VII. ENDOCRINE SYSTEM DISORDERS

Communication between cells is necessary to maintain homeostasis and coordinate growth and development. The primary function of the two major organ systems, the *nervous system* and the *endocrine system,* is intercellular communication. The endocrine system releases hormones that induce a more generalized (yet slower and more prolonged comparative with the nervous system) response as they reach target cells in widely separated organs or tissues. In this chapter our attention is directed to the diseases of hypophysis (pituitary gland), thyroid gland and adrenal glands.

PITUITARY ADENOMAS are benign neoplasms of the anterior lobe of pituitary gland and are often associated with the excess secretion of pituitary hormones and evidence of corresponding endocrine hyperfunction. They occur in both sexes at almost any age but are more frequent in men between the ages of 20 and 50 years. Pituitary adenomas have been classically subdivided according to the tinctorial properties of their cells as:

- *acidophilic adenomas,* associated with the overproduction of growth hormone,
- *basophil adenomas,* associated with the excess secretion of ACTH, and
- *cromophobe adenomas* with no endocrine hyperfunction.

Nowadays, when immunohistochemical methods are widely applied, pituitary adenomas are classified according to the hormone(s) elaborated by the neoplastic cells (lactotrope, somatotrope, corticotrope, gonadotrope, thyrotrope and, respectively, nonfunctional adenomas).

Pituitary adenomas range from small lesions, *microadenomas* (less than 10 mm in diameter), that do not enlarge the gland to expansive tumors that erode sella turcica and impinge on adjacent cranial structures, *macroadenomas*. Microadenomas do not produce symptoms unless they secrete hormones, but macroadenomas tend to cause both local symptoms, by virtue of their size, and systemic manifestations, as a result of the overproduction of hormones. The mass effects of pituitary macroadenomas include impingement on the optic chiasm, often with bitemporal hemianopsia and loss of central vision, oculomotor palsies when the tumor invades the cavernous sinuses, and severe headaches.

Microscopically, all adenomas have a fairly uniform appearance. The more or less uniform polygonal cells are arranged in sheets, cords, or nests, having only delicate, vascularized stroma. Small or large foci of ischemic necrosis may be present, and psammoma bodies may be found, accompanied by hemorrhage.

THYROID GLAND PATHOLOGY

NONTOXIC GOITER. The complete designation of this pathological entity is *diffuse nontoxic (simple) colloid goiter,* and specifies a form of goiter that (1) diffusely involves the entire gland without producing nodularity, (2) is not associated usually with either hyperfunction or hypofunction, and (3) presents enlarged follicles filled with colloid. It occurs in both, an *endemic* or a *sporadic* distribution. *Endemic* refers to the high incidence of simple goiter (more than 10% of the population) in certain areas of the world, mountainous regions, such as Alps, Andes, Himalayas, but also may occur in non-mountainous regions remote from the sea, such as central Africa. The dominant cause of the goiter is a deficient intake of iodine, leading to decreased synthesis of thyroid hormone and a compensatory increase in TSH. Hence the follicular cell hypertrophy and hyperplasia and goitrous enlargement. The enlarged mass of follicular cells increases hormone output until an euthyroid state is achieved.

Two stages can be identified in the evolution of the diffuse nontoxic goiter: the *hyperplastic* stage and *colloid involution*. In the stage of hyperplasia, the gland presents a mild enlargement. It is diffusely involved, markedly hyperemic and rarely exceeds 100 to 150 g. Histologically, the gland consists mainly of small closely packed acini lined by columnar epithelium and containing a small amount of poorly stained colloid. The duration of the hyperplastic stage is extremely variable. With increased mass of cells, the euthyroid state is reached and follicular cell growth ceases and is followed by colloid accumulation. Now the thyroid becomes markedly enlarged (sometimes to 500 g or more), translucent and brown due to the large amount of stored colloid. There are usually no symptoms, but pressure symptoms develop if the thyroid is retrosternal, i. e. stridor, by compressing the trachea, hoarseness, due to the pressure on recurrent laryngeal nerve, dysphagia, due to the pressure on esophagus. At this stage, follicles enlarge as they become filled with dense colloid, and the epithelium

undergoes progressive flattening. For unknown reasons the accumulation of colloid is not uniform throughout the gland and some follicles are hugely distended, whereas others remain small.

During the early stages of endemic goiter, administration of iodine brings about regression, but later is without effect. An important aspect of the diffuse goiter is that it may become transformed into a nodular goiter.

