one of the pericardial specimens showed cells from a malignant tumor while those from

joints and hydrocele sacs were all negative. Table I shows the distribution of the specimens.

Specimens Positive for Cancer. There were 610 positive diagnoses, or 30.1 per cent of the specimens. As will be explained later, a subsequent revision of the false positive diagnoses among these, made

TABLE I
Types of Fluids Examined

	Pleural	Abdominal	Pericardial	Synovial	Hydrocele	Total
Number	1,301	700	28	17	3	2,049
Per cent	63.5	34.2	1.4	0.8	0.1	100

in the light of knowledge of the source of the fluid, the clinical history, the sex and age of the patients concerned, and experience accumulated during the course of the examination, cut this total from 610 to 583 (30.1 to 28.8 per cent). Positive cases were rated Class IV or V.

Specimens Doubtfully Positive for Cancer. Doubtfully positive (Class III) diagnoses totalled 451, or 22.2 per cent. This rather high figure may be attributed to ignorance of clinical data, which would conduce to doubt and some skepticism in grading the smears. For example, if it were known that a given specimen was peritoneal fluid from a man of 50 years who was suffering from chronic alcoholism and suspected of having hepatic cirrhosis, the diagnosis of possible carcinoma, while not excluded, would at least be more unlikely after the smears had been examined and analyzed. The revision of false positive diagnoses, already referred to, did not affect the total of Class III reports.

Specimens Negative for Cancer. Negative diagnoses totalled 968, or 47.7 per cent. After revising the false positive diagnoses, this figure was increased to 995, or 49.0 per cent.

Table II presents the distribution of these diagnoses.

TABLE II
Distribution of Diagnoses in Cases Examined

	Positive	Doubtful	Negative	Total diagnoses
Number	610	451	968	2,029
Per cent	30.1	22.2	47.7	100
After revising false positive diagnoses				
Number	583	451	995	2,029
Per cent	28.8	22.2	49.0	100

REMARKS ON POSITIVE DIAGNOSES

Validity of Positive Diagnoses

Of the 610 positive diagnoses, 434, or 71.1 per cent, were subsequently confirmed by reliable data such as necropsy, biopsy, or incontrovertible clinical evidence. Ninety-four, or 15.4 per cent, were unconfirmed. These 94 patients were found to be chiefly in the private practice of physicians or from hospitals beyond our range of ready "follow-up." The bulk of the material, however, came from New York, Memorial, or Bellevue Hospitals and was reliably documented. As the matter of false positive diagnoses is the most significant and important part of this report, it will now be discussed at length.

Special Consideration of False Positive Diagnoses

The decision as to whether a given diagnosis was true or false rested upon the final discharge diagnosis of the hospital involved in the care of these patients; this was the only practical way in which the reports could be standardized. Such discharge diagnoses were almost always based upon reliable data, as defined; there was a small minority (about 10 per cent) in which the discharge diagnosis was open to question. Where the cytologic findings seemed to be strongly at variance with these diagnoses, there was room for doubt; the opinion of the cytologists may have been right and the general impressions of the clinicians wrong.

After determining the false positive reports in this way, a careful review of the smears involved was carried out in an attempt to learn the reason for the errors. If, after reviewing the data on the case together with the smears, a patient's smears no longer appeared to suggest the presence of tumor, that case was transferred from the positive to the negative column and appropriate adjustment was made in the totals. Even after this re-evaluation there were several instances in which the original (false) positive findings could not be altered with a clear conscience—the smears appeared to be just as menacing on review as they had been originally. In such cases it is possible that the discharge diagnoses were, in reality, "false negatives." For example: A patient was diagnosed as having a pleural effusion positive for cancer, but necropsy determined that death was due to pulmonary tuberculosis with pleuritis. It may seem presumptuous to suggest that a small bronchogenic carcinoma may have coexisted with tuberculosis and, because of its diminutive size, may have been undiscovered in a lung that was riddled with tuberculous lesions. Such difficulties have developed on occasion.[5] This review revealed that

hepatic cirrhosis, congestive heart failure, and tuberculosis were the conditions most frequently misdiagnosed as malignant tumor by the cytologist.

