Mycosis Fungoides: The Pathology of Extracutaneous Involvement

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A survey of the autopsy material of 45 clinically and histologically typical cases of mycosis fungoides (M.F.) revealed extracutaneous involvement in 32, or 71%. The lymph nodes showed diagnosable M.F. in 24 of these 32 cases. Viscera most commonly involved were, in order of decreasing frequency: lung, spleen, liver, kidney, thyroid gland, pancreas, bone marrow, and heart. Practically all organs and tissues of the body were found to be involved. Lesions of the lymph nodes and viscera have a characteristic, if not a specific cellular composition which closely resembles that of cutaneous lesions. The neoplastic cells are of lymphocytic origin. Among them, the hyperchromatic mycosis cells and the cells with convoluted, deeply indented, and cerebriform nuclei have considerable diagnostic value. They are usually essential for the differentiation of the cellular proliferation of M.F. from those of other malignant lymphomas. Mycosis fungoides is a pathologic as well as a clinical entity; the neoplastic cellular proliferation in both cutaneous and extracutaneous tissue is distinct and different from those of other lymphoid and histiocytic neoplasms which usually arise in extracutaneous sites, but occasionally also in the skin.

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The literature contains conflicting reports and views on several aspects of mycosis fungoides (M.F.), including the precise position of the disease in the general schema of malignant lymphomas and the incidence of involvement of extracutaneous sites. It is agreed by most, if not all observers that M.F. invariably arises in the skin, that it either is or has the propensity to become a malignant neoplastic disease, and that a certain proportion of patients eventually develops lesions in the lymph nodes and viscera. However, when we reviewed many of the reports on extracutaneous involvement, it was difficult to find convincing documentation of the claim that M.F., when it spreads to extracutaneous sites, often or always undergoes transformation into "reticulum cell sarcoma, lymphosarcoma, or Hodgkin's disease." We found it equally difficult to establish whether or not all cases included in a given series were, in fact, M.F., and whether some may not have been other forms of malignant lymphoma cutis. Finally, we could not reconcile reports by some authors who stated that extracutaneous involvement in M.F. is rare, particularly in the classical ("Alibert") form, with reports of others that it is common. We undertook the present study in order to: 1) establish the incidence of extracutaneous involvement in M.F., 2) describe the histopathologic features of this disease in the lymph nodes and viscera, and 3) determine whether the extracutaneous lesions are sufficiently characteristic to be distinguishable from other malignant lymphoid neoplasms that can be readily classified.

Materials and Methods

This study is based upon 45 autopsied patients with M.F. These were admitted to the Clinical Center of the National Cancer Institute between January, 1955 and March, 1965, and are part of a group of 144 patients with M.F. who were studied at the NCI between 1954 and 1969. A report on the clinical features and the followup data to January 1, 1971 has been published elsewhere. In order

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to be included in this study, the patients had to meet the following criteria: 1) their disease had to be clinically characteristic of M.F.; 2) skin biopsy sections had to be diagnostic of or consistent with M.F.; and 3) the postmortem sections had to be available for review.

The clinical appearance of the skin lesions is listed in Table 1. None of the patients in this series presented with the clinical picture of M.F. d’emblée.

All but one of the skin biopsies were reviewed by the authors. This was done without recourse to the clinical data, autopsy protocol, or autopsy sections. The biopsies were classified under two categories: 1) cutaneous infiltrate diagnostic of M.F., and 2) cutaneous infiltrate consistent with M.F. Multiple skin biopsies were sometimes necessary to establish one or the other of the above diagnoses.

### Table 1. Clinical Appearance of Skin Lesions in Mycosis Fungoides

<table>
<thead>
<tr>
<th>Initial skin involvement (clinical description)</th>
<th>No. of patients</th>
<th>Terminal skin involvement (autopsy observation)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple or generalized skin lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red and/or scaly pruritic eruption</td>
<td>12</td>
<td>Tumors and ulcers</td>
<td>11</td>
</tr>
<tr>
<td>Dermatitis, neurodermatitis</td>
<td>5</td>
<td>Few infiltrates, no ulcers</td>
<td>1</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>4</td>
<td>Tumors and ulcers</td>
<td>2</td>
</tr>
<tr>
<td>Psoritc rash (papular, urticarial, plaque-like)</td>
<td>5</td>
<td>Crusted and eczematomid lesions</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>9</td>
<td>One cm patch beneath lt. breast</td>
<td>1</td>
</tr>
<tr>
<td>Pruritic dry, scaly skin</td>
<td></td>
<td>Tumors and ulcers</td>
<td>7</td>
</tr>
<tr>
<td>Small, red, nontender elevated spots</td>
<td></td>
<td>Moderate erythematos, slightly infiltrating</td>
<td></td>
</tr>
<tr>
<td>Nodular eruption</td>
<td></td>
<td>nonscaling dermatosis</td>
<td></td>
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<tr>
<td>Erythematous macules and nodules</td>
<td></td>
<td>Tumors and ulcers</td>
<td>4</td>
</tr>
<tr>
<td>Spontaneously regressing sores</td>
<td></td>
<td>Vitiligo</td>
<td>1</td>
</tr>
<tr>
<td>Eczema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Rash,&quot; type not specified</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pruritus and erythema</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Generalized erythroderma</td>
<td></td>
<td></td>
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<tr>
<td>Single skin lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>10</td>
<td>Tumors and ulcers</td>
<td>8</td>
</tr>
<tr>
<td>Small, pruritic elevation (rt. thigh)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small, red, slightly scaly spot (rt. forearm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing dryness and scaling (calf, over site</td>
<td></td>
<td>Diffuse petechiae and ecchymoses</td>
<td>1</td>
</tr>
<tr>
<td>Ulcerated, erythematous, circinate lesion (rt.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>foot)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Scaly lesion, 1 cm in diameter (rt. thigh)</td>
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<td></td>
<td></td>
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<tr>
<td>Scaly, pruritic lesion (rt. calf)</td>
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<tr>
<td>Erythematous, pruritic plaque (lt. buttock)</td>
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<td></td>
<td></td>
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<tr>
<td>Psoriasis (lt. ankle)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flat red area (lt. thigh)</td>
<td></td>
<td>Diffuse petechiae and ecchymoses</td>
<td>1</td>
</tr>
<tr>
<td>Pruritic, red, slightly raised annular ring (lt.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>calf)</td>
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dermal infiltrate, often in the form of circumscribed clusters, the so-called Pautrier microabscesses (Fig. 2).

3. The presence in the dermal infiltrate of so-called mycosis cells which, according to Lever,35 “differ from histiocytes by having larger, more irregularly and more deeply staining nuclei,” and which we would describe as cells having hyperchromatic, often irregular and deeply indented nuclei (Fig. 3). These are larger than the nuclei of the predominating atypical lymphoid cells in the M.F. infiltrate. In skin biopsies, hyperchromatic mycosis cells were uncommon; they were found as a supportive microscopic feature in cases where the histologic picture would have been diagnostic even without them. However, they were often indispensable for the recognition of M.F. in visceral lesions obtained at autopsy, where their presence greatly assisted in the differentiation between M.F. and other malignant lymphomas.

The descriptions of cutaneous M.F. in the literature contain frequent references to a polymorphous cellular dermal infiltrate that

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**Fig. 1.** Skin (biopsy). A cellular infiltrate involving the dermis extends to the basement membrane of the epidermis. A Pautrier microabscess is evident in the epidermis (H & E, x106, reduced from 130; Acc. No. S64-2574).