HYPERTHYROIDISM refers to the clinical consequences of an excessive amount of circulating thyroid hormones, inducing a hypermetabolic state of the target tissues. Prolonged hypersecretion of thyroid hormone can result from (1) an excess of production of TSH (rare), (2) the presence of an abnormal thyroid stimulator (Graves' disease), and (3) intrinsic disease of the thyroid gland (toxic multinodular goiter or a functioning adenoma).

Graves' disease, also known as **Basedow disease** in continental Europe, is an autoimmune disorder characterized by diffuse goiter with hyperthyroidism, and infiltrative ophtalmopathy (exophtalmos), and, infrequent, infiltrative dermopathy. The *etiology* of Graves' disease is not fully understood and seems to involve an interplay between immune mechanisms, heredity, sex, and, possibly, emotional factors. The autoimmune theory is sustained by the presence of IgG antibodies directed against components of the plasma membrane of thyroid follicular epithelium, presumably the TSH receptor. These antibodies function as agonists, stimulating the TSH receptor, thereby activate adenyl cyclase and increase thyroid hormone secretion. Under this continuous stimulation, the thyroid becomes diffusely hyperplastic and excessively vascular.

Typically, patients have a warm, moist, flushed skin, a wide-eyed stare, and general hyperdynamic circulatory state (tachycardia, palpitations, widened pulse pressure, peripheral vasodilatation).

The thyroid in Graves' disease is symmetrically, but not markedly enlarged, usually weighing 35 to 40 g. The capsule is intact and not adherent. The cut surface loses the normal tan translucence consecutive to the decreased amount of stored colloid, the parenchyma has a firm, dark red, meaty appearance closely resembling normal muscle.

Microscopically, the thyroid is diffusely hyperplastic and highly vascular. The dominant feature - "too many cells" - is imparted by an increased number of closely packed acini of various sizes, an increase in height of the lining epithelium to form tall columnar cells and an increase in the number of follicular cells, causing them to pile up in pseudopapillary buds – without fibrovascular cores. Colloid is markedly diminished and has a pale pink, watery appearance, showing small void vacuoles at the contact surface with the epithelial cells - "moth-eaten" aspect. Lymphocytes and plasma cells infiltrate the interstitial tissue and may aggregate to form large germinal follicles.

The course of Graves' disease is characterized by exacerbations and remissions. Treatment of the disorder includes the use of antithyroid medication, destruction of thyroid tissue with radioactive iodine or, less commonly performed today, surgical ablation of the gland. Unfortunately, despite successful relief of hyperthyroidism, exophtalmos often persists and may even worsen.

THYROIDITIS is a term that encompasses a heterogeneous group of inflammatory disorders of the thyroid gland, including those that are caused by infectious agents and autoimmune mechanisms.

The **acute suppurative** or **infectious thyroiditis** is produced by microbial (Staphylococcus, Streptococcus, Salmonella etc.) and fungal hematogenous seeding of the thyroid. The inflammatory involvement cause painful enlargement of the gland, but almost always the condition is self-limited or controllable with appropriate therapy.

Subacute (De Quervain's) thyroiditis is an infrequent, self-limited viral infection of the thyroid characterized by granulomatous inflammation, occurring after upper respiratory tract infections (i. e. influenza virus, adenovirus, echovirus, coxsackievirus, mumps virus). The thyroid gland is enlarged and the cut surface is firm and pale. Microscopic examination reveals, initially, an acute inflammatory reaction with scattered disrupted follicles replaced by neutrophils forming microabscesses. This is followed by the appearance of a patchy infiltrate of lymphocytes, plasma cells, and macrophages throughout the thyroid. Destruction of follicles allows the release of colloid, which elicits a conspicuous granulomatous reaction. Numerous giant multinucleated cells of the foreign body type, often containing colloid, are present. Fibrosis of the thyroid may follow the inflammatory reaction resolution, but the normal thyroid architecture is usually restored.

Hashimoto thyroiditis, also termed **lymphocytic thyroiditis,** is an autoimmune disease characterized by the presence of circulating antibodies to thyroid antigens. The disease arises most commonly in the fourth and fifth decades and afflicts women more often than men. Patients with Hashimoto thyroiditis exhibit high titers of circulating antimicrosomal antibodies, which have been shown to be cytotoxic to thyroid epithelial cells *in vitro*. In addition, the intense infiltration of the thyroid parenchyma by lymphocytes and plasma cells suggests cell-mediated destruction of gland.