Cirrhosis. Seventeen mistakes were made in diagnosing cirrhosis; after review, 13 smears were judged to be negative, but the other 4 still appeared to warrant a positive diagnosis of malignant tumor; were these 4 to be resubmitted as presumably new specimens, they would still be considered positive. Figures 1, 3, 11, and 13 illustrate the pitfalls that exist in diagnosing this condition. How can these be overcome? It was found that the mesothelial cells in the smears were almost always to blame for such mistakes. Histiocytes sometimes were troublesome also. Both of these cell-types can be recognized by their uniformity in shape and size (though this may vary in histiocytes) and by their low "n/N ratio" (obtained by dividing the diameter of the nucleolus by that of the nucleus, as proposed by Quensel[6,7]). I found this procedure to be helpful when making a similar investigation in 1937.[1] The n/N ratio of non-neoplastic cells usually lies between 0.15 and 0.20, while that of neoplastic cells ranges between 0.25 and 0.40. After acquiring experience while making these measurements, it becomes possible to estimate the ratio with sufficient accuracy to establish the diagnosis without resorting to the ocular micrometer.

Cells in cirrhotic ascitic fluids show low n/N ratios; they tend to be grouped in tightly integrated clusters which may be ovoid, or may have a close resemblance to epithelial pearls. They may even produce rosette-like groups or pseudo-acini, as has been shown in the article of Luse and Reagan.[3] They are illustrated in Figures 1, 3, and 11 of the present article. They often are found in mitotic division, but the figures are normal and delicate, rather than coarse and disorderly. Under the stimulation of inflammation, the karyosomes may become misleadingly coarse and overstained, while the cytoplasm may show extensive vacuolization and resemble that of the signet ring cells of mucous carcinoma. Mesothelial cells can be avidly phagocytic, particularly in the presence of pus.

Histiocytes may become large and comparatively dense, and their nuclei may undergo some metaplastic thickening and hyperchromasia.

Congestive Heart Failure. Congestive heart failure produces similar fluid sediments and hence there is confusion similar to that caused by cirrhosis. There were 13 false positive diagnoses in this group which, after revision, were reduced to 5. The cells presented in slightly smaller numbers than they did in the ascitic fluids, a fact that

increased the difficulty in diagnosis. Here again it is a matter of carefully studying the nuclear characteristics and paying due attention to the n/N ratio.

Tuberculous Inflammation. There were 12 false positive diagnoses on fluids which proved to be tuberculous rather than neoplastic in origin. Revision reduced this number to 6. It should be emphasized that lymphocytes are often very numerous in tuberculous exudates, leading to a misdiagnosis of lymphoma. The mesothelial cells are dense and substantial and the histiocytes take on their familiar epithelioid appearance, all of which makes for difficulty in decision. Langhans giant cells are present to be sure, Luse and Reagan[3] having found them in 11 per cent of their tuberculous fluids, but as they noted them also in 32 per cent of cirrhotic effusates and in 31 per cent of those resulting from congestive heart failure, such giant cells cannot be said to offer much assistance in diagnosis.

Lupus Erythematosus Disseminatus. There were 3 cases of disseminated lupus in this series, one of them falsely diagnosed as malignant tumor. A study of the smears revealed large numbers of cells that appeared more histiocytic than mesothelial ("L. E. cells"). They had a rather denser cytoplasm than did histiocytes and their nuclei were irregularly elongated, lobulated, or multiple and somewhat resembled those of Reed-Sternberg cells. They were seldom conspicuously vacuolated.

Negative Cases Contrasted with False Positives

Were we to drop the topic of false positive diagnosis at this point, a misleading impression might be created. The question arises: How many of these borderline and difficult diagnoses were correctly made in the course of the study? Thus far we have been concentrating on errors; how about the successful diagnoses? Tables III and IV present the results obtained in connection with false positives (Table III) and the revision of these combined with a tabulation of correct diagnoses of the troublesome conditions just discussed (Table IV). The former table is self-explanatory; in Table IV the conditions are listed in the left-hand column, next come the total number of cases studied, and then the number and percentage of those correctly diagnosed. The column labelled UFP lists the number of unrevised false positives and is followed by their percentage of total cases. The next column presents the revised false positive diagnoses (RFP) by numbers and is followed by percentages of totals. Finally, the changes

brought about by the revision are set down by number and percentage of total cases.

