Arsenic-Induced Lesions

Prepared By:
José A. Centeno, Ph.D.¹
Leonor Martínez, M.D.¹
Elena R. Ladich, M.D.¹
Norbert P. Page, D.V.M., M.S.¹
Florabel G. Mullick, M.D., SES¹
Kamal G. Ishak, M.D., Ph.D.¹
Baoshan Zheng, Ph.D.⁵
Herman Gibb, Ph.D.²
Claudia Thompson, Ph.D.³
David Longfellow, Ph.D.⁴

Sponsored By:
¹Armed Forces Institute of Pathology
American Registry of Pathology
²U.S. Environmental Protection Agency
³National Institute of Environmental Health Sciences
⁴National Cancer Institute
U.S. Geological Service

Contributor:
⁵Institute of Geochemistry & Academia Sinica, P.R. China

April 2000
Preface

José A. Centeno, Ph.D.

The public health concern for environmental exposure to arsenic (\(^{35}\text{As}_{75}\)) has been widely recognized for decades. However, recent human activities have resulted in even greater arsenic exposures and the potential increase for chronic arsenic poisoning on a worldwide basis. This is especially the case in China, Taiwan, Thailand, Mexico, Chile, and India. The sources of arsenic exposure vary from burning of arsenic-rich coal (China) and mining activities (Malaysia, Japan) to the ingestion of arsenic-contaminated drinking water (Taiwan, Philippines, Mexico, Chile). The groundwater arsenic contamination in Bangladesh and the West Bengal Delta of India has received the greatest international attention due to the large number of people potentially exposed and the high prevalence of arsenic-induced diseases. Recent estimates suggest that as many as 20 to 30 million people are at risk from drinking arsenic-contaminated water in Bangladesh, which is obtained from the millions of tube wells that appear to be contaminated with naturally occurring arsenic.

Several epidemiological studies have documented the global impact of arsenic contamination and the characterization of the sources of exposure. However, the mechanisms of arsenic-induced health effects, including cancer, are not well characterized. Research is needed to provide a better understanding of the pathobiology of arsenic-induced diseases. Environmental pathology studies are needed to better define the potential toxic effects that arsenic may induce in one or more organ systems. One of the impediments to research on the histologic characteristics of arsenic-induced diseases has been the lack of well-characterized tissues from exposed populations. While tissues and clinical data may be available in various locations around the world, they have not been systematically collected and evaluated using well-established criteria for pathologic diagnosis.

The Armed Forces Institute of Pathology (AFIP) is participating in an international research effort aimed at the development of an International Tissue and Tumor Repository for Chronic Arsenosis (ITTRCA). A component of this registry is to provide a mechanism by which to describe the underlying pathology and morphology of arsenic-induced lesions. One hundred and seventy-five cases currently available at the ITTRCA have been reviewed. These cases were retrieved from the archives of the National Tissue Repository of the AFIP. The major thrust of the ITTRCA is to facilitate the formulation of a standardized system of nomenclature for the study of skin lesions and other arsenic-induced changes in tissues by the use of archival materials. This syllabus represents an international collaborative effort on this line of research, designed to enhance our understanding of the morphologic basis of arsenic-induced diseases.
Acknowledgments

This study was supported, in part, by an interagency collaborative agreement between the Armed Forces Institute of Pathology, the National Center for Environmental Assessment (US Environmental Protection Agency), the National Institute of Environmental Health Sciences, the National Cancer Institute (Chemical and Physical Carcinogenesis Branch), and the US Geological Survey. The authors are grateful for the support and efforts of all contributors, collaborators, and participants of the International Tissue and Tumor Repository for Chronic Arsenosis (ITTRCA), especially, Dr. Claudia Hopenhayn-Rich (University of Kentucky), Dr. Catteerina Ferriccio (Pontificia Universidad Católica de Chile), Dr. G. N. Guha Mazumder (Institute of Post-Graduate Medical Education and Research, India), Dr. Michael Harbut (Center for Occupational & Environmental Medicine, Michigan), Dr. Mariano Cebrián (CINVESTAV-IPN, México), and Dr. Chien-Jen Chen (National Taiwan University, Taiwan).

We are particularly grateful for the fine efforts and dedication of the ITTRCA Steering Committee members, including Dr. Herman Gibb (National Center for Environmental Assessment-US Environmental Protection Agency), Dr. Robert B. Finkelman (US Geological Survey), Dr. Claudia Thompson (National Institute of Environmental Health Sciences), Dr. David Longfellow and Dr. Yung-Pin Liu (Chemical and Physical Carcinogenesis Branch - National Cancer Institute), and Dr. Judith Mumford (US EPA).
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td>5</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>6</td>
</tr>
<tr>
<td>1.0 INTRODUCTION</td>
<td>9</td>
</tr>
<tr>
<td>2.0 OVERVIEW OF NORMAL EPITHELIUM</td>
<td>10</td>
</tr>
<tr>
<td>3.0 ARSENIC-INDUCED LESIONS</td>
<td>11</td>
</tr>
<tr>
<td>3.1: Epithelium</td>
<td>13</td>
</tr>
<tr>
<td>3.2: Liver</td>
<td>15</td>
</tr>
<tr>
<td>3.3: Other organs</td>
<td>20</td>
</tr>
<tr>
<td>4.0 CONTENTS OF SYLLABUS AND STUDY SET</td>
<td>21</td>
</tr>
<tr>
<td>5.0 REFERENCES</td>
<td>24</td>
</tr>
<tr>
<td>6.0 CASE REPORTS</td>
<td>27</td>
</tr>
<tr>
<td>Case 1: Skin pigmentation</td>
<td>27</td>
</tr>
<tr>
<td>Case 2: Early arsenical keratosis</td>
<td>28</td>
</tr>
<tr>
<td>Case 3: Early arsenical keratosis</td>
<td>29</td>
</tr>
<tr>
<td>Case 4: Early arsenical keratosis</td>
<td>30</td>
</tr>
<tr>
<td>Case 5: Early arsenical keratosis</td>
<td>30</td>
</tr>
<tr>
<td>Case 6: Early arsenical keratosis</td>
<td>31</td>
</tr>
<tr>
<td>Case 7: Early arsenical keratosis</td>
<td>32</td>
</tr>
<tr>
<td>Case 8: Exfoliative dermatitis, arsenical pigmentation, and arsenical keratosis</td>
<td>33</td>
</tr>
<tr>
<td>Case 9: Arsenical keratosis</td>
<td>34</td>
</tr>
<tr>
<td>Case 10: Arsenical keratosis and Bowen’s disease</td>
<td>35</td>
</tr>
<tr>
<td>Case 11: Arsenical keratosis</td>
<td>36</td>
</tr>
<tr>
<td>Case 12: Arsenical keratosis</td>
<td>36</td>
</tr>
<tr>
<td>Case 13: Squamous cell carcinoma and arsenical keratosis</td>
<td>36</td>
</tr>
<tr>
<td>Case 14: Arsenical keratosis</td>
<td>37</td>
</tr>
<tr>
<td>Case 15: Arsenical keratosis and liver fibrosis</td>
<td>39</td>
</tr>
<tr>
<td>Case 16: Basal cell carcinoma and arsenical keratosis</td>
<td>39</td>
</tr>
<tr>
<td>Case 17: Basal cell carcinoma and Bowen’s disease with arsenical keratosis</td>
<td>40</td>
</tr>
<tr>
<td>Case 18: Squamous cell carcinoma and arsenical keratosis</td>
<td>41</td>
</tr>
<tr>
<td>Case 19: Early basal cell carcinoma and arsenical keratosis</td>
<td>42</td>
</tr>
<tr>
<td>Case 20: Hepatocellular carcinoma and cirrhosis</td>
<td>43</td>
</tr>
<tr>
<td>Case 21: Angiosarcoma of the liver</td>
<td>44</td>
</tr>
<tr>
<td>Case 22: Angiosarcoma of the liver</td>
<td>45</td>
</tr>
<tr>
<td>Index</td>
<td>47</td>
</tr>
</tbody>
</table>