**Fig. 2.** Same section as in Fig. 1. Pautrier microabscess at high magnification. Note the infolding of the nuclei of the neoplastic cells. There is no basement membrane between the cellular aggregates and the epidermal cells (H & E, x1000).
consists, in addition to the abnormal lymphoid cells, of a variety of nonspecific inflammatory elements such as normal-appearing lymphocytes, plasma cells, histiocytes, and mature eosinophilic granulocytes. We did not consider the presence of such cells to be an essential feature for the diagnosis of M.F., however, since they probably represent a host reaction to the neoplastic proliferation. Great variations in the type and abundance of these inflammatory cells were encountered particularly for eosinophils; this was less true for plasma cells and least for normal-appearing lymphocytes. Histiocytes were usually present in small to moderate numbers. Inflammatory cells were either scarce or lacking in biopsies obtained at the tumor stage.

Among the diagnostic criteria for cutaneous M.F. we have listed Pautrier microabscesses, which were found in at least one skin biopsy in 29 of 44 patients of whom slides were available for review by the authors. We consider these “microabscesses” as highly characteristic, if not pathognomonic of M.F. Van Scott and Haynes are of the same opinion, and Lever considers them “almost pathognomonic.” The only statement to the contrary which we were able to find in the literature was contained in a report on reticulum cell sarcoma of the skin by Kim, Winkelmann, and Dockerty. These observers found Pautrier microabscesses in 4 of 16 cutaneous reticulum cell sarcomas which were not preceded by the clinical picture of M.F.; they pointed out that “microabscesses of the Pautrier type are neither pathognomonic of nor limited to M.F.” Although we cannot exclude the possibility that Pautrier microabscesses may occasionally occur in malignant lymphomas of the skin other than M.F., the problem of differentiating between M.F. and “reticulum cell sarcoma” did not arise in any of the skin biopsies of our series.

The presence of Pautrier microabscesses is only one aspect of the affinity of the neoplastic cells of M.F. for epithelial structures. This “epitheliotropy,” to which we will refer later in observations on the kidney, may manifest itself in the epidermis by the presence of tumor cells either singly or in small clusters (Fig. 4), or in the form of diffuse infiltrations (Fig. 5). The intraepidermal tumor cells are often surrounded by optically clear areas which are perhaps attributable to epidermoly-sis. In some instances, these diffusely infiltrating cells extend to the superficial epidermis. For the purposes of the diagnostic criteria for cutaneous M.F. employed in this report, the invasion of the epidermis by tumor cells (“exocytosis”), even when it did not assume the aspects of Pautrier microabscesses, was considered to be as diagnostic of M.F. as the microabscesses themselves. An infiltration similar to that involving the epidermis may also be observed in hair follicles (Fig. 6).

While our histologic criteria and those given by most other authors are of great diagnostic value, particularly when considered in conjunction with the clinical appearance of the skin lesions (Table 1), defining the disease in terms of the precise identification of the neoplastic cells has been problematic. The size of the M.F. cells and their configuration under the light microscope have suggested to some histopathologists that they may be “reticulum cells” or histiocytes, similar to what has been thought to be true for the neoplastic cells of Hodgkin’s disease and the so-called reticulum cell sarcomas. Electron-microscopically, however, only Fisher et al. have maintained that the neoplastic cells of M.F. are “variants of reticulum cells” and that they...
are devoid of any specificity for M.F.; other observers have not confirmed this interpretation. Brownlee and Murad left the possibility open that M.F. cells might be lymphoid cells. Lutzner, Hobbs, and Horvath have emphasized that the cells which they call M.F. cells, and which show the characteristic deep infoldings of the nuclei, do not possess the phagolysosomes characteristic of histiocytes. They also emphasized the morphologic similarity between Sézary and M.F. cells. Broome et al. and Brouet et al. have actually demonstrated by immunologic methods that the circulating tumor cells in Sézary syndrome are T lymphocytes. Labaze et al. suggested the possibility that the Sézary cells represent "transformed lymphocytes," and stressed the ultrastructural similarities between Sézary and M.F. cells. More recently, Edelson et al. were the first to demonstrate that the neoplastic...
cells obtained from cutaneous lesions of M.F. have surface properties of thymus-derived lymphocytes.

**Results**

**Gross Observations**

*Skin:* The terminal skin manifestations observed at the time of autopsy are listed in the right column of Table 1. The left column of the table shows that at the time of initial clinical presentation, the skin showed a variety of lesions which were generalized in 35 patients and localized in 10. The terms used are either diagnostic or descriptive, depending on the way they were given in the clinical records. In the right column, the gross appearance of the lesions as observed at autopsy is listed, showing that 27 of the 35 patients who originally had multiple or generalized skin lesions had multiple tumors and ulcers at the time of death, and that 8 of 10 patients who originally had a single skin lesion had tumors and ulcers which were multiple at the time of death.

None of the patients had M.F. d’emblée. There was only one patient in our series who had generalized erythroderma, which persisted throughout the entire illness. Sézary cells were demonstrated in this patient’s blood, but his skin biopsy showed the classical picture of M.F. with Pautrier microabscesses. The total duration of his illness was 5½ years. In contrast to other reported cases of Sézary syndrome in which visceral lesions were not observed, the lymph nodes and spleen were microscopically involved, the spleen weighing 830 g. The tongue contained an ulcerated lesion which was histologically characteristic of M.F.

In only one of our cases were no skin lesions noted at autopsy. This patient was clinically diagnosed as having M.F., manifested by pruritus and erythema of the shoulder and chest, and the histologic picture in the skin biopsy obtained 1 year prior to death was diagnostic of M.F. He died from staphylococcus bronchopneumonia, like many of the patients in the series.

*Extracutaneous Tissues and Organs:* Thirty-two out of the 45 patients (71%) showed gross and/or microscopic evidence of M.F. in extracutaneous organs and tissues (Table 2). In addition to the organs listed in Table 2, other organs and tissues occasionally showed gross and/or microscopic evidence of M.F. These were not included in the table because sections were not taken routinely at autopsy, so that percentage figures comparing
involved and uninvolved organs would not have been of value. The tissues and organs not listed in Table 2 in which M.F. was demonstrated were: urinary bladder, 2; retroperitoneal or mesenteric fat, 8 (1 with gross tumor); salivary gland, 4 (2 with gross tumor); tonsil, 1; esophagus, 4; larynx, 2 (both had gross tumors); trachea, 2 (1 with gross tumor); seminal vesicle, 1; uterus, 1; vagina, 1; tongue, 5 (2 with gross tumors); stomach, 4; intestine, 6; chest wall, 2 (both of which had gross tumors); and peripheral nerve, 3.

In the parenchymal organs the infiltration was, in some instances, interstitial and diffuse, not leading to the formation of circumscribed visible tumor masses. This was frequently true for the spleen and, in some cases, for the lungs in which patchy or confluent infiltrations may convey the impression of a pneumonia-like process (Fig. 7). Only occasionally were multiple small or large nodules evident in an enlarged spleen which then was similar to the gross appearance of other malignant lymphomas.

A gross description of all the organs involved in M.F. does not appear necessary because of the lack of specificity of the tumefactions and the diffuse organ enlargements. Such descriptions will be limited to certain organs which are either strikingly different from the organs involved in other malignant lymphomas or which may be of clinicopathologic interest. Included are the lymph nodes, spleen, heart, liver, kidneys, lungs, and bone marrow.

**Lymph nodes:** One of the gross features of lymph node involvement in M.F. was that the individual nodes often remained discrete (Fig. 8) even when they were greatly enlarged; it was uncommon that they formed fused masses, except in the retroperitoneal area. They had no specific features permitting them to be distinguished from lymph nodes of other malignant lymphomas. The sectioned surface was usually pale and homogeneous. A mottled appearance was evident in the tracheobronchial and bronchopulmonary nodes because of residual anthracosis (Fig. 8).