Of 113 cirrhotic ascitic fluids, 96 were correctly diagnosed as non-neoplastic, or 85 per cent; the other conditions showed less accuracy in diagnoses and fell in the 60 to 65 per cent range. Study and revision, however, were fruitful and there was a 20 per cent reduc-

TABLE III

Comparison of Types of Positive Diagnoses

	Confirmed	Unconfirmed	False	Total diagnoses
Number	434	94	82	610
Per cent	71.1	15.4	13.5	100
After revising false positive diagnoses				
Number	434	94	55	583
Per cent	74.4	16.1	9.5	100

TABLE IV

Analysis of Correct Negatives and False Positives

	Total	CN	% Tot.	UFP	% Tot.	RFP	% Tot.	Ch.	% Tot.
Cirrhosis	113	96	85.0	17	15.0	3	2.6	14	12.5
Congestive heart failure	34	21	62.0	13	38.2	5	14.7	8	23.5
Tuberculous inflammation	31	19	61.0	12	39.0	6	19.4	6	20.0
Pulmonary infarct	13	8	61.5	5	38.5	5	38.5	0	0.0
Pleural effusion	5	4	80.0	1	20.0	1	20.0	1	20.0
Lupus erythematosus disseminatus	3	2	66.6	1	33.4	1	33.4	0	0.0
*Pneumonia	2	2	100.0	0	0.0	0	0.0	0	0.0
Totals	201	152	75.6	49	24.4	21	10.4	29	14.4

* Pneumonia included in this list because of mistaken diagnosis on two cases in laboratory reports. CN=correct negatives; % Tot.=percentage of total given in column 1; UFP = unrevised false positives; RFP = revised false positives; Ch. = change.

tion in false positives in congestive heart failure and tuberculous inflammation. Pulmonary infarct, however, was unchanged by the revision. It remains a very troublesome condition as it produces highly metaplastic mesothelial cells. It should be pointed out that the false positive diagnoses, when reckoned in percentages, apply only to the conditions listed in the table and not to the series as a whole, in which they were far lower.

The results just discussed apply only to the diagnoses on a selected

series of troublesome, non-neoplastic conditions. When we consider the whole series of 2,029 cases, there are 13.5 per cent false positive diagnoses before the revision and 9.5 per cent after it. This shows improvement over the figures obtained during an examination of cell-blocks in 1937[1] in which correct positive diagnoses ranged from 65 to 70 per cent, according to the nature of the sediments examined.

REMARKS ON DOUBTFULLY POSITIVE DIAGNOSES

All Class III diagnoses were reviewed and compared in order to ascertain how many of the patients whose fluids were thus graded actually had cancer and how many did not. Clinical data on these patients were difficult to obtain, as the staff was more apt to collect and to check data with definitely positive or negative, rather than doubtfully positive diagnoses. Of the 451 Class III diagnoses, 135 were found to apply to patients who had proved carcinoma (30.0 per cent). There were 238 diagnoses that could not be effectively documented and on patients proved to be non-cancerous there were 100, or 22.2 per cent.

DEGREE OF AGREEMENT IN DIAGNOSIS WITH LABORATORY STAFF

It would be quite natural for the reader to be curious as to how my diagnoses compared with those of the laboratory staff, which comprised several screeners and cytologists, the make-up of the personnel varying over the decade covered by the investigation. Reference to Table V will show that the degree of agreement has been

TABLE V

Degree of Agreement in Diagnosis with Laboratory Staff

	Complete agreement	Technical disagreement	Essential agreement	Definite disagreement	Total diagnoses
	A	B	C	D	
Number	1,368	503	1,871 (A+B)	158	2,029
Per cent	67.4	24.8	(92.2)	7.8	100

entered in four columns under the headings complete agreement, technical disagreement, essential agreement, and definite disagreement. Two of these terms need no elucidation. Technical disagreement is an expression that implies a difference in the exact class allotted to the final diagnosis without indicating serious divergence in meaning. If a fluid graded Class II by the staff were to be rated Class III by me, this would be a technical disagreement since a rather

fine shade of interpretation may have swung the balance one way or the other. In the first instance the staff, unwilling to suspect the presence of tumor on the basis of their evidence, issues a Class II diagnosis; in the second, I am unwilling to overlook certain dubious aspects of the smears and, disinclined to concede that the presence of tumor has been entirely ruled out, issue a Class III diagnosis. In contrast to this, a Class II diagnosis that implies the absence of cancer is so widely at variance with one of Class IV, which indicates good evidence of its presence, that the divergence of opinion should be listed as definite disagreement.