In most cases of Hashimoto thyroiditis, the patient notes a gradual onset of a goiter associated with a progressive hypothyroid state.

On gross examination, the gland is diffusely enlarged, firm, and slightly lobular, weighing 60 to 200 g. The cut surface is pale tan and fleshy and exhibits a vaguely nodular pattern.

Microscopically, the thyroid displays:

1. a conspicuous infiltrate of lymphocytes, plasma cells, macrophages, which, focally, is arranged in lymphoid follicles, often with germinal centers.
2. destruction and atrophy of the thyroid follicles, which are replaced by the inflammatory infiltrate and interstitial fibrosis. Isolated follicles contain small amount of deeply stained colloid.
3. oxyphilic metaplasia of the follicular epithelial cells – Hürthle or Askanazy cells or oncocytes. These Hürthle cells have an abundant, brightly eosinophilic granular cytoplasm, and they are thought to represent a degenerated state of the follicular epithelium.

Many patients require no treatment for Hashimoto thyroiditis. Thyroid hormone is administrated to alleviate hypothyroidism and to decrease the size of the gland. Surgery is reserved for cases that are unresponsive to hormone therapy or in which pressure symptoms are troublesome.

Riedel thyroiditis is a rare disease, of unknown cause, characterized by glandular atrophy, hypothyroidism, and replacement of the thyroid by fibrous tissue, with adhesion to surrounding structures. The term “thyroiditis” is something of a misnomer since the disease also involves extrathyroidal soft tissue of the neck and is often associated with progressive fibrosis in other locations, including the retroperitoneum, mediastinum, and orbit.

On gross examination, a part or entire thyroid is stony hard and is described as “woody”. Characteristically, fibrosis extends beyond the borders of the gland and may be mistaken for a neoplasm. Microscopic examination reveals admixed areas of dense, hyalinized fibrous tissue and a chronic inflammatory infiltrate replacing the parenchyma with other areas where thyroid follicles are normally preserved.

THYROID ADENOMAS are by definition benign neoplasm. With rare exceptions, they all are derived from follicular epithelium and so might all be called *follicular adenomas.*

On gross examination, follicular adenoma is a solitary, circumscribed nodule, 1 to 3 cm in diameter, which protrudes from the surface of the thyroid. The cut surface of the tumor is soft and paler than surrounding parenchyma. Hemorrhage, fibrosis, and cystic change are common. Microscopically, a variety of patterns can be identified that recapitulate stages in the embryogenesis of the normal thyroid, and so they have been divided into several subtypes:

- *embryonal* (a trabecular pattern in which poorly formed follicles contain little or no colloid),
- *fetal* (cells tend to be arranged in microfollicles containing little colloid),
- *simple* (mature follicles with normal amount of colloid), and
- *colloid* (large follicles containing abundant colloid);
- or, more simply, into *microfollicular* and *macrofollicular* patterns.

THYROID CANCERS, almost all ***carcinomas***, are uncommon, representing less than 1% of all cancer deaths. The morphologic variants of thyroid carcinoma with their frequencies are as follows:

papillary carcinoma – 75 to 85%
follicular carcinoma – 10 to 20%
medullary thyroid carcinoma – 5%
anaplastic carcinoma – rare.

Papillary carcinoma is the predominant form of thyroid cancer. It often appears as multifocal tumoral nodules, and regional lymph node metastases are present at the time of diagnosis in 50% of cases. On cross section, these lesions are gray-white and firm and sometimes have foci of calcification or areas of cystic change. This form of thyroid carcinoma is rarely encapsulated but instead infiltrates

surrounding thyroid parenchyma and sometimes the perithyroidal soft tissue. Histologically, this cancer type ranges from predominantly papillary (about a third) to follicular appearance (another third) to equal parts of papillary and follicular architecture (the last third). At least 2/3 of cases reveal some branching papillae having a fibrovascular stalk covered by a single to multiple layers of cuboidal epithelial cells. Despite of the considerable architectural and cellular variations, the characteristic hallmarks of papillary carcinoma can be found in all:

- hypochromatic "empty" nuclei – "orphan Annie eyes",
- nuclear grooves,
- eosinophilic intranuclear inclusions representing invaginations of cytoplasm,
- psammoma bodies - calcific lamellations, usually in the cores of papillae.