**Spleen:** Grossly apparent, circumscribed tumors were observed in only 2 of 19 microscopically involved spleens. These 2 spleens weighed 980 and 780 g; the larger was described as having an appearance identical to that of the "porphyrie" spleen of Hodgkin’s disease. The other spleen contained multiple nodules measuring up to 1.5 cm in diameter. For the remaining 17 in which circumscribed tumors were absent, the presence of “follicles” was recorded in only 1. All others showed a diffuse, homogeneous appearance without dis-

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**Fig. 7.** Lung. Note the patchy, often confluent areas of infiltration (Acc. No. A63-83).
tinctive features, regardless of the size of the spleens which ranged in weight from 130–1800 g. Thus, only 2 spleens had a gross appearance resembling that observed in other malignant lymphomas, particularly Hodgkin’s disease.

For the purpose of correlation of splenic weight with certain gross and microscopic features, the spleens were divided into four categories: those with 1) gross nodules, 2) diffuse microscopic involvement, 3) doubtful microscopic involvement, and 4) no evidence of microscopic involvement. The results of this correlation are given in Table 3, which shows that, after the two spleens with gross tumors are excluded because of their small number, the largest weights were recorded in those spleens which were diffusely infiltrated by tumor cells, and that the mean and median weights were significantly lower in the doubtful and negative groups.

**Heart:** Gross involvement of the heart was observed in 7 out of 12 patients in whom neoplastic infiltrations were found microscopically. In 6 hearts, the tumor nodules, either solitary or multiple, ranged in size from 1 to 6 cm. Their distribution in the myocardium was haphazard, without predilection for a specific site. Both ventricles, the right atria, and the interventricular septa were found to be involved. In one patient, narrow streaks, each 0.4 cm wide, were present in the anterior wall of the right ventricle. As Roberts and associates\(^4^7\) pointed out, the gross appearance of the tumor nodules involving the heart in M.F. does not differ in any way from that of other malignant lymphomas. The 4 cases illustrated by Roberts and associates\(^4^7\) are included in this series, and the reader is referred to that publication for detailed descriptions and illustrations of the heart in M.F. We compared the weights of the hearts containing gross tumors with those in which M.F. was evident only microscopically. Using 375 g as the upper limit of normal weight,\(^4^7\) we found that, among the 6 hearts with gross tumors, this weight was exceeded in 5 (400, 420, 420, 440, and 460 g) or 80%, and that, in 4 hearts with microscopic involvement only, it was exceeded in only one (410 g) or 25%. By comparison, in 24 patients who had neither M.F. of the heart nor known hypertension nor any intrinsic cardiovascular disease, 6 hearts (25%) weighed in excess of 375 g. Thus, cardiac enlargement can be attributed to M.F. only when gross tumors are evident.

**Liver:** Of 17 patients who had microscopic evidence of M.F. in the liver, 11 showed gross involvement. Seven of these had multiple nodules ranging from 0.1 to 5.5 cm. Two had solitary nodules measuring 2 and 5 cm, and 2 were described as having tumor infiltrates, but no further detail was given. Of the 6 remaining cases, 4 had no gross abnormality, 1 was described as showing chronic congestion, and in 1 a gross description was not available. In 11 cases with gross involvement, the mean weight of the liver was 2004 g (range of 1200–3030 g); in 6 patients with

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**Table 3. Spleen Weights in Patients with Mycosis Fungoides**

<table>
<thead>
<tr>
<th>Forms of splenic involvement</th>
<th>No. of cases</th>
<th>Weight range (g)</th>
<th>Mean wt. (g)</th>
<th>Median wt. (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross tumors present</td>
<td>2</td>
<td>780, 980</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Microscopic evidence of M.F. without gross tumors</td>
<td>14*</td>
<td>130–1800</td>
<td>554</td>
<td>290</td>
</tr>
<tr>
<td>Microscopic evidence of M.F. equivocal</td>
<td>8</td>
<td>120–490</td>
<td>256</td>
<td>205</td>
</tr>
<tr>
<td>No microscopic evidence of M.F.</td>
<td>17†</td>
<td>50–400</td>
<td>168</td>
<td>110</td>
</tr>
</tbody>
</table>

* Weights of 3 spleens with microscopic M.F. were not available.
† Weight of 1 spleen without M.F. was not available.
microscopic involvement only, it was 1822 g (range of 1400–2050 g). In 4 cases with questionable involvement, the mean was 1938 g (range of 1430–2140 g), and in 24 microscopically uninvolved livers, 1923 g with a range of 1000–3500 g. This lack of significant difference of average hepatic weights in the four groups is in contrast to the appreciable differences between the weights of the involved and uninvolved spleens.

Kidney: Among the kidneys of 14 patients with microscopic renal involvement, 11 contained circumscribed tumors. There was great variability in the gross appearance of the tumors, which ranged from a small, single, unilateral, intracortical, subcapsular tumor nodule to massive, irregular, bilateral tumor masses extending from the cortices through the medulla into the renal pelvis. In most instances, the nodules were distinct and well circumscribed. Occasionally an indistinct, more diffuse nodular infiltrate was observed. The cut surfaces of the tumors were usually white and homogeneous, but were occasionally hemorrhagic. In one patient the ureters were enveloped by tumor.

Lung: In 18 of 21 patients with microscopic involvement of the lung, gross evidence of M.F. was observed. Fifteen of these were found to have multiple nodules that were usually bilateral and measured between 0.5 and 4.0 cm. In 3 patients, the tumor involvement was diffuse in the form of patchy and/or confluent pulmonary infiltrations (Fig. 7). Occasional tumors showed central areas of necrosis. In 1 patient the lung was merely described as congested, and in two no gross observations were available. The appearance of the lungs was also altered by a variety of other gross changes, the most frequent of which (12 cases) was pneumonia. Other changes included pulmonary abscesses in two lungs and thromboembolic manifestations in 4, 2 of them with pulmonary infarcts.

Bone marrow: Grossly visible lesions in the bone marrow were recorded in 2 out of 12 cases in which the marrow was histologically involved. An example is illustrated in Fig. 9, which shows circumscribed white tumor nodules as well as patchy, ill-defined, gross infiltrations alternating with areas of red marrow. This appearance lacks specificity compared with other neoplasms involving the vertebrae. Thomas et al.52 reported that involvement of the bone marrow by M.F. only rarely produces radiographically perceptible bone tumors; our findings are consistent with these observations.
Other organs: Gross tumor nodules and diffuse infiltrations were recorded in many tissues and organs in addition to those already described, but lack any distinctive features worthy of separate mention. These sites include the thyroid, submaxillary glands, adrenal, mesentery, chest wall, tongue (Fig. 10), larynx, trachea, and, in one instance, the brain.

Microscopic Observations

The infiltration of both skin and extracutaneous tissues at autopsy exhibited distinctive features which pertain both to the architecture of the cellular infiltration and to its cytology. The following histologic features were considered to be characteristic of M.F.:

1. A proliferation of atypical mononuclear cells (Figs. 11-14), which were usually larger than the neoplastic lymphocytes of malignant lymphomas of the lymphocytic type and often as large as the cells of malignant lymphomas of the histiocytic type (reticulum cell sarcoma).

2. The presence of distinctive cells which fall into two general categories: a) cells with deeply indented, infolded nuclei (Fig. 12), probably corresponding to the cells with serpentine and cerebriform nuclei observed under the electron microscope; and b) cells characterized by relatively large hyperchromatic nuclei (Figs. 11, 13-15) which may or may not be deeply indented. Their nuclei may be so hyperchromatic that nuclear detail is obscured. These are the cells referred to as mycosis cells in the literature and in this report.

3. An infiltration of organs and tissues that is not accompanied by the destructive effects usually observed in malignant lymphomas and other malignant neoplasms (Figs. 16-18); that is, preserved parenchyma is often evident in the wake of a pronounced neoplastic proliferation.

4. A certain affinity for epithelial structures which is particularly evident in the epidermis and skin appendages, but may also be observed occasionally in mucous
This variant has been interpreted as pleomorphic "reticulum cell sarcoma" (Figs. 22–24).