Complete agreement was attained in 1,368 (67.4 per cent) of the diagnoses before the revision; technical disagreement was noted in 503 (24.8 per cent) and definite disagreement in 158 (7.8 per cent) of the series. If it be permissible to combine the columns of complete agreement and technical disagreement under the heading of column C, which is essential agreement, there would be a 92 per cent agreement in diagnosis between the staff and me, which is excellent. Since I worked in ignorance of any data except the serial number of the smear, this is very close agreement and the figures indicate the comparative values of examinations that are purely objective and those in which subjective data are adduced in making the diagnosis.

RESULTS OF RAPID DIAGNOSIS OF TYPE AND SITE OF ORIGIN OF TUMORS

In view of the fact that I published an article on the rapid diagnosis of type and site of origin of tumors 2 years ago,[4] it was of interest to ascertain how accurate a determination of the types and original sites in the present series could be made in a cursory fashion while examining a far larger number of smears with the primary purpose of diagnosing the presence of tumor. In the former investigation only Class IV smears were examined; they were very carefully studied, considerable time being devoted to each smear. In the present work all fluids (irrespective of their grades) were examined rapidly to determine the presence or absence of tumor. The results in this examination were so disappointing that it became evident that such determinations can be carried out with reasonable accuracy only when considerable time and study can be devoted to each smear. Diagnoses of the probable type and site of origin of all tumors observed in the course of this present investigation were listed and analyzed, but the final results were too mediocre to warrant further discussion or publication.

SUMMARY

The examination of cells in serous effusions is of distinct value in confirming or ruling out suspicions of tumor. It does not assist in the early detection of malignant growths, since these are already far advanced when cells are exfoliated into these effusions. Mesothelial cells and histiocytes present the chief stumbling-blocks in the interpretation of smears or sections of cell-blocks, as they may be confused readily with cells shed from malignant tumors after they have undergone metaplasia attributable to inflammatory, rather than neoplastic stimuli. The determination of the types of tumors found in smears of these fluids as well as their probable site of origin is possible only after special and rather prolonged study of each smear. Cursory examinations such as suffice for the assignment of a class or grade to a smear will not suffice to establish the more subtle features just mentioned.

So far as accuracy in diagnosing the presence or absence of malignant tumor in smears of serous fluids is concerned, of 610 positive diagnoses 434, or 71.1 per cent, were confirmed by reliable data, such as necropsy, biopsy, or incontrovertible clinical evidence. Among the 610 positive diagnoses, there were 82 that were proved to be false; revision of these diagnoses, made with the aid of further study and reference to the clinical data which were unknown during the original examination, reduced the total to 55, or 9.5 per cent, which is not excessive. This revision also reduced the total of positive diagnoses from 610 to 583, or 28.7 per cent of the total series compared to the original 30.1 per cent. There were 968 negative reports, which were increased to 995 by this revision; or 47.7 per cent increased to 49.0 per cent. The comparatively large percentage of positive reports in this series is attributable to the fact that the fluids sent in for appraisal came from patients suspected of harboring malignant tumors, rather than from those merely plagued with effusions. A comparison of my diagnoses with those of the members of the staff demonstrates a very satisfactory degree of agreement. Complete agreement existed in 67.4 per cent of the diagnoses, essential agreement in 92.2 per cent; this is discussed fully in the text of this paper.

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LEGENDS FOR FIGURES

All photomicrographs were taken by Mr. Constantine Railey at a magnification of × 600.

FIG. 1. Cluster of mesothelial cells from sediment of ascitic fluid in cirrhosis. Double contour suggested.

FIG. 2. Concentrically arranged cluster of mesothelial cells in which double contour is clearly evident.

FIG. 3. Mesothelial cells from ascitic fluid in a case of cirrhosis; both laboratory staff and I were misled into a false positive diagnosis by the metaplasia present in these cells.

FIG. 4. Metaplastic mesothelial cells from a fluid from a patient with tuberculous pleuritis. Double contour may be noted.

FIG. 5. Multinucleated and highly metaplastic cell from a fluid of undiagnosed causation. Discharge diagnosis: "Amyloidosis of skin and kidneys." Laboratory staff and I both classified this as Class V.

FIG. 6. Extraordinary cells, from sediment of pleural effusion, diagnosed by both laboratory staff and myself as Class V. Discharge note: "No tumor demonstrated at thoracotomy." This does not disprove that a tumor might have been overlooked.