Table 1. Summary of case reports .......................................................... 23
1.0 INTRODUCTION

It has been known for many years that arsenic exposure can cause a wide variety of toxic effects ranging from death following acute high-dose exposure to latent effects and cancer from chronic exposure with lower doses. Arsenic has been used for centuries as an intentional poison as well as in medicinals, patent medicines, and pesticides. Most uses of arsenic for medical treatment and pesticide applications have been discontinued, although arsenic is still found in folk medicines in some countries as well as in some pesticides. Until the availability of antibiotics (in the late 1940s) and other therapies, it was common practice to treat syphilis and psoriasis with arsenicals. Several of the patients described in the case reports in this syllabus developed lesions attributed to treatment with arsenic-containing medicines or exposure to arsenical pesticides.

While concern for arsenic exposure from medicines has decreased, the concern for arsenic contamination of the environment has increased. Indeed, some geographic areas (e.g. China, India, Bangladesh, Inner Mongolia, Chile, Mexico) have now become heavily contaminated with exceptionally high levels of arsenic in drinking water (Guha Mazumder et al, 1999 a & b) and other environmental media (Centeno et al, 1999; Finkelman et al, 1999). This situation has become an important international problem. The Armed Forces Institute of Pathology (AFIP) is participating in an international effort to better understand the toxic effects of arsenic under various chronic exposure situations. Biological mechanisms by which arsenic induces chronic effects, including cancer, are not well understood and are the subject of considerable research efforts.

The diagnostic criteria for arsenic pathology has not been well documented in the literature, due to the large spectrum of lesions that may be present in arsenic-exposed persons and the lack of international agreement on the criteria for diagnosis of the lesions. In addition, the types of lesions may differ somewhat depending on the species of arsenic encountered, the route of exposure, and the dose and duration of exposure.

It is the purpose of this study set to make available for review a
set of microscopic slides of frequently encountered but rather specific pathologic lesions found in arsenic-exposed persons. The syllabus and study set should be useful to toxicologists, environmental scientists, public health scientists, medical students, pathology residents, and experienced pathologists. For this reason, a discussion of the normal skin and liver is presented, which should facilitate understanding of the pathological lesions that are provided with each case report.

2.0 OVERVIEW OF NORMAL EPITHELIUM

The most common lesions resulting from arsenic exposure take place in the skin. For this reason, most of the slides in this syllabus pertain to pathological changes in the skin, particularly within the epidermis. To orient those not particularly familiar with the structure of the skin and the terminology used, a short overview of skin anatomy and physiology and specific descriptive pathological terms is presented.

The skin is composed of three basic layers: the epidermis, dermis, and subcutaneous tissue. The epidermis is the outermost layer, followed by the dermis, and the innermost layer, the subcutaneous tissue. The epidermis protects the body from potential invading organisms or toxic substances and is further divided into five layers or strata (Figure 1). The outermost layer of cells, known as the *stratum corneum*, consists of flattened, keratinized dead cells. This layer, also known as the *cornified layer*, consists largely of squamous epithelial cells that have moved upward from the underlying cell layers, lost their nutrient supply, become packed with keratin, and died. Keratin is a strong, durable, flexible, water-resistant protein. When epithelium contains large amounts of keratin it is considered “keratinized” or “cornified.”

Lying directly under the *stratum corneum* is the *stratum lucidum*, a clear layer of flattened and densely packed cells that produce the
keratin. It is thickest in areas where highly keratinized skin is needed, such as on the soles of the feet and palms of the hands. Toxicity to cells in this layer can result in a change in the normal amount of keratin.

Lying directly under the stratum lucidum is the stratum granulosum. That layer (frequently referred to as the granular layer) contains cells that have stopped dividing but have started to produce large amounts of enzymes and proteins, having moved upward and away from the blood supply.

Lying beneath the stratum granulosum is the stratum spinosum (referred to as the spiny layer). It consists of cells only a few layers thick that appear spiny because of projections connecting adjacent cells. Cells in this layer continue to divide, but at a reduced rate, as they move upward toward the stratum granulosum.

The deepest layer of cells in the epithelium is the stratum germinativum, sometimes referred to as the basal layer. This layer of cells is firmly attached to the basement membrane that separates the epidermis from the loose connective tissue of the underlying dermis. It is in this layer that new skin cells are constantly generated and then move upward to form the entirety of the epithelium. Within this layer are the melanocytes as well as squamous, columnar-like cells. The melanocytes produce melanin, a yellow-brown to black pigment that provides the color to the epidermis. Toxins acting on cells in the stratum granulosum can interfere with the normal cellular proliferation and replacement of skin cells as well as the distribution and amount of coloring to the skin. The number of layers within the stratum granulosum can vary considerably, giving rise to epidermal ridges (also referred to as rete ridges) extending down into the dermis and separating the dermal papillae. This innermost layer is also known as the malpighian or prickle layer and the cells are often referred to by pathologists as the prickle cells.

The skin is a dynamic organ with cells constantly dying and being replaced. The replacement process as described is normally an orderly movement of cells from the stratum granulosum upward to the stratum corneum. On the way through progression of the four upper layers, the cells leave their nutrient supply behind, produce keratin, lose their nuclei and granules and die, forming scales in the outermost hard surface of the skin. This continuous process of epithelial proliferation and cell replacement is known as keratinization.
Figure 2A-F. GROSS APPEARANCE OF ARSENIC INDUCED SKIN LESIONS
3.0 ARSENIC-INDUCED LESIONS

Following absorption, arsenic is distributed widely in the body, with greatest concentrations appearing in the skin, liver, kidneys, lungs, and spleen. Only small amounts appear to cross the blood-brain barrier. Arsenic tends to concentrate in ectodermal tissues including the skin, hair, and nails, even with low-level exposures. As might be expected, the skin is a primary target organ for arsenic toxicity, especially with chronic exposures.

Epidemiologic studies have confirmed the role of arsenic in the induction of cancers of the skin and provide suggestive evidence of its role in causing lung cancer and urinary bladder cancer. Several reports suggest a role of arsenic in cases of liver cancer (angiosarcomas) and several other internal cancers. In nearly all cases where internal cancers are attributed to arsenic exposure, there has been cutaneous evidence of arsenic exposure in the form of arsenical keratosis, hyperpigmentation, and multiple cutaneous malignancies (Maloney, 1996). The cases presented in this syllabus include a range of pathological conditions that can be related to arsenic exposure including keratosis, hyperkeratosis, parakeratosis, pigmentation, squamous cell carcinoma, and basal cell carcinoma. Selected pictures are provided (Figures 2A-2E) to illustrate the gross clinical appearance of these arsenic-induced lesions. Cancers of the liver have also been observed including hepatocellular carcinoma, and angiosarcoma of the liver. A brief overview of these skin and liver lesions is provided to orient the use of this syllabus.