3. The occasional occurrence of mononuclear and/or multinucleated cells with nuclear features indistinguishable from those of Sternberg-Reed cells. If these are associated with a significant number of inflammatory cells such as plasma cells and eosinophils, it is easy to understand why a diagnosis of Hodgkin's disease might be made.

In the great majority of our cases, the histologic picture of either the classical form or one of its variants was similar in all tissues and organs. In exceptional cases, however, we were able to find the less malignant-appearing classical picture of M.F., with the relatively bland-appearing large mononuclear cells and a scattering of hyperchromatic mycosis cells, side by side with a cellular proliferation resembling pleomorphic reticulum cell sarcoma. The most striking example of this is the observation of both histologic aspects in two sections from different areas.

membranes and other epithelial organs, particularly in the renal tubules (Figs. 19 and 20).

When the classical histologic picture of M.F. is evident at autopsy (Figs. 11, 13–15, 17, and 18), it is easily distinguishable from other malignant lymphomas. The following deviations from this picture may be encountered, however:

1. A relatively uniform proliferation of mononuclear cells, the lymphoid appearance of which is accentuated by the nuclear pyknosis so frequently seen in postmortem material (Fig. 21). Such proliferations are likely to resemble so-called "lymphosarcoma;" the best clue as to the true nature of the infiltration is the finding of occasional mycosis cells.

2. A proliferation of much larger cells with marked cellular pleomorphism, usually including multinucleated and bizarre giant tumor cells which, at times, assume the proportions of cellular monstrosities.
of the mesentery in the same patient (Figs. 25 and 26).

In most of the cases, the cellular proliferation at the time of death consisted only of neoplastic cells in both the cutaneous and extracutaneous lesions. This is in contrast to the relative abundance of inflammatory cells in many of the cutaneous biopsy specimens. In a small number of postmortem cases, an inflammatory reaction was noted which was
rarely severe. Eosinophils were on occasion particularly numerous, while in other instances the inflammatory reaction contained significant numbers of plasma cells, lymphocytes, and/or histiocytes. A strong similarity existed between the inflammatory reaction in the skin and that in the visceral lesions of the same patient. Multinucleated giant cells

**Fig. 17.** Thymus showing preservation of the epithelium which is surrounded by infiltrations of lymphoid cells. Some large hyperchromatic nuclei are evident (H & E, x125; Acc. No. A66-114).

**Fig. 18.** Thymus. The infiltration by neoplastic cells is massive, yet the thymic epithelium is largely preserved (H & E, x210; Acc. No. A60-205).
the atypical lymphoid cells have inserted themselves between the renal tubular epithelium and the tubular basement membrane, leading to partial detachment of the tubular epithelial cells from the basement membrane. The interstitial tissue is edematous, but is only slightly infiltrated by neoplastic cells (H & E, x234, reduced from 260; Acc. No. A57-44).

of the Langhans type were found in three instances, both in the skin and in some of the viscera (Fig. 27). These cells are sometimes difficult to distinguish from bizarre, multinucleated giant tumor cells with a similar peripheral arrangement of the nuclei (Fig. 28). The characteristic features of M.F. in the various organs will be described in detail.

Skin: At autopsy the skin was usually
atrophic; this atrophy was often pronounced in cases where cellular infiltration was scarce or lacking. The subepidermal corium frequently appeared somewhat edematous, and on occasion it had the appearance of scar tissue. Skin appendages were atrophic or absent. Melanin pigment was often quite abundant and was present predominantly in macrophages. Many of these changes have been reported by Edgcomb and associates in patients with M.F. following therapy with high-energy electrons. Involvement of the epidermis may have a variety of aspects. On occasion, typical Pautrier microabscesses were evident; in other instances, individual cells infiltrated the epidermis either throughout its entire thickness (Fig. 5) or predominantly the basal and adjacent Malpighian cell layers (Fig. 4). At times this infiltration was pronounced, and many cells, often arranged in small clusters, imparted to the epidermis a peculiar vacuolated appearance (Figs. 4 and 5). In other cases, tumor-like infiltrates in the dermis extended to the basement membrane of the epidermis without infiltrating it. Large clusters of cells were evident between papillae of the corium. In tangentially cut sections of the epidermis, these clusters simulated Pautrier microabscesses, but differed from them by being separated from the epidermis by distinct basement membranes; this was particularly evident in PAS-stained sections.

**Lymph nodes:** The microscopic observation

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of lymph nodes obtained by biopsy and at autopsy will be described together. Biopsies of enlarged lymph nodes were available for 20 of our patients. Of the first lymph node biopsies performed on each of these patients, 14 were positive for M.F., 2 were doubtful, and in 4 no evidence of M.F. was demonstrable. Of the 14 lymph nodes which were interpreted as positive, involvement was diffuse in 10 and focal in 4. Residual dermatopathic lymphadenitis was evident in 4 of the 10 diffusely involved lymph nodes, whereas it was the predominant histologic feature in the 4 lymph nodes with focal involvement by M.F.

Considerable diagnostic difficulties may be
lymph node biopsies with diffuse involvement. Cytologically, the cellular proliferation of M.F. may range from a rather uniform cell population, in which nuclear atypia is less conspicuous than in other malignant lymphomas (Fig. 29), to a more pleomorphic picture with considerable variation in nuclear size and configuration (Fig. 22). In the smaller cells, of the size range of large lymphocytes, the cytoplasm does not appear particularly characteristic, but the nuclear structure and configuration do present some features which should direct attention to M.F. even if the clinical history were not known. The nuclei are more pale (Fig. 29) than those of normal lymphocytes or of the neoplastic cells of well-differentiated or poorly differentiated lymphosarcomas. The nuclei may be indented, although such indentation may be either lacking or not readily perceptible under the light microscope. There are also larger cell forms (Figs. 12 and 22), of a size equal to or greater than histiocytes. Their cytoplasm, rather than being pale and eosinophilic, is amphophilic or slightly basophilic. Often these large "retic-
Fig. 27. Tumor of myocardium, showing multinucleated giant cells of the Langhans type surrounded by the atypical lymphoid cells of mycosis fungoides. These multinucleated cells (inset) do not exhibit the nuclear atypia observed in giant tumor cells of the type illustrated in Fig. 28 (H & E, x120; inset x520; Acc. No. A60-205).

ULUM-cell-like tumor cells show marked pyroninophilia in contrast to the lack of pyroninophilia in the more lymphoid-appearing cells of M.F. As to the nuclear structure, the striking feature is the irregular clumping of the chromatin, often conveying the impression that multiple, irregular, deeply blue-staining nucleoli are present (Fig. 22): these may be interconnected by chromatin strands. Whether the predominating cells are the smaller or larger types, intermingling of large and small forms may occur and, at times, multinucleated giant cells may be prominent. Cells with deeply indented cerebriform nuclei (Fig. 12) are particularly striking in some instances, but are absent in others. In general, the diagnosis

Fig. 28. Subcutis showing infiltration of fat tissue by atypical lymphoid cells. A hyperchromatic mycosis cell is evident (arrow). Next to it, a multinucleated giant cell shows a peripheral arrangement of the nuclei which is similar to that of the giant cells of the Langhans type. However, the nuclei are quite atypical and have large nucleoli, strongly suggesting that, in contrast to the cells illustrated in Fig. 27, this is a truly neoplastic cell (H & E, x380; Acc. No. A63-83).
of M.F. is relatively easy if the cellular proliferation occurs in the form of cohesive masses. However, we have also seen sections in which only small clusters or single neoplastic cells were evident. When they belong to the larger cell population, they are recognizable with relative ease, but when they are smaller, they may be almost indistinguishable under the light microscope from surrounding non-neoplastic elements, so that it is quite
possible to miss a positive diagnosis of M.F. at a stage where the lymph node contains only individual cells or small clusters.