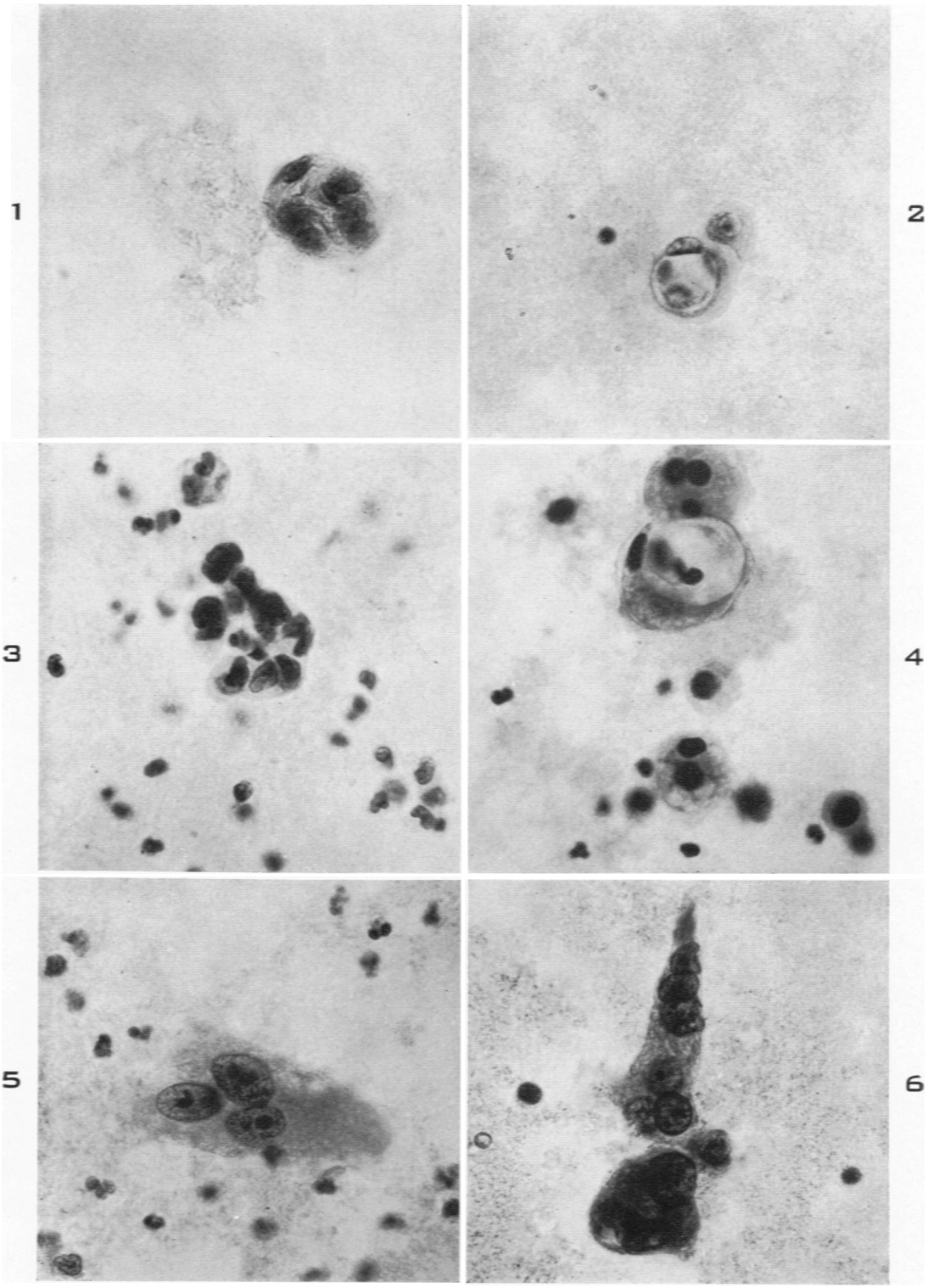
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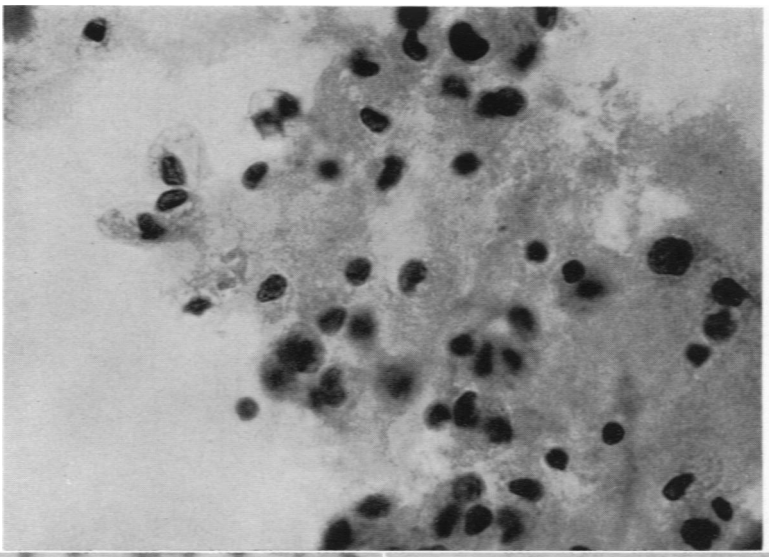
FIG. 7. Histiocytes in a pleural effusion, diagnosed as Class I.