3.1 EPITHELIUM

3.11 Arsenical keratosis

Arsenical keratosis in its fully developed form is a well-established clinical syndrome, characterized by several specific pathological features, including hyperkeratosis, parakeratosis, arsenical pigmentation, and squamous cell carcinoma in situ (indistinguishable from Bowen’s disease). One of the distinguishing histologic features of arsenical lesions is the absence of dermal solar elastosis. The lesions are normally most pronounced on the feet and hands, although they can occur on the trunk and other areas of the extremities (Farmer and Hood, 1990). In the early stages of arsenical keratosis, the presence of squamous cell carcinoma in situ may not be evident. We refer to this situation as “early arsenical keratosis.”

In many cases of arsenical keratosis, malignancies other than Bowen’s disease may be found, including squamous cell carcinoma, basal cell carcinomas, and internal malignancies. Of
the 22 cases presented in this syllabus, seven had malignancies in addition to arsenical keratosis.

3.1.2 Definitions of Epithelial Lesions

Keratosis is a general term that indicates abnormality in keratinization.

Dyskeratosis refers to irregular keratinization.

Hyperkeratosis is a term used to describe hypertrophy of the stratum corneum (cornified layer).

Parakeratosis is a condition where epithelial proliferation becomes more rapid than normal, the cells progress upward so fast that there is no longer a granular layer, and the outer layer of cells still retain their nuclei.

Acanthosis is a condition in which there is hyperplasia and thickening of the prickle cell layer (stratum granulosum).

Arsenical keratosis is an arsenic-specific dermal condition with several distinct pathological entities. Squamous cell carcinoma in situ, which is analogous to that observed in solar keratosis, is a frequent lesion. Other lesions observed are hyperkeratosis, acanthosis, disorder in the arrangement of the squamous cells, nuclear atypicalities (such as hyperchromasia), clumping or dyskeratosis, and vacuolization of the epidermal cells.

Bowen’s disease is an intraepidermal squamous cell carcinoma, referred to as squamous cell carcinoma in situ. It is considered a precancerous dermatosis. Common causes of Bowen’s disease are arsenic and solar radiation.

Dermal hypopigmentation is a decrease in the degree of pigmentation of the skin.

Dermal hyperpigmentation is an increase in the degree of pigmentation of the skin.

Melanosis is a disturbance in melanin pigmentation.

Skin tumors are named for the cells from which they originate. The most common skin tumors are squamous cell tumors (papillomas or carcinomas), basal cell carcinoma, and melanomas. The term epithelioma (often encountered in the older literature) refers to any tumor arising from epithelial cells. Arsenic has been implicated in the induction of squamous cell tumors,
basal cell cancers, and melanomas.

**Squamous cell carcinomas** are true, invasive carcinomas of the surface epidermis, consisting of irregular masses of epidermal cells that proliferate downward and invade the dermis. The invading tumor masses are composed of varying proportions of normal squamous cells and of atypical squamous cells.

**Basal cell carcinomas** (basal cell epitheliomas) arise from the characteristic cell referred to by some as basalioma cells. They have a large, oval or elongated nucleus and relatively little cytoplasm. The cytoplasm of individual cells is poorly defined. The nuclei resemble those of the basal cells of the epidermis, but basalioma cells differ from basal cells by not showing intercellular bridges by light microscopy.

**Melanomas** are tumors arising from the melanocytes. The term melanoma usually is synonymous with malignant melanoma.

### 3.2 LIVER

The great susceptibility of the liver to damage by an enormous array of pharmaceutical and environmental chemicals is a consequence of its primary role in the metabolism and detoxification of foreign compounds. The liver is vulnerable to a wide variety of toxic substances, and as such may exhibit any form of known hepatic lesions. The pathologic effects of drugs and toxins on the liver can be broadly classified into acute and chronic. Acute liver injury includes hepatocellular injury (spotty, submassive, or massive necrosis), acute combined hepatocellular and cholestatic injury, acute intrahepatic cholestasis, microvesicular steatosis, and vasculitis. Morphologic changes associated with chronic exposures include chronic hepatitis, macrovesicular steatosis, phospholipidosis, cholestatic lesions, steatohepatitis, granulomatous reactions, fibrosis, cirrhosis, vascular lesions, and neoplasms (Ishak and Zimmerman, 1995). Historically, many agents with hepatotoxic potential were encountered occupationally in the munitions, rocketry, plastics, agricultural, paint, cosmetic, pharmaceutical, and other chemical industries (Zimmerman and Maddrey, 1993). In the United States today, hepatic injury caused by adverse reactions to medicinal agents is more commonly encountered than occupational exposure to toxic chemicals (Zimmerman, 1999).

The liver is the major organ for detoxification of arsenic, which accumulates in this organ after exposure. One of the earliest descriptions of arsenic-induced liver disease dates back to the late 19th century, when Sir Jonathan Hutchinson described a
young man with psoriasis who developed ascites after treatment with Fowler’s solution (arsenic trioxide) (Hutchinson, 1895). Currently in the United States, medicinal arsenic preparations are avoided, with some rare exceptions (for example, in the treatment of refractory acute promyelocytic leukemia or some parasitic infections) because of serious side effects (Huang et al., 1998). Worldwide, environmental exposures remain a significant problem. Chronic liver diseases which can be ascribed to arsenic toxicity include steatosis, cirrhosis, hepatoporal sclerosis (noncirrhotic portal hypertension), angiosarcoma, and perhaps hepatocellular carcinoma (Zimmerman, 1999). Of the 22 patients in this syllabus, three had liver neoplasms at autopsy; two were angiosarcomas and the third was a hepatocellular carcinoma. In addition, in the absence of archival material, we present a brief discussion of the entity known as hepatoporal sclerosis (non-cirrhotic portal fibrosis). It is included because several reports in the literature have provided suggestive evidence of arsenic as an etiological factor.

### 3.2.1 Normal Hepatic Histology

The basic functional unit of the liver is the liver lobule, which exists in two dimensions as a roughly hexagonal structure approximately 1-2 mm in diameter (MacSween and Scothorne, 1994). The lobule is constructed around a central vein with portal triads defining the corners. Plates or cords of hepatocytes radiate centrifugally toward the portal areas from the central vein like spokes in a wheel (Figure 3). Each hepatic plate is one cell thick in the adult, and is bathed on either side by blood within the hepatic sinusoids, which maximizes contact of hepatocytes with blood flowing through the liver. The sinusoids are lined by endothelial cells and macrophages called Kupffer cells. Each portal tract (also known as a portal triad) consists of a collagenous supporting stroma, which contains interlobular bile...
ducts and branches of the portal vein and hepatic artery. The liver is unusual in that it has a dual blood supply that is both arterial and venous. The portal veins receive their blood mainly from the venous outflow tract of the gastrointestinal tract and spleen. The blood enters the liver nearest the portal tract, and thus the hepatocytes immediately abutting the portal tract (limiting plate) receive highly oxygenated blood. The hepatocytes near the central vein are most remote from the blood supply and are therefore most susceptible to anoxic injury. The hepatocytes secrete bile into a system of canaliculi, which form an anastomosing network between hepatocytes. From each lobule, bile canaliculi drain toward the interlobular bile ducts of the portal tracts to which they are connected by canals of Hering.

