café-au-lait in color; have irregular serpiginous borders; and are found primarily on the neck, chest, back, shoulder, and pelvic region. The skeletal manifestations are managed as for other polyostotic fibrous dysplasia while the endocrinopathies are treated medically, for example with aromatase inhibitors for precocious puberty.

Metastatic Tumors

Metastatic tumors are the most common form of skeletal malignancy, greatly outnumbering primary bone cancers. The pathways of spread include (1) direct extension, (2) lymphatic or hematogenous dissemination, and (3) intraspinal seeding (via the Batson plexus of veins). Any cancer can spread to bone, but in adults more than 75% of skeletal metastases originate from cancers of the prostate, breast, kidney, and lung. In children, metastases to bone originate from neuroblastoma, Wilms tumor, osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma.

Skeletal metastases are typically multifocal. However, carcinomas of the kidney and thyroid may present with solitary lesions. Most metastases involve the axial skeleton (vertebral column, pelvis, ribs, skull, and sternum). The red marrow in these areas, with its rich capillary network and slow blood flow, facilitates implantation and growth of the tumor cells. Metastases to the small bones of the hands and feet are uncommon and usually originate from cancers of the lung, kidney, or colon.

The radiographic appearance of metastases may be purely *lytic* (bone destroying), purely *blastic* (bone forming), or *mixed* lytic and blastic. Furthermore, some cancers are associated with predominantly one pattern or the other. For example, prostatic adenocarcinoma is predominantly blastic whereas carcinomas of the kidney, lung, and gastrointestinal tract and malignant melanoma produce lytic lesions. Bidirectional interactions between metastatic cancer cells and native bone cells account for the changes that manifest in the bone matrix. Tumor cells do not directly resorb bone in lytic lesions. Rather, they secrete substances such as prostaglandins, cytokines, and PTHrP that upregulate RANKL on osteoblasts and stromal cells thereby stimulating osteoclast activity. At the same time, tumor cell growth is supported by the release of matrix-bound growth factors (e.g., TGF-β, IGF-1, and FGF) as bone is resorbed. Sclerotic metastases may be produced by tumor cells secreting WNT proteins that stimulate osteoblastic bone formation.

The presence of bone metastases unfortunately carries a dim prognosis since it indicates wide dissemination of the cancer. Treatment strategies aim at managing symptoms and limiting further spread. Therapeutic options include systemic chemotherapy, localized radiation and bisphosphonates. Surgery may be necessary to stabilize pathologic fractures.

KEY CONCEPTS

Bone Tumors and Tumor-Like Lesions

Primary bone tumors are classified according to the normal cell or matrix they produce. The remainder is grouped according to clinicopathologic features. Most primary bone tumors are benign. Metastases, especially adenocarcinomas, are more common than primary bone neoplasms.

Major categories of primary bone tumors include:

- **Bone forming:** Osteoblastoma and osteoid osteoma consist of benign osteoblasts that synthesize osteoid. Osteosarcoma is a tumor of malignant osteoblasts, predominantly involving adolescents with an aggressive clinical course.
- **Cartilage forming:** Osteochondroma is a polypoid exostosis with a cartilage cap. Sporadic and syndromic forms arise from mutations in the *EXT* genes. Chondromas are benign intramedullary tumors producing hyaline cartilage, usually arising in the digits. Chondrosarcomas are malignant tumors of cartilage, involving the axial skeleton in adults.
- **Ewing sarcoma family of tumors** consists of are aggressive malignant small round cell tumors most often associated with t(11;22).
- **Fibrous cortical defect** and **fibrous dysplasia** are unusual examples of disorders caused by gain-of-function mutations that occur during development

JOINTS

Joints allow movement while providing mechanical stability. They are classified as *solid (nonsynovial)* and *cavitated (synovial)*. The solid joints, also known as *synarthroses*, provide structural integrity and allow only minimal movement. They lack a joint space and are grouped according to the type of connective tissue (fibrous tissue or cartilage) that bridges the ends of the bones. Fibrous synarthroses include the cranial sutures and the bonds between roots of teeth and the jawbones. Cartilaginous synarthroses (synchondroses) are represented by the symphyses (manubriosternalis and pubic). Synovial joints, in contrast, have a joint space that allows for a wide range of motion. Situated between the ends of bones formed via enchondral ossification, they are strengthened by a dense fibrous capsule reinforced by ligaments and muscles. The boundary of the joint space consists of the synovial membrane, which is firmly anchored to the underlying capsule and does not cover the articular surface. Its contour is smooth except near the osseous insertion, where it is thrown into numerous villous folds. Synovial membranes are lined by two types of cells that are arranged one to four layers deep. Type A synoviocytes are specialized macrophages with phagocytic activity. Type B synoviocytes are similar to fibroblasts and synthesize hyaluronic acid and various proteins. The synovial lining lacks a basement membrane, which allows for efficient exchange of nutrients, wastes, and gases between blood and synovial fluid. Synovial fluid is a plasma filtrate containing hyaluronic acid that acts as a viscous lubricant and provides nutrition for the articular hyaline cartilage.

Hyaline cartilage is a unique connective tissue ideally suited to serve as an elastic shock absorber and wear-resistant surface. It lacks a blood supply and does not have lymphatic drainage or innervation. Hyaline cartilage is