FIG. 8. Metaplastic mesothelial (?) cells from exudate in empyema. Acute inflammation often causes this metaplasia and resulting confusion in diagnosis.

FIG. 9. Histiocytes from a peritoneal effusion, diagnosed as Class I.

FIG. 10. Concentric cluster of probable histiocytes; the cytoplasm is clear and transparent, the cellular outline is indistinct. Not suggestive of neoplastic origin.

FIG. 11. Two vacuolated mesothelial cells and some histiocytes from a smear of sediment of ascitic fluid in cirrhosis.



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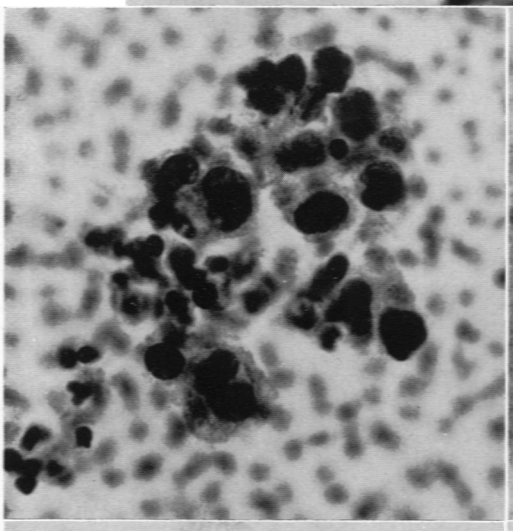

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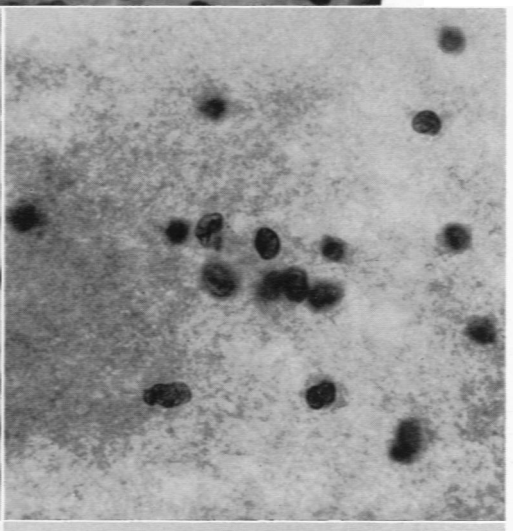

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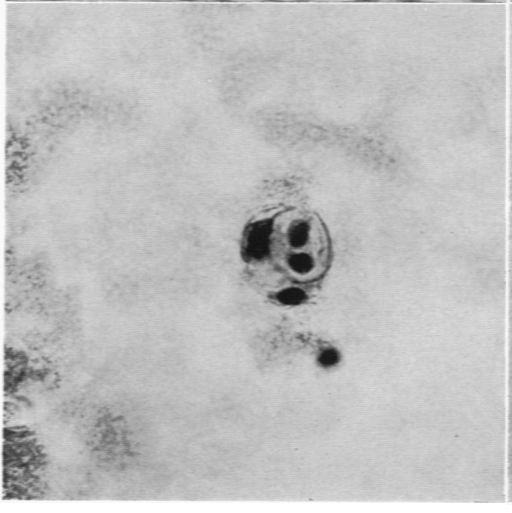