The classic hexagonal lobule contains within it metabolic lobules, also known as acini. The acinus is a three-dimensional physiological concept based on the direction of blood flow in the lobule. The parenchyma of the acinus is divided into three zones, zone 1 being closest to the vascular supply at the periphery (portal tract), zone 3 most distal at the terminal hepatic vein, and zone 2 intermediate. This zonation holds functional significance since a metabolic gradient of activity exists for many hepatic enzymes, and many forms of hepatic injury demonstrate a zonal distribution (Crawford, 1999).

3.2.2 Neoplasms of the Liver

Angiosarcoma

Angiosarcoma of the liver, also known as hemangioendothelial sarcoma, is a malignant neoplasm of the liver constituting only 2% of all primary liver tumors in Western countries. It has become a subject of interest because of its relationship with environmental carcinogens such as vinyl chloride monomer, thorium dioxide, and inorganic arsenic. The Centers for Disease Control (CDC) conducted a nationwide hepatic angiosarcoma case-finding study for the years 1964-1974 and identified 168 cases (Falk et al, 1981b). Of these, 42 (25%) were associated with a known etiologic factor such as vinyl chloride monomer, Thorotrast, inorganic arsenic, or treatment with anabolic steroids. The remaining 126 cases (75%) were of uncertain etiology. The study found that hepatic angiosarcoma most often affects males, peaks in the sixth to seventh decades of life (somewhat earlier than other sarcomas of the liver), and appears to occur more often in industrialized portions of the country. In addition, groups with chemical exposure were found to be at higher risk, raising the possibility that some of the idiopathic cases may be related to presently unidentified environmental or occupational exposures (Falk et al, 1981b).
The relationship of chronic arsenic intoxication to angiosarcoma of the liver has been well documented. Roth (1957) described the correlation between hepatic angiosarcoma and arsenic-containing pesticide exposure in German vineyard cultivators in the 1940s and 1950s. Regelson (1968) was the first to report a case in the American literature. A nationwide review of deaths from angiosarcoma of the liver identified seven cases with a history of prolonged use of Fowler’s solution (inorganic potassium arsenite), which provided further support for the association between chronic arsenic exposure and angiosarcoma (Falk et al, 1981a). Several reports in the literature have followed those seminal papers, one of which documents a case of angiosarcoma and hepatocellular carcinoma (noncirrhotic portal hypertension) in the same patient with chronic arsenic salt exposure. The latent period in these studies varied from 13-29 years (Regelson, 1968; Roth, 1957; Falk et al, 1981a; Duenas, 1998).

Grossly, the pathologic features demonstrate an enlarged liver (may be greater than 3000 grams), which on sectioning often reveals multiple masses, ranging in appearance from large cavernous areas to smaller dark red or solid gray areas. Microscopic examination reveals two major growth patterns, solid and cavernous (Figures 4A-4B). The cavernous pattern exhibits plump, fusiform, hyper-chromatic endothelial cells layered along dilated sinusoids or cavitory spaces. The solid pattern shows sheets of anaplastic spindled tumor cells, which may or may not demonstrate microvascular structures. Focal areas of hemorrhage and
necrosis are common (Kanel and Korula, 1992). The tumor originates in the endothelial cells of the hepatic sinusoids and positive staining with Factor VIII-related antigen, an endothelial marker, is characteristic of angiosarcoma. Other antigens like CD31 and CD34 can also be detected immunohistochemically.

Hepatocellular Carcinoma

Recent studies have documented a significant association between hepatocellular carcinoma (HCC) and ingested inorganic arsenic. A study in Taiwan reported a dose-response relationship between HCC risk and arsenic level in drinking water (Chen and Wang, 1990). In addition, a recent review describes the association between inorganic arsenic exposure and HCC as documented in Japan and Germany (Chen and Lin, 1994). Worldwide, however, most cases of HCC are related to chronic infection with viral hepatitis B or C, aflatoxin exposure, alcohol abuse, and genetic hemochromatosis.

Histologically, hepatocellular carcinomas range from well differentiated to quite anaplastic undifferentiated lesions. In the moderate to well differentiated types, trabeculae are more than two to three cells thick and are composed of tumor cells that exhibit round to oval nuclei with a high N/C ratio and prominent nucleoli. They are surrounded by sinusoidal spaces. The malignant cells often have an abundant eosinophilic cytoplasm and may contain bile, fat, glycogen, or cytoplasmic inclusions. Canaliculi are often demonstrable between tumor cells. In addition, other clues helpful in diagnosis are the presence of mitoses, tumor within vascular structures, and infiltration of tumor into adjacent liver. Although other variants of hepatocellular carcinoma exist, it is beyond the scope of this syllabus to provide a comprehensive review.

3.2.3 Hepatoportal Sclerosis (Noncirrhotic Portal Fibrosis)

Hepatoportal sclerosis (HS), also known as noncirrhotic portal fibrosis, idiopathic portal hypertension, or Banti’s syndrome, is defined as a disorder of unknown etiology characterized by splenomegaly, anemia, and portal hypertension in the absence of liver cirrhosis, extrahepatic portal vein obstruction, blood diseases, parasitic diseases, granulomatous diseases, congenital hepatic fibrosis, and other known diseases (Okuda, 1989). Clinically it is manifested by splenomegaly and episodes of gastrointestinal hemorrhage due to esophageal varices.

Histologically, HS is characterized by thickening and sclerosis of the wall of large portal vein branches. Increased perivascular fibrosis is seen in the portal tracts, which may show obliteration or sclerosis of portal vein branches. The portal vein lumen is
reduced and organized thrombi with recanalization may be seen. The bile ducts may show concentric periductal fibrosis. Lobular architecture is maintained with some mild fibrous bridging between the portal areas and the portal and central areas.

Although the etiology of HS is not known, chronic arsenic ingestion has been associated with the development of the disease in several different reports. Nevens et al (1990) described eight patients who had received an arsenic preparation for psoriasis as Fowler's solution some years previously. In addition, these patients also showed characteristic arsenical skin changes. Datta et al (1979) reported nine patients from northern India with HS and found high levels of arsenic in the majority of their livers. It has been postulated that arsenic is an etiological factor in the production of HS in some patients, perhaps because of damage to the intrahepatic portal veins.

3.3 OTHER ORGANS

The evidence for a causal relationship between arsenic exposure and cancer is strong and indisputable for cancers of the skin and lung. The causal relationship between skin cancer and arsenic exposure can often be made with confidence since frequently there are other lesions known to be caused by arsenic, such as hyperkeratosis, hyperpigmentation, or hypopigmentation. Cancers of the internal organs do not have similar exposure biomarkers so that their association with a particular etiologic agent cannot be established with the same level of confidence. The evidence for such cancer-arsenic associations has come from epidemiologic studies since there are no suitable animal models to conduct research on these issues.