In four patients, more than one lymph node was available for examination. For two of these patients, the picture was identical in the two consecutive biopsies which were taken at intervals of 4 weeks and 8 months, respectively. Both cases showed evidence of diffuse involvement, in one with residual lymphocytic nodules and in the other with complete replacement of normal lymphoid tissue.

In two other patients, the involvement appeared to be progressive. In one, it was focal in the initial biopsy, and diffuse without preserved islands of normal lymphoid tissue in the second biopsy taken 2 years later. In the other patient, the involvement was diffuse with residual lymphoid tissue in the initial biopsy, and diffuse without residual lymphoid tissue 3 months later.

Of the 20 patients in whom lymph node biopsies were obtained during life, 17 or 85%, had extranodal visceral involvement at the time of death. If these 20 cases are broken down into those in which lymph node biopsies were positive, doubtful, and negative, respectively, the figures are 86% (12/14), 100% (2/2), and 75% (3/4) for positive visceral involvement. These differences are not statistically significant.

The lymph nodes obtained at autopsy were examined and evaluated without prior knowledge of the results of the biopsy studies. Twenty-four were interpreted as positive for M.F., 5 as equivocal, and 16 as negative. To find out how frequently M.F. in the lymph nodes is an indicator of other extracutaneous involvement, we determined how many patients in each group had visceral involvement. These findings are presented in Table 4, which illustrates that all patients in whom an unequivocal diagnosis of M.F. was made on the basis of lymph nodes had unequivocal evidence of visceral involvement at necropsy. Of 5 patients in whom evidence of M.F. was equivocal in the lymph nodes, 4 had definite evidence of visceral involvement at necropsy; in 1 case an unequivocal diagnosis of visceral M.F. could not be made. Of 16 patients in whom the lymph node was interpreted as negative, 4 had evidence of visceral involvement and 12 did not.

In order to determine the reliability of a positive diagnosis of M.F. in lymph node biopsies, we compared the results of the examination of the 20 lymph nodes obtained at biopsy with those of the lymph nodes obtained from the same patients at autopsy. Our data indicate that, in 11 of 14 patients with a positive lymph node biopsy, the autopsy lymph nodes were also positive for M.F.; in 1, they were doubtful, and in 2, negative. For 2 cases in which the lymph node biopsies were interpreted as doubtful, the lymph nodes at autopsy were positive. Among 4 cases in which the lymph node biopsies were interpreted as negative, the lymph nodes at autopsy were positive in 1, doubtful in 1, and negative in 2. In the 14 patients with positive lymph node biopsies, the median time interval between biopsy and autopsy was 5.75 months with a range from 1 to 27 months; in the 6 patients with doubtful or negative lymph node biopsies, the median interval was 12.5 months with a range of 1 to 43 months.

Heart: Infiltration of the heart by M.F. (Fig. 21) was predominantly interstitial and occurred in broad and/or narrow strands. Atrophy of the muscle cells was a conspicuous feature. In focal areas, myocardial tissue was completely replaced by tumor. Infiltrations of the pericardium, endocardium, and veins were evident. Mural thrombi were found in areas of endocardial infiltration. In some instances, necrosis was observed within the neoplastic infiltrations. Benign-appearing multinucleated giant cells of either the Langhans or the foreign body type were observed in 3 out of 12 cases in close association with the neoplastic proliferation (Fig. 28). Occasionally, the neoplastic infiltration was predominantly in the pericardium.

Spleen: The histologic picture in the spleen showed great variability, ranging from barely perceptible clusters of abnormal cells to massive and diffuse infiltrations of the red pulp, at times with complete obliteration of the architecture of the white and the red pulp. Focal involvement was less common than diffuse infiltration. In a few spleens, the neoplastic proliferation showed a predilection for
lymphatic sheaths (Fig. 11), and in others the foci were irregularly distributed through the red and white pulp. The perifollicular zone of the red pulp was frequently involved.

Apart from the characteristic appearance of the cellular proliferation, some other features are of value in differentiating M.F. from other malignant lymphomas in the spleen. In contrast to M.F., malignant lymphoma of the lymphocytic type always appears to arise in the white pulp, and encroaches upon the red pulp to a varying extent without obliterating it completely. Malignant lymphoma of the histiocytic type (reticulum cell sarcoma) involves the spleen in the form of large nodular masses, and the diffuse infiltration characteristic of M.F. is hardly ever observed. Hodgkin's disease shows a predilection for the white pulp, but no diffuse infiltration of the red pulp. As previously pointed out, in M.F. the foci of neoplastic cells do not commonly produce grossly visible lesions in the form of nodules; such nodules were observed in only 2 of 19 microscopically involved spleens. It is noteworthy that, although we were able to interpret 19 spleens as involved by M.F. and 18 as uninvolved, it was not possible to establish or exclude M.F. in the remaining 8. It seemed difficult to differentiate in postmortem sections between the cells of M.F. and those of other nucleated cellular elements in the pulp cords. Trapping of circulating M.F. cells in the splenic cords is probably not rare, but the relatively benign appearance of some of their nuclei often makes it impossible to establish their nature in H & E-stained sections, particularly when they are not evident in cohesive masses.

Liver: Differences in distribution of the cellular infiltrations from one case to the other were probably most striking in the liver (Figs. 15 and 16). In some patients, the pattern was that classically observed in Hodgkin's disease and in malignant lymphomas of the lymphocytic type, practically all of the infiltrations being located in the portal areas with encroachment upon the peripheral portions of the hepatic lobules (Fig. 15). In other cases, the hepatic parenchyma was occupied by tumor masses that bore no recognizable relation to portal triads, and in still other cases again a diffuse infiltration of M.F. cells between the liver cell plates (Fig. 16) strongly resembled the parenchymal infiltrations seen in myeloid leukemias and malignant histiocytoses. The preservation of hepatic parenchyma in the form of atrophic liver cell plates in the wake of an expanding intra-lobular infiltration was a striking feature (Fig. 16). Sometimes the infiltration was scant and present in the form of individual cells rather than cohesive cell masses. Among these cells which were present between liver cell plates, hyperchromatic mycosis cells often made the diagnosis relatively easy.

In several instances, only very rare cells were found between the liver cell plates, and slight infiltrations were present in the portal triads. Individual cells consistent with those observed in M.F. were evident, but the difficulty of making an unequivocal diagnosis of hepatic involvement arose in these sparsely infiltrated livers. For the purpose of this study, therefore, we classified 17 cases as grossly and/or microscopically positive for M.F., 4 cases as showing equivocal involvement, and 24 as negative. Because hepatic involvement seems to be rare in the absence of splenic involvement in Hodgkin's disease, we attempted to assess this relationship for M.F. in our microscopic studies and obtained the following data: In 12 of the 17 patients with liver involvement, both liver and spleen showed gross and/or microscopic evidence of M.F. In the remaining 5 patients, the spleens weighed 50–190 g and showed no evidence of gross involvement. Three of these (50, 95, and 100 g) were microscopically negative, and 2 (130, 190 g) were interpreted as equivocal. This indicates that the presence of M.F. in the liver may occur in the absence of splenic involvement. In 4 of 19 patients in whom the spleens were grossly and/or microscopically positive, no microscopic evidence of disease was observed in the liver, and in 2 others, evidence of hepatic involvement was equivocal.

Kidney: In most instances, the renal involvement showed the characteristic pattern observed in other malignant lymphomas, namely an interstitial infiltration with preservation of both tubules and glomeruli. In addition, tumor cells were found entrapped in glomerular capillaries as well as lying free within the space of Bowman (Fig. 31), and even within the lumen of the tubules. An unusual feature was a peculiar relationship of the neoplastic cells to tubular renal epithelium. Occasionally the neoplastic cells infiltrated
between the basement membranes of the tubules and the epithelial lining (Fig. 19), presenting a picture of "epitheliotropy" similar to that seen in the epidermis of the skin and the squamous epithelium of mucous membranes. In one instance, they completely replaced the tubular lining, thus simulating the picture of adenocarcinoma (Fig. 20).