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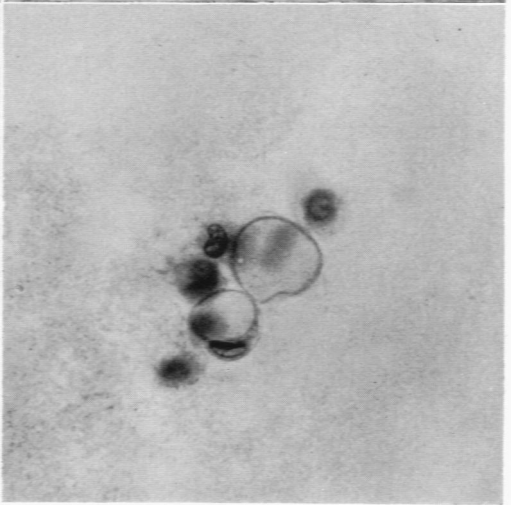

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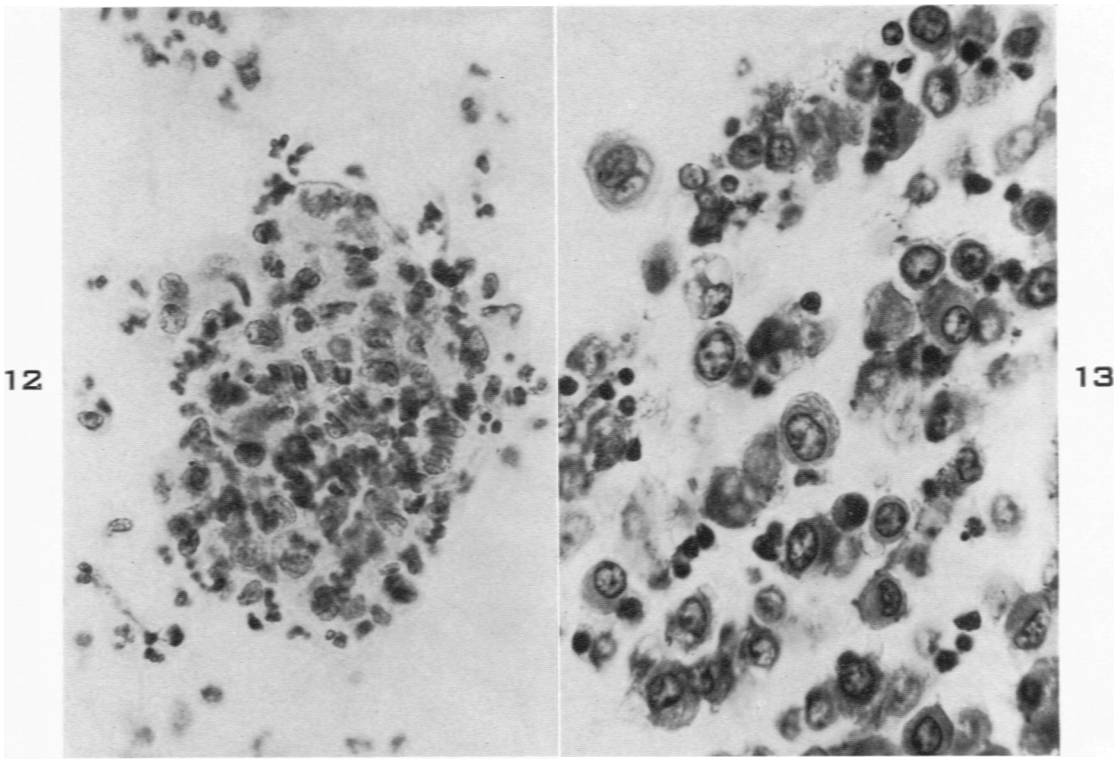