According to a recent epidemiologic study from a blackfoot disease-endemic area of Taiwan, high mortality was found in males and females for skin, liver, lung, bladder, kidney, and nasal cancers, and possibly other sites. Generally speaking, the outcomes of this study corroborate the results of several other studies suggesting a relationship between arsenic exposure and cancers of the internal organs. (Tsai et al, 1999). For example, arsenic has been implicated as a bladder carcinogen in separate studies from Argentina, Chile, and Taiwan (Biggs et al, 1998 and Hopenhayn-Rich et al, 1996). In addition, the results of a recent study in Cordoba, Argentina add to the evidence that arsenic ingestion increases the risk of kidney cancers (Hopenhayn-Rich et al, 1998). An association between carcinoma of the lung and inhaled arsenic is well established; more recent studies have shown that ingested arsenic may also be an etiological factor in the development of lung cancer (Tsai et al, 1999).
In conclusion, the results of these studies indicate that the health effects of arsenic are systemic and may involve multiple organs. Epidemiologic studies strongly support the potential relationship between chronic arsenic exposure and mortality from certain cancers. At the present time, the biological mechanisms by which arsenic exerts its toxic and carcinogenic activities are not well understood. In order to completely assess the potential adverse health risks of arsenic in various exposure situations, it will be important to understand not only the mechanism(s) of action, but metabolic and toxicokinetic principles of arsenic activity as well. The search for biomarkers of exposure continues to be equally important as a means of identifying individuals susceptible to carcinogenesis. However, establishing clear carcinogenic endpoints of arsenic exposure remains the overriding goal in determining intervention and preventing risks. In this Syllabus, we are presenting three cases of internal cancers that have strong evidence for an association with arsenic exposure: two cases of angiosarcoma of the liver and one case of hepatocellular carcinoma.

4.0 CONTENTS OF SYLLABUS AND STUDY SET

The Syllabus consists of 22 cases that are a representative sample of the 175 arsenic cases contained in the AFIP archives. It provides a description of each case, including clinical history and histologic findings. Photomicrographs are available for most of the cases. Of the 22 cases, 14 involve skin lesions, one case pertains to both the skin and liver, and seven cases demonstrate cancers of either the skin or liver (Table 1).

The Study Set provides microscopic slides for all 22 cases and is available for review at the AFIP-ITTRCA located at the AFIP Department of Environmental and Toxicologic Pathology.
Table 1. Summary of case reports

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnoses</th>
<th>Age/ Sex</th>
<th>Source of Arsenic Exposure</th>
<th>Route of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skin pigmentation</td>
<td>24 M</td>
<td>Neoarsphenamine</td>
<td>Injections</td>
</tr>
<tr>
<td>2</td>
<td>Early arsenical keratosis</td>
<td>41 M</td>
<td>Arsenic fumes – smelter</td>
<td>Inhalation</td>
</tr>
<tr>
<td>3</td>
<td>Early arsenical keratosis</td>
<td>34 M</td>
<td>Fowler’s solution</td>
<td>Oral</td>
</tr>
<tr>
<td>4</td>
<td>Early arsenical keratosis</td>
<td>27 M</td>
<td>Syphilis treatment</td>
<td>Oral</td>
</tr>
<tr>
<td>5</td>
<td>Early arsenical keratosis</td>
<td>25 M</td>
<td>Mapharsen (syphilis)</td>
<td>UK</td>
</tr>
<tr>
<td>6</td>
<td>Early arsenical keratosis</td>
<td>48 M</td>
<td>Arsenical drug</td>
<td>Oral</td>
</tr>
<tr>
<td>7</td>
<td>Early arsenical keratosis</td>
<td>21 M</td>
<td>Neosalvarsan</td>
<td>Injections</td>
</tr>
<tr>
<td>8</td>
<td>Exfoliative dermatitis, arsenical pigmentation, and arsenical keratosis</td>
<td>40 M</td>
<td>Arsphenamine</td>
<td>Injections</td>
</tr>
<tr>
<td>9</td>
<td>Arsenical keratosis</td>
<td>63 M</td>
<td>Acatco (patent medicine)</td>
<td>Oral</td>
</tr>
<tr>
<td>10</td>
<td>Arsenical keratosis</td>
<td>76 F</td>
<td>Fowler’s solution</td>
<td>Oral</td>
</tr>
<tr>
<td>11</td>
<td>Arsenical keratosis</td>
<td>79 M</td>
<td>Possible syphilis treatment</td>
<td>UK</td>
</tr>
<tr>
<td>12</td>
<td>Arsenical keratosis</td>
<td>51 M</td>
<td>Unknown but suspected</td>
<td>UK</td>
</tr>
<tr>
<td>13</td>
<td>Squamous cell carcinoma and arsenical keratosis</td>
<td>51 M</td>
<td>Arsenical insecticide</td>
<td>Inhalation/dermal</td>
</tr>
<tr>
<td>14</td>
<td>Arsenical keratosis</td>
<td>47 F</td>
<td>Arsenic tonic</td>
<td>Oral</td>
</tr>
<tr>
<td>15</td>
<td>Arsenical keratosis and liver fibrosis</td>
<td>36 M</td>
<td>Arsenical rodenticide</td>
<td>Inhalation</td>
</tr>
<tr>
<td>16</td>
<td>Basal cell carcinoma and arsenical keratosis</td>
<td>26 M</td>
<td>Arsenic compound (UK)</td>
<td>UK</td>
</tr>
<tr>
<td>17</td>
<td>Squamous cell carcinoma and arsenical keratosis</td>
<td>37 M</td>
<td>Arsenic medication for asthma</td>
<td>UK</td>
</tr>
<tr>
<td>18</td>
<td>Early basal cell carcinoma and arsenical keratosis</td>
<td>47 F</td>
<td>Fowler’s solution</td>
<td>Oral</td>
</tr>
<tr>
<td>19</td>
<td>Hepatocellular carcinoma and cirrhosis</td>
<td>32 M</td>
<td>Fowler’s solution</td>
<td>Oral</td>
</tr>
<tr>
<td>20</td>
<td>Angiosarcoma of the liver</td>
<td>76 M</td>
<td>Fowler’s solution</td>
<td>Oral</td>
</tr>
<tr>
<td>21</td>
<td>Angiosarcoma of the liver</td>
<td>14 M</td>
<td>Contaminated drinking water</td>
<td>Oral</td>
</tr>
</tbody>
</table>
5.0 REFERENCES


Roth F. The sequelae of chronic arsenic poisoning in Moselle vintners. German Med Month. 1957;2:172-175.


Selected Related Literature


Skin Pigmentation

This is a case of skin pigmentation of the arsenical type, which occurred in a 24-year-old male who had received treatment for syphilis for five months with Neoarsphenamine injections. He developed itching and vesicopapules in patches over the entire trunk and face which persisted for several weeks. The lesions finally disappeared; however, later the patient noted gradually increasing dark pigmented macules and amacular patches over the face and trunk.

One microscopic slide is provided of the skin lesions. The skin shows the corneum to be thin and atrophic in many areas of the rete. The rete pegs have disappeared and in other areas they persist as thin, elongated projections. The connective tissue of the papillae and corium is poorly stained and there is some fragmentation of the collagen. The basal layer is pigmented. A few leukocytes and some melanophages are present in the dermis (Figure 5).

Figure 5. ARSENICAL PIGMENTATION. The pigmentation can be clearly observed in this slide prepared with Osborne’s stain.
Early Arsenical Keratosis

This 41-year-old male had a clinical history of working for eight years in a copper smelter, where he had been exposed to arsenic fumes. He presented six years after the occupational exposure with arsenical pigmentation of the skin and cirrhosis of the liver. He also had a history of consuming unknown quantities of Fowler’s solution for an unknown period of time.

Three slides are presented for this case.