Lung: The histologic pattern in the lung was usually characterized by a heavy infiltration of the alveolar walls by tumor cells (Fig. 32). Often, however, the tumor cells were also evident within the alveoli (Fig. 33), with or without fibrinoid material. Some lung lesions were close to and some were distant from the mediastinum. However, contiguous extension of the disease from tracheobronchial or bronchopulmonary lymph nodes into the parenchyma, a feature characteristic of Hodgkin's disease, was not demonstrable in M.F. The pulmonary lesions of M.F. appeared to be truly metastatic and, most likely, the result of hematogenous spread.

Bone marrow: Histologic evidence of bone marrow involvement was found in 12 of 31 patients with extracutaneous disease. In 1 patient, bone marrow was not available for study. The distributional features of bone marrow involvement were usually multifocal, as in Hodgkin's disease and other malignant lym-
phomas (Fig. 13). Occasionally, the infiltration was diffuse (Fig. 14). Hyperchromatic mycosis cells (Figs. 13 and 14) were the most helpful cytologic feature differentiating the nodules from other forms of malignant lymphoma. In a few cases the histologic picture was pleomorphic, featuring multinucleated cellular monstratosities and presenting a picture resembling that of a pleomorphic reticulum cell sarcoma (Fig. 23). However, it was precisely these peculiar giant tumor cells with bizarre and deeply indented nuclei which, even in the cytologically very atypical forms, strongly suggested M.F., since similar cells are rarely if ever observed in other malignant lymphomas.

Fibrosis of the type seen in Hodgkin’s disease with bone marrow involvement was not evident in H & E-stained sections, and reticulum stains showed only a moderate increase in argyrophilic fibers.

Other organs: Microscopic evidence of M.F. was found in practically every organ and tissue in this series, but it was difficult to present incidence figures from the organs not listed in Table 2 because sections were not taken routinely from them. In some locations, for example the salivary glands, microscopic sections were available only because gross tumors called attention to the presence of lesions. The microscopic observations recorded here are limited to certain salient features. In the thymus, the preservation of the epithelial component in the presence of either slight or massive involvement was a striking feature (Figs. 17 and 18). In the peripheral nerves the neoplastic cellular infiltration showed a predilection for the perineural sheaths, with invasion of the periphery of the nerves in some cases (Fig. 34). Severe pain and motor paralysis have been correlated with such infiltrations.41 In the central nervous system, the infiltration was largely limited to the meninges (Fig. 35). Brain involvement was found in only one of our cases; others have been reported in the literature.19,48,53,56 In the mesentery (Figs. 25 and 26) the pattern of invasion is identical to that in other lymphomas, with heavy infiltration between fat cells which are often preserved. The cellular proliferation in skeletal muscle (Fig. 36) resembles that in the myocardium (Fig. 21). Endocrine glands such as the parathyroid (Fig. 37) appeared to be involved more frequently than in other malignant lymphomas.

The diagnostic significance of individual hyperchromatic mycosis cells in tissues other than those already described cannot be overemphasized; no similar cells occur in other malignant lymphomas. This appears to be true also for cells with deeply indented cere-
briform nuclei, at least light microscopically. Occasionally, the mycosis cells may be evident singly rather than as a part of cohesive cellular proliferation, a striking example being that illustrated for the endometrium (Fig. 38). Of great interest is the similarity of the cellular infiltration in the mucous membranes lined by squamous epithelium, such as the oral cavity, the nasopharynx, and the upper larynx, with that observed in the skin, even to the extent that typical Pautrier micro-abscesses may be seen. In our series we had a
FIG. 36. Skeletal muscle (diaphragm). The tissue is heavily infiltrated by atypical lymphoid cells. The muscle fibers on the left are still preserved, those on the right are destroyed, and the sarcolemma sheath is lined in a gland-like fashion. Note the similarity to the pattern in the kidney from the same case (Fig. 21) (H & E, ×125; Acc. No. A63-106).

FIG. 37. Parathyroid. The glandular tissue is in part preserved, in part extensively replaced by proliferation of lymphoid cells among which mycosis cells with hyperchromatic nuclei are readily discernible (H & E, ×200; Acc. No. A64-27).

patient in whom Pautrier microabscesses were evident in the squamous epithelial lining of a tonsil involved by M.F.

For a list of actual sites of involvement at autopsy that is probably the most complete account of such involvement, the reader is referred to the report by Epstein and associates which covers a larger series of cases originating from the Clinical Center of the National Cancer Institute. The cases of the
present series were included in that report. The literature on internal organ involvement prior to 1955 has been reviewed by Bluefarb. Additional cases have been reported since that time.

**Length of Survival and Causes of Death**

In order to determine the comparative survival times of patients with and without extracutaneous involvement, we tabulated the duration of the disease from the onset of skin lesions and from the time of the diagnostic biopsy, as shown in Tables 5 and 6. These tables show what appears to be a paradox, namely, that the average survival of patients without extracutaneous involvement following clinical onset of the disease as well as following the diagnostic biopsy was shorter than that of patients with extracutaneous involvement. We therefore attempted to establish the principal anatomical cause of death in both groups. These are shown in Table 7, which illustrates that, in Group I, the cause of death was known for 12 out of 13 patients. Eleven of the 12, or 92%, died from pneumonia or septicemia or both. These fulminat-

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**Table 5. Mycosis Fungoides: Duration of Illness**

<table>
<thead>
<tr>
<th>Duration of illness (years)</th>
<th>Number of patients without extracutaneous involvement at autopsy</th>
<th>Number of patients with extracutaneous involvement at autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3-5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>5-10</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>10-20</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Over 20</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total number</strong></td>
<td><strong>13</strong></td>
<td><strong>31</strong></td>
</tr>
<tr>
<td><strong>Average duration</strong> (years)</td>
<td><strong>6.8</strong></td>
<td><strong>9.8</strong></td>
</tr>
</tbody>
</table>

* One patient with a history of psoriasis dating back 52 years is not included because the precise onset of M.F. could not be determined.

**Table 6. Mycosis Fungoides: Duration of Illness from Diagnostic Biopsy to Death**

<table>
<thead>
<tr>
<th>Duration of illness (years)</th>
<th>No. of patients without extracutaneous involvement</th>
<th>No. of patients with extracutaneous involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1-2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2-3</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>3-4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total number</strong></td>
<td><strong>13</strong></td>
<td><strong>32</strong></td>
</tr>
<tr>
<td><strong>Average duration</strong> (years)</td>
<td><strong>1.8</strong></td>
<td><strong>3.3</strong></td>
</tr>
</tbody>
</table>

* Two patients who lived less than 3 months were excluded from the computation.
Table 7. Causes of Death in Patients with Mycosis Fungoides