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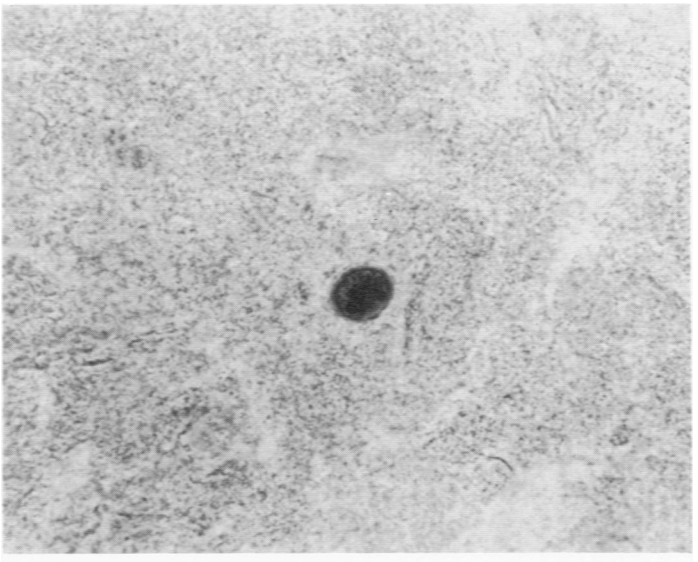
FIG. 12. Large cluster of probable "L.E. cells" from pleural effusion in lupus erythematosus disseminatus. Nucleoli are small and not prominent.

FIG. 13. Section of a cell-block prepared from the same fluid as that shown in Figure 11, for comparison with that figure. While metaplastic, these cells show small nucleoli and a low nucleolar-nuclear ratio. (See text.)

FIG. 14. Completely isolated cell from an ovarian carcinoma in smear of sediment from a pleural effusion.

FIG. 15. Field at periphery of section from cell-block made from the same sediment. Although neoplastic cells are still sparsely represented, several of them are congregated in this microscopic field, rather than just one.

FIG. 16. Section from a cell-block of sediment of fluid from a case of pseudomucinous adenocarcinoma of ovary. There is a rosette-like arrangement of the neoplastic cells. Unfortunately this characteristic picture is not regularly present in cases of ovarian carcinoma. (Cf. Fig. 15.)



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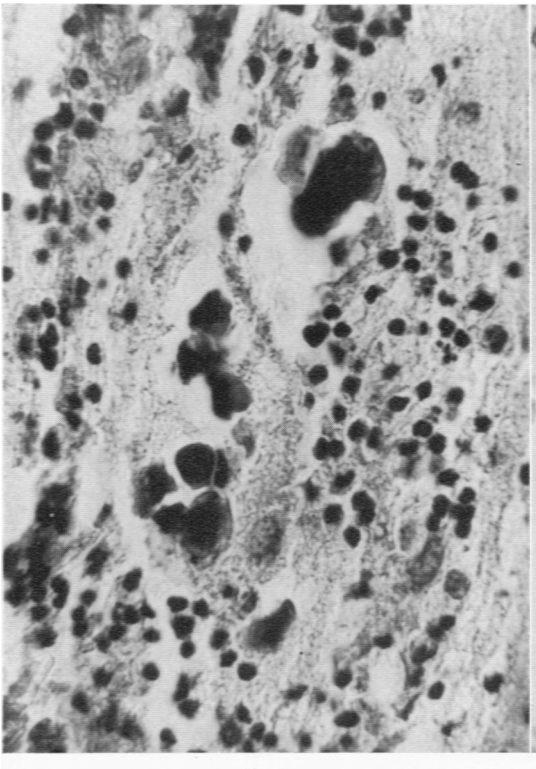

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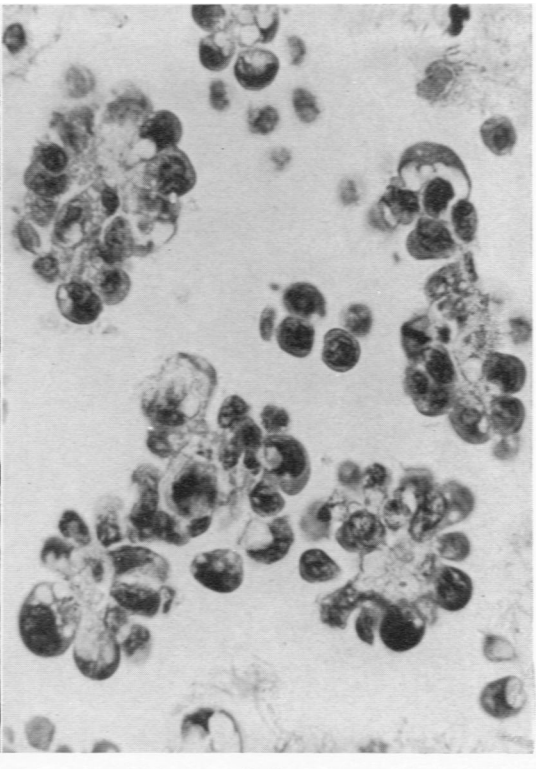

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