Microscopic slide 1. A slide of the skin lesions stained with H&E reveals hyperkeratosis, a varying degree of atrophy of the prickle cells, and pigmentation of the basal cells. There is also dilatation of the superficial capillaries and some edema in the upper part of the cutis.

Microscopic slides 2 and 3 demonstrate staining by the Osborne method, and are positive for the presence of arsenic. Brown and yellow crystals of arsenic trisulphide are deposited in the basal cells (Figure 6).

Figure 6. EARLY ARSENCIAL KERATOSIS. Osborne’s stain. The epithelium shows hyperkeratosis and pigmentation of the basal cells. Crystals of arsenic trisulphide can be observed in the basal cells.
Early Arsenical Keratosis

This 34-year-old man was treated for psoriasis with Fowler’s solution for three years (26 drops daily) about eight years previously. The presence of arsenic in the skin lesions was confirmed with Osborne’s arsenic stain. The patient presented with early lesions of the palms and feet, which were diagnosed as an early form of arsenical keratosis.

The section of the skin shows marked hyperkeratosis and parakeratosis, and the stratum granulosum is absent in some areas. There is marked acanthosis. In other areas the prickle cells show dyskeratotic changes. The upper dermis does not demonstrate significant changes. Osborne’s stain was positive (slide not included).

The epidermis demonstrates hyperkeratosis, parakeratosis, and some disarrangement of the squamous cells. There is vacuolization of some cells and chronic inflammation of the upper dermis. The patient also had a squamous cell carcinoma (microscopic slides not included), which metastasized and caused the patient’s death.
Case 4

Early Arsenical Keratosis

This case demonstrates arsenical keratosis on the skin of the legs and back. The patient was a 27-year-old male who had been treated with an arsenical compound for syphilis in 1940. No specific information on doses and concentrations was available. The antiluetic treatment consisted of alternate courses of arm and hip injections. About nine months after beginning the arsenical treatment, a reddened, itchy, papular eruption appeared on both arms. The eruption apparently healed, only to reappear on the legs, back, face, and penis. He was treated at first with mild zinc oxide lotion and calamine, and then with sulfur, salicylic acid, and silver nitrate, without relief. Following withdrawal of the arsenical treatment, some improvement of the skin lesions was noted.

One microscopic slide is presented of the skin lesions. The section is not well orientated. However, it can be seen that there is hyperplastic squamous epithelium, with the epidermis broken down. The basal layer of the epidermis shows some liquefaction necrosis and detached portions of proliferating squamous epithelium. Considerable inflammatory infiltration is present in the epithelium. Chronic inflammation can be observed in the upper dermis.

Case 5

Early Arsenical Keratosis

This is a case of early arsenical keratosis of the left arm. It involved a 25-year-old male who had been treated with the drug Mapharsen for latent syphilis. The skin condition developed during the period of arsenical treatment. No data are available on the duration of treatment or dose level.

One microscopic slide is provided of the skin lesions. The skin shows mild hyperkeratosis and some acanthosis. There are some vacuolated squamous cells. Chronic inflammation can also be observed in the upper dermis.
Case 6

Early Arsenical Keratosis

This is a case of early arsenical keratosis and marked hyperkeratosis of the right toe. The patient was a 48-year-old male who had a history of chronic ingestion of a drug containing arsenic.

One microscopic slide is provided of the skin lesions. The epidermis shows some acanthosis with elongation of the rete ridges; some cells demonstrate vacuolization and mild disarrangement. Mild chronic inflammation can be observed in the upper dermis (Figure 7).

Figure 7. EARLY ARSENICAL KERATOSIS. The epidermis shows hyperkeratosis and acanthosis.
Case 7

Early Arsenical Keratosis

This is a case of exfoliative dermatitis of the face, chest, and abdomen. The patient was a 21-year-old male who was treated for approximately three months with Neosalvarsan (0.6 gm/week) for syphilis. Three weeks prior to hospital admission, he noticed that the skin had become inflamed and was hard and scaly in places. The hospital admission was two days after the last syphilis treatment, at which time he was found to have a severe exfoliative dermatitis covering the whole body, with wide fissures in the skin and much coning. The skin condition worsened, despite treatment, with lesions developing in the mouth and the skin continuing to exfoliate until many areas of the chest, forearms, and face were entirely free of normal skin. The patient died five days after admission with the cause of death listed as exfoliative dermatitis.

Microscopic slide 1 shows severe hyperkeratosis and desquamation of large areas of keratinized or hyaline-like material. In the upper dermis macrophages containing brown granules can be seen. The malpighian layer demonstrates macrophages with pigment. There are dense bands of collagenous fibers, which in many areas have undergone hyalinization. Scattered hair follicles and sweat glands surrounded by scattered chronic inflammatory cells are noted.

Microscopic slide 2 demonstrates marked hyperkeratosis and desquamation with some areas of keratinized or hyaline-like material. Immediately beneath the epithelial layer are large numbers of chronic inflammatory cells and many macrophages containing granular, brown pigment. Deposits of this pigment are also seen in the deeper cells of the malpighian layer. The upper dermis contains chronic inflammatory cells (Figure 8).

Figure 8. EARLY ARSENICAL KERATOSIS.
Exfoliative Dermatitis, Arsenical Pigmentation, and Arsenical Keratosis

This 40-year-old male had a history of several injections of arsphenamine for treatment of tertiary syphilis. No other data on the extent of the arsenic exposure was presented in the clinical record. The patient presented with exfoliative dermatitis.

The section of skin shows hyperkeratosis with a mild degree of acanthosis, some intercellular and intracellular edema in the prickle cell layer, pyknosis, karyorrhexis, and increased melanin pigmentation of the basal cell layer. There are some mitotic figures and pleomorphism in the epidermis. In the upper portions of the dermis there is a diffuse perivascular infiltrate of lymphocytes and polymorphonuclear leukocytes and few chromatophores with melanin pigment (Figure 9).

Figure 9. ARSENICAL KERATOSIS AND ARSENICAL PIGMENTATION. The epithelium shows hyperkeratosis and acanthosis. There is increased melanin pigment in melanocytes of the basal layer.
Arsenical Keratosis

The patient was a 63-year-old man who took an arsenic-containing patent medicine (Ascatco) for asthma about 20 years prior to the initial appearance of skin lesions. The Ascatco contained 0.11 grains arsenous oxide per ounce, and he estimated that he had consumed 20 ounces per year for a couple of years. The initial appearance of keratosis on the trunk occurred about 20 years after he had discontinued the Ascatco. Six years after the appearance of the keratosis, a tumor developed which necessitated amputation of a finger (reported as an epithelioma). Subsequently, numerous tumors (over 50), also diagnosed as epitheliomas, developed on the trunk. They were described as squamous cell epitheliomas, except for one basal cell epithelioma. Interestingly, arsenical keratosis appeared on the hands but not on the feet. Although there was extensive arsenical keratosis, there was no evidence of arsenical pigmentation.

The section of a biopsy from the skin of the thorax shows an ulcer that is covered by serosanguineous material. There are areas of hyperkeratosis, acanthosis, and complete disarrangement of the epidermal cells (Figure 10). The epithelial cells show vacuolization, intercellular edema, individual cell keratinization, pleomorphism, and mitotic figures.

NOTE: This case was reported in *Arch Dermatol Syphil.* 1935;32:218.