<table>
<thead>
<tr>
<th>Cause of death (C.O.D.)</th>
<th>Group I (without visceral M.F.)</th>
<th>Group II (with visceral M.F.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. % of known C.O.D.</td>
<td>No. % of known C.O.D.</td>
</tr>
<tr>
<td>Staphylococcus pneumonia and/or septicemia</td>
<td>3 11.1</td>
<td>8 57.2</td>
</tr>
<tr>
<td>Pseudomonas or other gram-negative pneumonia and/or septicemia</td>
<td>2 4</td>
<td>4 1</td>
</tr>
<tr>
<td>Bronchopneumonia, causative organism not specified</td>
<td>5 10 2</td>
<td>1 32.1</td>
</tr>
<tr>
<td>Septicemia, causative organism not specified or other than above</td>
<td>1 1</td>
<td>1 10.7</td>
</tr>
<tr>
<td>Total septicemia and/or pneumonia</td>
<td>11 91.7</td>
<td>16 57.2</td>
</tr>
<tr>
<td>Death from visceral M.F.</td>
<td>0 0</td>
<td>0 10</td>
</tr>
<tr>
<td>Death from unrelated causes</td>
<td>1 8.3</td>
<td>3 30.7</td>
</tr>
<tr>
<td>Total number in which C.O.D. was known</td>
<td>12 100</td>
<td>28 100</td>
</tr>
<tr>
<td>Total number in which C.O.D. was uncertain</td>
<td>1 1</td>
<td>4 1</td>
</tr>
</tbody>
</table>

ing infections were always associated with ulcerated cutaneous tumors that usually contained the same organisms which were cultured from the lungs and/or the heart blood. In Group II, in which extracutaneous involvement was evident, the cause of death could be established in 28 out of 32 patients. In only 16 of these, or 57%, death was due to infectious complications. In 3 it was attributable to unrelated diseases, and in 9 it was directly or indirectly related to visceral M.F. This suggests that the patients in the first group died from the infectious complications before the disease had spread to extracutaneous sites, whereas the patients in Group II included a considerable number who were kept alive sufficiently long to reach the state of extracutaneous involvement. This could also account for the previously mentioned differences in reported incidence of extracutaneous involvement, which was particularly low in a group reported by Allen.1 Many of his cases antedate the time when effective control of infectious disease by antibiotics became feasible. Perhaps the high incidence of visceral involvement in our series is attributable to the excellent care, with specific emphasis on effective general and anti-infectious therapy, which these patients received in a research hospital. It is of added interest that patients in both groups had a relatively short survival after diagnostic biopsy compared with the total duration of the disease. This is in keeping with the observation that it is difficult to make a definitive histologic diagnosis during the premycotic stage of the disease; in most instances, M.F. is not unequivocally established histologically until the infiltrative stage is evident.

Discussion

The data collected from the present series of 45 cases appear to be eminently suited to answer the questions which we posed in the introduction. First, the cases presented constitute a series of clinically typical and histologically characteristic examples of classical M. F., in which every effort was made, and we believe successfully so, to exclude primary malignant lymphoma cutis. None of the patients in this series had M.F. d’emblée. In our opinion, when rigid criteria for the diagnosis of M.F. are established as outlined in the MATERIALS AND METHODS section, the differentiation between M.F. and malignant lymphoma cutis should not be too difficult. Occasionally, however, a problem may arise at the tumor stage, but only in two special situations: 1) when cells indistinguishable from Sternberg-Reed cells are found, and 2) when the cells of M.F. become unusually atypical and bizarre. In the first instance, Hodgkin’s disease, and in the second, pleomorphic reticulum cell sarcoma may be simulated. Sternberg-Reed cells were observed in 2 patients of our series; 1 of these had been reported on previously.56 A histologic picture resembling pleomorphic reticulum cell sarcoma was evident in three patients at necropsy.

We shall not deal with the problem of differentiating M.F. from nonspecific inflammatory changes in the skin. Although this problem does exist, we did not encounter it since all of the cases selected were based upon definitive criteria which included clinically typical manifestations, histologic features that were diagnostic or characteristic of M.F., and the availability of autopsy material.
Regarding the extracutaneous lesions, the differences between M.F. and other malignant lymphoid tumors were either striking or could be established after careful analysis of the histopathologic features. In lymph nodes, partial preservation of normal lymphoid tissue was the rule rather than the exception even when replacement of the normal lymphoid tissue was extensive (Fig. 29). Cellular atypia was often not pronounced, and the problem was not so much one of differentiation from other malignant lymphomas, but of recognition of focal M.F. in lymph nodes where the picture of dermatopathic lymphadenitis predominated. Nuclear features that helped to differentiate the cells of M.F. in lymph node sections from non-neoplastic lymphoid cells were primarily the delicate chromatin structure and the presence of deeply infolded nuclei. When cells with hyperchromatic nuclei, so-called mycosis cells, were evident, the diagnosis became relatively easy.

The architectural similarity between lymph nodes with dermatopathic lymphadenitis and those partially involved by M.F. was at times striking, because the histiocytic proliferation in dermatopathic lymphadenitis may replace the perifollicular lymphoid tissue extensively.

As in M.F., lymphoid follicles with reaction centers may be evident and may be surrounded partially or completely by the histiocytic proliferation of dermatopathic lymphadenitis. However, the histiocytes in dermatopathic lymphadenitis have an abundant, faintly acidophilic and often vacuolated cytoplasm. Their nuclei are round, ovoid or elongated with optically clear areas between the nuclear membranes and relatively small but distinct nucleoli. Some of the nuclei are irregular and have infolded nuclear membranes; others, particularly those which contain melanin, have larger nuclei with regular outlines.

Since the lymph nodes are the only tissue other than the skin that usually is available for study in the living patient, we were very much interested in the relationship between lymph node and visceral involvement. We first compared lymph nodes obtained by biopsy with those obtained at autopsy, and then the involvement of lymph nodes with that of other extracutaneous sites, with the following results: In 14 of 20 patients, the biopsied lymph nodes showed unequivocal M.F., and 11 of the 14 had M.F. in the lymph nodes at autopsy; in 1, the lymph nodes available at autopsy were interpreted as doubtful, and in the remaining 2, as negative for M.F. In the 2 patients whose lymph node biopsies were interpreted as doubtful, unequivocal M.F. was found in the lymph nodes obtained postmortem. Of 4 patients who had only dermatopathic lymphadenitis in lymph node biopsy specimens, all had dermatopathic lymphadenitis at autopsy, but 1 also had definite and 1 had questionable involvement by M.F. in postmortem lymph node sections.

In a comparison of our observations on lymph node biopsies with involvement of organs other than lymph nodes at autopsy, such organ involvement was observed in 12 out of 14 patients (86%) when the lymph node biopsies were histologically positive; in 2 out of 2 patients when they were histologically doubtful; and in 3 out of 4 patients in whom M.F. was not demonstrable in the lymph nodes obtained by biopsy. Our observations suggest that patients who have lymph node enlargement that is significant enough to warrant a biopsy are likely to have a high incidence of visceral M.F., regardless of whether or not M.F. is demonstrable in the lymph node biopsy sections. Even in patients in whom lymph node biopsies were not taken, however, 15 out of 25, or 60%, showed evidence of visceral involvement at autopsy.

In correlating the involvement of lymph nodes obtained at autopsy with extranodal visceral involvement, we found that all 24 patients with M.F. in the lymph nodes also had other organ involvement by M.F. Of 5 patients in whom the diagnosis of M.F. was considered to be doubtful in the lymph nodes, 4 had positive and 1 equivocal evidence of visceral M.F. Of 16 patients in whom M.F. was not demonstrable in the lymph nodes, 4 had visceral M.F. and 12 did not. These figures bring out the important fact that lymph node involvement is a strong indication of extranodal visceral M.F., and that the barrier to the spread of the disease is probably in the skin and not in the lymph nodes. On the other hand, the presence of visceral M.F. in 4 cases in which the disease was not demonstrable in the lymph nodes at autopsy could be due either to under-diagnosis of M.F. in the lymph nodes, a possibility which we strongly suspect, or to the skipping of lymph nodes in the spread of M.F., with dissemination directly from the skin by the hematogenous route.
We have had no way of ascertaining which of these two is the more likely possibility.

Two observations are relevant to the difficulty of recognizing M.F. in lymph node lesions: 1) the cells which Lutzner et al. described as being characteristic of M.F. in the electron microscope were found by these authors in seven biopsied lymph nodes which had been considered by light microscopy to be negative for M.F.; and 2) in three patients of a different series of cases, lymph node biopsy specimens diagnosed light-microscopically as dermatopathic lymphadenitis revealed karyotype abnormalities which were indicative of neoplasia and which were identical to the abnormalities in the skin lesions of these same patients.