Figure 10. ARSENICAL KERATOSIS. The epithelial cells are pleomorphic and irregularly oriented. Note the absence of dermal solar elastosis.
Case 10

Arsenical Keratosis and Bowen's Disease

This is a case of Bowen’s disease in association with arsenical keratosis. The patient was a 76-year-old woman who had a history of taking Fowler’s solution for psoriasis for an unknown period of time.

One microscopic slide is provided of the skin lesions. The epithelium shows features characteristic of arsenical keratosis including hyperkeratosis, parakeratosis, and acanthosis. Squamous cell carcinoma \textit{in situ} is seen arising in the keratotic lesion. Microscopically, the cells exhibit marked nuclear pleomorphism, scattered mitotic figures and disorderly arrangement within the hyperplastic epidermis (Figure 11).

\textbf{Figure 11. BOWEN’S DISEASE.} Atypical and pleomorphic keratinocytes with scattered mitotic figures are present at all levels of this hyperplastic epidermis.
Case 11

**Arsenical Keratosis**

The patient was a 79-year-old male who had a history of arsenic treatment for syphilis, who developed a lesion of the left tibia.

The section of biopsy of the skin of the left tibia shows papillomatosis, hyperkeratosis, and acanthosis. The malphigian rete shows disorderly arrangement of the cells, with dyskeratosis, hyperchromatic nuclei, and vacuolization. The upper dermis demonstrates some lymphocytes around the vessels.

Case 12

**Arsenical Keratosis**

The biopsies of skin lesions from this 51-year-old male are strikingly similar to arsenic-induced dermal lesions, although there is no known history of arsenic exposure.

Microscopic slide 1. This microscopic slide shows early arsenical keratosis. The skin demonstrates hyperkeratosis, acanthosis, and some disorder and vacuolization in the epidermal cells. The upper dermis contains chronic inflammation.

Microscopic slide 2. The skin shows some hyperkeratosis and marked acanthosis with disorganized cells that show hyperchromatic nuclei and pleomorphism. The upper dermis demonstrates chronic inflammation.

Case 13

**Squamous Cell Carcinoma and Arsenical Keratosis**

This 51-year-old man had been exposed to an arsenic-containing spray insecticide 25-30 years prior to admission. On a previous admission approximately 6 years before, multiple skin lesions had been removed. At the time of this current admission he had developed verrucous skin lesions on the face and neck, one of which was biopsied.

The section of skin shows marked hyperkeratosis, acanthosis, and thickening and elongation of the rete pegs. The epidermal cells demonstrate pleomorphism and vacuolization. The nuclei show hyperchromatism and some mitotic figures. Dense chronic inflammation can be seen in the dermis. The patient was diagnosed with squamous cell carcinoma of the skin.
Case 14

Arsenical Keratosis

This 47-year-old woman had received arsenic in the form of a tonic since she was 14 years of age. She presented with lesions on the skin of the right forearm. Numerous arsenical keratoses had been removed in the past.

A biopsy of one of the skin lesions shows epidermal hyperkeratosis, parakeratosis, horn pearl formation, acanthosis, and disorganized arrangement of squamous cells. Cytoplasmic vacuolization and multinucleation with many mitoses are also seen (Figure 12).

Figure 12. ARSENICAL KERATOSIS. The epidermis demonstrates acanthosis and disorganization of squamous cells.
Arsenical Keratosis and Liver Fibrosis

This patient was a 36-year-old male who worked in an environment that was sprayed weekly with an arsenic-containing rodenticide. He presented with an eight-month history of weakness and paresthesias of the legs and feet. He also noted the appearance of pink to purple spotty discoloration of the skin in both inguinal regions, which subsequently spread to the arms and legs and then into his mouth, producing soreness. Weeks later, he noted some scaliness and thickening on the soles of his feet. On admission, he was found to have an enlarged liver. His fingernails and toenails revealed Mees’ line. He rapidly became disoriented, lethargic, extremely tachypneic, and died shortly after admission. The immediate cause of death was pneumonia.

Two microscopic slides are provided for this case from the autopsied liver.

Microscopic slide 1. This microscopic slide of the liver shows hepatocellular degeneration with minimal regeneration of the liver cells. Portal areas contain lymphocytes. A Masson trichrome-stained section showed an increase in the amount of connective tissue in some of the lobules and in other areas around the central veins (Figure 13).

Microscopic slide 2. This microscopic slide of the skin was taken from the plantar surface of the foot and shows a surface covered by a thick layer of keratin. The epithelium shows variation in size of the rete pegs, some being small and delicate, others being broad. In the subjacent dermis, there is some increase in vascularity with a scattered, loose, perivascular infiltration of lymphocytes and monocytes.

The microscopic findings in this case are consistent with diagnoses of arsenical keratosis and liver fibrosis.

Figure 13. LIVER FIBROSIS. Bridging fibrosis with expansion of portal areas.
Case 16

Basal Cell Carcinoma and Arsenical Keratosis

This 26-year-old male had ingested arsenic during childhood. He presented with skin lesions on the neck when he was 21 years of age.

One slide is provided of the skin lesions. The biopsy of the lesions of the skin of the neck shows marked hyperkeratosis and parakeratosis associated with acanthosis and irregular downward proliferation of the rete pegs. The upper portion of the epidermis shows hyperchromatic nuclei, many of which are surrounded by clear areas. However, as the basal portions of the epithelium are approached, the cells assume a more basophilic appearance, with uniformity in appearance and a scanty cytoplasm with indistinct cytoplasmic outline. The upper portion of the dermis shows a moderate, chronic inflammatory infiltrate (Figure 14). The patient also had an early basal cell carcinoma.

Figure 14. ARSENICAL KERATOSIS. A disorderly arrangement of atypical squamous cells is seen in the acanthotic epithelium.
Case 17

Basal Cell Carcinoma and Bowen’s Disease with Arsenical Keratosis

This is a case of keratosis of the right fingers and breast. The patient was a 37-year-old man who had been treated for asthma for two years with a medicine suspected to have contained arsenic. In addition to keratosis, the patient also had Bowen’s disease.

Three microscopic slides are provided of the skin lesions.

Microscopic slide 1. The skin demonstrates hyperkeratosis, marked acanthosis, and some squamous cells with vacuolization and moderate disarrangement of the squamous cells. There is elongation and projection of the rete ridges into the superficial dermis. The upper dermis shows mild chronic inflammation.

Microscopic slide 2. Skin shows moderate keratinization, marked acanthosis, and parakeratosis. The epithelium shows marked vacuolization of many of the squamous cells in the epithelium and a moderate number of mitoses. In some areas the cellular maturation is poor and many mitoses are noted. Occasional pieces of stratified squamous epithelium contain whorls of epithelial cells; there are elongations of the epidermis downward into the dermis and the basal cells are arranged perpendicular to the basement membrane. The diagnosis is basal cell carcinoma (Figure 15).

Microscopic slide 3. Skin demonstrates moderate hyperkeratosis, parakeratosis, and marked thickening of the epithelium with anastomosing rete pegs. The malpighian zone contains many vacuolated epithelial cells, many of which contain deep-staining nuclei. Some nuclei show mitoses. Giant cells are noted in the malpighian zone containing eosinophilic cytoplasm and dark pyknotic nuclei. Areas of dyskeratosis are noted. The orientation of the nuclei and progression of maturation are poor.