The extracutaneous and extranodal lesions of M.F. are characterized by their great variability in gross distribution, microscopic architectural features, and cellular composition. In both gross and microscopic distribution of lesions, M.F. may show as widespread an involvement as any other malignant lymphoma. Fifty-nine different sites have been reported by Epstein and associates, with an average of 6.3 organs or tissues involved per case. Certain gross and microscopic features appear to be characteristic of M.F., however: 1) Lymph nodes are usually discrete rather than matted; 2) the incidence of lung involvement is greater than that of spleen, liver, or bone marrow, and is not usually associated with prominent mediastinal masses as in Hodgkin's disease; 3) the incidence of involvement of thyroid, parathyroid, pancreas, and thymus is relatively high; and 4) gross lesions in the bone marrow are rare in comparison with the relative frequency of microscopic involvement, which correlates well with the almost consistent absence of radiologic evidence of M.F. in bone. Our observation of almost 40% of bone marrow involvement in patients dying with visceral M.F. is worthy of note since such involvement has been reported to be rare.

Architectural features which are characteristic and perhaps unique for M.F. are: 1) the great variability with which various areas of the same organ may be involved and 2) the preservation of parenchymal tissue in the presence of a heavy neoplastic proliferation which, at times, does not appear to be destructive to the extent of completely replacing the parenchymal cells. The liver is probably the best example of this variability of the neoplastic infiltration. Either portal areas, as in Hodgkin's disease, or hepatic parenchyma with infiltration between cell plates, as in myeloid leukemia and malignant histiocytosis, may be the principal sites of involvement. In the lung the infiltration may be interstitial, intra-alveolar, or both.

In the spleen, the neoplastic cells usually invade the red pulp diffusely, but occasionally both red and white pulp are involved in a haphazard fashion. In the kidney, the infiltration may be primarily interstitial, similar to that seen in other malignant lymphomas, or the glomeruli and tubules themselves may be affected, with M.F. cells evident in the glomerular tufts, in the space of Bowman, and inside the tubular basement membranes. In any organ or tissue, M.F. cells, particularly the hyperchromatic mycosis cells, may be seen singly, in contrast to Sternberg-Reed cells which are always a part of a cohesive cell mass. We have observed individual mycosis cells in the basal cell layer of the epidermis, in the liver, the uterus, and the bone marrow. In the marrow they are difficult to distinguish from megakaryocytes.

The presence of inflammatory cells in the microscopic lesions of M.F. is variable. In the early skin lesions of M.F. the typical neoplastic "elements" are rare, and inflammatory cells "often dominate the histologic picture," as if the inflammatory reaction attempted to contain the neoplastic proliferation. As the disease progresses toward the tumor stage, inflammatory cells may become scant or absent, and tumor cells dominate the field; this is the prevalent feature at autopsy. Only in 6 of 32 patients did visceral lesions show a pronounced admixture of inflammatory cells. These were predominantly plasma cells in 3 and predominantly eosinophilic granulocytes in the 3 others. When plasma cells were abundant in the visceral tumors, they were equally numerous in the skin lesions; this was true also for the eosinophils. In most patients, however, inflammatory cells were few or absent in both cutaneous and extracutaneous lesions even when they had been abundant in the diagnostic skin biopsies. This suggests that an immunologic barrier ("host resistance") to the spread of the disease is present in the skin and that, once this barrier is broken, the neoplastic proliferation progresses in an uninhibited fashion.

It is our conclusion from assessment of the clinical and histopathologic observations on
Infiltrative and tumor stages on the one hand and the extracutaneous lesions on the other. These findings are in accordance with the views previously expressed by Sternberg-Reed et al. when involving the viscera, progresses into lymphosarcoma, reticulum cell sarcoma, or Hodgkin’s disease, our observations indicate that the lesions in the lymph nodes and viscera have a characteristic, if not specific cellular composition which closely resembles that of the cutaneous lesions in the same patient. The neoplastic infiltration is manifested by the proliferation of predominantly mononuclear cells ranging in size from 10 to 20 μm, with occasional cells that were indistinguishable from Sternberg-Reed cells, and those exceptions in which we did find occasional cells that were indistinguishable from Sternberg-Reed cells. Both patients had the clinical features of M.F., one for 25 years, the other for 10 years, and for most of these periods the disease was limited to the skin. This is certainly not a clinical picture to be expected in Hodgkin’s disease.

In summary, we found that M.F. retains its specific and distinctive histologic and cyto-logic features throughout the course of the disease, and that great morphologic similarities exist between the skin lesions at the infiltrative and tumor stages on the one hand and the extracutaneous lesions on the other. These findings are in accordance with the views previously expressed by a minority of students of this disease. The question arises whether there is a distinctive cell which allows one to make a diagnosis of M.F. in autopsy sections with unequivocal certainty. Our experience seems to suggest that the diagnosis is cumulative rather than being based on a single feature, but that one cell type, with hyperchromatic and frequently indented nuclei, is highly characteristic of M.F. and is found in the great majority of patients at autopsy. We also believe, but cannot be certain, that the cells described by Lutzner et al. as mycosis fungoides cells, which are characterized electron-microscopically by deeply infolded, convoluted, serpentine, and cerebriform nuclei, are highly characteristic even though they have been reported to occur also in cutaneous lesions other than M.F. These cells can be recognized under the light microscope in well-prepared sections. Lutzner et al. found “cells with features indistinguishable from M.F.” in a cutaneous “reticulum cell sarcoma.” The only extracutaneous neoplastic disease in which cells with convoluted nuclei morphologically similar to and occasionally indistinguishable from those found in mycosis fungoides were seen was in poorly differentiated lymphocytic lymphoma with a nodular (follicular) pattern. As to the origin of the M.F. cells, ultrastructural studies suggest that they are lymphoid rather than histiocytic cells. Studies of the characteristics of the cell surface membranes in Sézary syndrome seem to indicate that the circulating Sézary cells are T lymphocytes. If the views of those observers who consider Sézary syndrome to be a variant of M.F. are correct, it is very likely that the cells in the tissues of patients with M.F. and those circulating in the blood of patients with Sézary syndrome have the same origin. Moreover, the T lymphocyte derivation of neoplastic cells obtained from cutaneous lesions of M.F. has recently been reported.

Summary

A survey of the autopsy material in 45 clinically and histologically typical cases of M.F. revealed extracutaneous involvement in 32 (71%). Contrary to reports in the literature according to which M.F., when involving the viscera, progresses into lymphosarcoma, reticulum cell sarcoma, or Hodgkin’s disease, our observations indicate that the lesions in the lymph nodes and viscera have a characteristic, if not specific cellular composition which closely resembles that of the cutaneous lesions in the same patient. The neoplastic infiltration is manifested by the proliferation of predominantly mononuclear cells ranging in size...
from large lymphocytes to histiocytes. These cells show a relatively even distribution of the nuclear chromatin and small, but distinct nucleioli. Scattered throughout the lesions are larger cell forms with hyperchromatic nuclei which are often deeply indented, the so-called mycosis cells. Other cells in which the nuclei exhibit numerous cerebriform infoldings appeared to be similar to, if not identical with, the cells observed electron-microscopically by Lutzner et al.\textsuperscript{38} in M.F. and Sézary syndrome. In a relatively small number of cases, bizarre and often multinucleated cellular monstrosities were evident. The hyperchromatic mycosis cells and the cells with convoluted, cerebriform nuclei are most helpful and at times essential for the differentiation of the cellular proliferation of M.F. from that of other malignant lymphomas. Our observations confirm that M.F. is both a clinical and a pathologic entity; they indicate further that the neoplastic cellular proliferation in both cutaneous and extracutaneous tissues is distinct in M.F. and differs histologically from the proliferation of other lymphoid neoplasms which usually arise in the lymph nodes or extracutaneous lymphoid tissue, but occasionally also in the skin.

REFERENCES
29. Holzmann, V. H., und Hoebe, N.: Zur Frage der nosologischen Selbständigkeit der Mycosis fungoides