Figure 15. BASAL CELL CARCINOMA. There are elongations of the epidermis downward into the dermis with nuclear palisading of the peripheral cell layer.
Case 18

Squamous Cell Carcinoma and Arsenical Keratosis

This is a case of a 47-year-old female who developed keratosis at a suture line of previous surgical amputation of the middle finger, proximal phalanx. The patient was treated as a child for persistent eczema with irradiation and Fowler's solution. Amputation of the middle finger, at the metatarsal phalangeal joint, had been performed for lesions diagnosed as a squamous cell carcinoma. She apparently healed well, but three years later keratosis developed at the suture line.

Two microscopic slides are provided of the skin lesions.

Microscopic slide 1. The skin of the right finger demonstrates ulceration of the epidermis with marked hyperkeratosis, focal parakeratosis, and acanthosis with finger-like projections. The tumor consists of disorderly foci of atypical squamous cells proliferating into the dermis. The dermis shows a moderate inflammatory reaction. The diagnosis is squamous cell carcinoma (Figure 16).

Microscopic slide 2. The skin shows ulceration, marked parakeratosis, and acanthosis. The basal layer shows atypical cells with hyperchromasia and increased nuclear to cytoplasmic ratio. The appearance suggests a diagnosis of malignancy.

Figure 16. SQUAMOUS CELL CARCINOMA. Pleomorphic, atypical keratinocytes extend into the dermis
Early Basal Cell Carcinoma and Arsenical Keratosis

This case of arsenical keratosis occurred in a 48-year-old man who was apparently treated for epilepsy two years prior to admission with an arsenic-containing drug. He presented with several skin lesions similar to psoriasis on the buttock, right knee, and right wrist.

Two microscopic slides are provided of the skin lesions.

Microscopic slide 1. The skin shows hyperkeratosis, acanthosis, disarrangement of the epidermal cells, pleomorphism, vacuolization, and hyperchromatism. Some mitotic figures can be observed. Lymphocytes and plasma cells are noted in the upper dermis. The diagnosis is arsenical keratosis (Figure 17).

Microscopic slide 2. The skin shows marked hyperkeratosis, acanthosis, and elongation of the rete ridges. The epidermal cells show pleomorphism and some hyperchromatic nuclei with mitotic figures. In the upper dermis, some areas of desmoplastic stroma can be seen with chronic inflammation and some pleomorphic cells. These features are consistent with early basal cell carcinoma.

Figure 17. ARSENICAL KERATOSIS. The epithelium shows marked hyperkeratosis and acanthosis
Hepatocellular Carcinoma and Cirrhosis

This patient was a 32-year-old white male with a history of using Fowler’s solution daily for three years, 10 years prior to admission to a hospital for pain in the epigastric region. He had hepatomegaly and laboratory studies suggesting liver disease; a needle biopsy of the liver revealed fatty metamorphosis. Jaundice increased and the patient’s condition rapidly deteriorated. He died two months after admission. Autopsy revealed bile staining of the organs, bile nephrosis, and 3000 cc of bloody ascites. The liver weighed 6,200 grams; a section showed a large necrotic hemorrhagic tumor that had replaced two-thirds of the liver parenchyma. Death was attributed to hepatic insufficiency caused by cirrhosis of the liver, hemorrhagic necrotic hepatoma, plus acute hemorrhage into the periportal cavity.

One microscopic slide is provided of the liver lesions. Microscopically, the liver sections show necrosis and a malignant epithelial-type tumor. The tumor cells show considerable pleomorphism and an eosinophilic cytoplasm. The nuclei are irregular, hyperchromatic, and occasionally multinucleated. Small amounts of hemosiderin are deposited in the periportal zones, and there is an associated cirrhosis. The diagnosis is hepatocellular carcinoma and cirrhosis (Figure 18).

Figure 18. HEPATOCELLULAR CARCINOMA. The nuclei are irregular, hyperchromatic, and occasionally multi-nucleated.
Angiosarcoma of the Liver

This 76-year-old male was treated for psoriasis with Fowler's solution 35 years prior to admission to the hospital. He presented with chest pain and was noted to have progressive peripheral edema and increased abdominal girth. He was diagnosed with renal failure, hepatomegaly, ascites, and hepatic venous outflow occlusion. Treatment was unsuccessful and he subsequently died. At autopsy, the liver was grossly enlarged, weighing 2,700 grams, and had a yellow-to-golden surface coloration.

Two microscopic slides are provided of the liver lesions. Microscopically, the liver contains a florid proliferation of malignant endothelial cells in a sinusoidal pattern. The neoplastic endothelial cells have distorted the intervening hepatic architecture. There is marked hemorrhage and necrosis of the hepatic parenchyma and bile stasis (Figure 19). These findings are typical of liver angiosarcoma.

Figure 19. ANGIOSARCOMA OF THE LIVER. Section showing marked hemorrhage and necrosis.
Angiosarcoma of the Liver

The patient was a 14-year-old male who lived in an area of Argentina where the water was contaminated with arsenic. Since the age of five, he had lesions involving the soles and palms. At first, these lesions consisted of hypochromatic macules that later developed into hyperkeratotic lesions. He experienced abdominal pain 30 days prior to admission. Hepatic disease was manifested by malaise, jaundice, and edema in the lower extremities. On admission, he had ascites and a tender liver palpated 7 cm below the costal margin. Liver tests suggested the presence of liver disease. In addition, he had hyperkeratosis of the soles and palms. On the fourth day in the hospital, he suddenly went into shock and died. Autopsy findings revealed bloody ascites, and a liver that weighed 2,450 grams with a large necrotic hemorrhagic tumor (18x15x12 cm) in the right lobe.

Four microscopic slides are provided of the liver lesions. Microscopic slide 1 is an H&E stain of liver section and shows fibrous-connective tissue formed into nodules. Microscopic slide 2 is an H&E stain of the liver that shows diffuse proliferation of atypical endothelial cells infiltrating existing sinusoidal spaces. Microscopic slide 3 is a Masson stain of liver which shows increased fibrous-connective tissue formed into nodules. Microscopic slide 4 is a Factor VIII related-antigen immunostain, which is positive for the malignant endothelial cells (Figure 20).

The histological findings are consistent with a diagnosis of angiosarcoma of the liver.

Figure 20. LIVER FIBROSIS.  Factor VIII related-antigen immunostain positive for malignant endothelial cells.
Index

Angiosarcoma of the liver ................................. 13, 16-18, 44, 45
Basal cell carcinoma ....................................... 13, 15, 39, 40, 42
Bowen's disease (squamous cell carcinoma in situ) ..... 14, 35, 40
Dermatitis, exfoliative ........................................ 33
Fowler's solution (arsenic trioxide) ............... 28, 29, 35, 41, 43, 44
Hepatocellular carcinoma ................................ 16, 19, 43
Hepatoportal sclerosis .................................... 16, 19, 20
Hypopigmentation .......................................... 13
Hyperpigmentation ......................................... 27, 33
Keratosis, arsenical ................................. 13, 14, 28-32, 34-37, 39, 40-42
Liver; normal histology ................................... 16, 17
Osborne's stain ............................................. 27, 28
Psoriasis ......................................................... 1
Skin; anatomy and physiology ....................... 10, 11
Squamous cell carcinoma ......................... 13, 14, 36, 41
Syphilis ......................................................... 1