Follicular carcinoma of the thyroid is defines as a malignant neoplasm that is purely follicular and does not contain any papillary or other elements. Typically, they are encapsulated tumors, gray to pink colored and present foci of fibrosis and calcification. Microscopically, follicular carcinoma present a microfollicular architecture with relatively uniform, orderly, cuboidal cells lining colloid-filled follicles, which is sometimes exceedingly difficult to differentiate from follicular adenoma. What clears up the diagnosis is the presence of microscopic invasion into the capsule and blood vessels carcinomatous emboli.

Medullary carcinoma of the thyroid is a tumor derived from the parafollicular or C cells of the thyroid, which are distinguished by their secretion of calcitonin. On gross examination, medullary carcinoma tends to arise in the superior portion of the thyroid as a single or multiple nodular lesions. The tumor tissue is firm, whitish-gray, and infiltrative. Frequently, there is spotty calcification and minimal to extensive fibrosis. Histologically, the tumor cells are usually polygonal or spindled and disposed in cellular nests separated by a scant to abundant fibrovascular stroma. In about half of the cases, the stroma contains broad bands or aggregates of amyloid deposition.

Anaplastic (undifferentiated) carcinoma is a highly aggressive thyroid cancer, which is usually rapidly fatal. It presents as large masses in the gland, which are poorly circumscribed and frequently extend into the soft tissue of the neck. The cut surface is hard and grayish white. There are basically three histologic patterns: (1) spindle cells "sarcoma-like" proliferation, (2) giant cells lesion, and (3) small cell carcinoma. The tumor tends to invade and occlude the vessels, producing foci of infarction within the tumor.

ADRENAL GLAND PATHOLOGY

ADRENAL CORTEX TUMORS. The proliferative lesions of the adrenal cortex range from diffuse hyperplasia to nodular hyperplasia to benign and malignant tumors, and they may be or not associated with steroidogenesis.

The *functional adenoma* is an encapsulated, firm, yellow mass, measuring about 4 cm in diameter, associated with the atrophy of the adjacent cortex. Microscopically, it is composed of mixtures of lipid-rich and lipid-poor cortical cells with little variation in cell and nuclear size. The *nonfuctional adenoma* is a poorly encapsulated mass of yellow-orange adrenocortical tissue ranging up to 2.5 cm in diameter associated with a normal thickness of the adjacent cortex. The microscopic aspect is similar with that of functional adenoma.

Adrenal carcinoma, commonly (80% of cases) *functional,* tends to be large, soft, unencapsulated mass, frequently exceeding 200 to 300 g in weight. The cut surface has a variegated pink, brown, or yellow color, often with necrosis, hemorrhage, and cystic change. The contralateral adrenal cortex is atrophic. Microscopically, both clear and compact cells are present with varying degrees of nuclear pleomorphism, abnormal mitotic figures and, sometimes, vascular invasion. *Nonfunctional adrenal carcinoma* is a highly malignant and large tumor, when discovered, exceeding 20 cm in diameter and 1 kg in weight. Histologically, it ranges from lesion showing mild degrees of atypia to wildly anaplastic neoplasm composed of monstrous giant cells.

Adrenal cancers have a strong tendency to invade the adrenal vein, vena cava, and lymphatics. Metastases to regional and periaortic lymph nodes are common as well as distant hematogenous spread to the lungs, bones etc.

PHEOCHROMOCYTOMA refers to a rare tumor of chromaffin cells of the **adrenal medulla** that secretes catecholamines. Such tumor also originates in extra-adrenal sites, in which case it is termed paraganglioma.

Pheochromocytoma tends to be encapsulated, spongy, reddish mass, with prominent central scars, hemorrhage, and cystic degeneration. On the light microscope, the cells are arranged either in large trabeculae, punctuated by thin-walled sinusoids, or in small alveoli ("zellballen") enclosed within a fibrovascular stroma derived from the tumor capsule. Cellular and nuclear pleomorphism is often present and may include multinucleated giant and bizarre cells. Mitotic figures are rare. Because malignant and benign pheochromocytomas may have an identical histologic appearance, the only absolute criterion of malignancy is metastasis to the related lymph nodes, liver, lungs and bones.

NEUROBLASTOMA, a malignant tumor of neural crest origin, composed of neoplastic neuroblasts, may arise in the adrenal medulla or sympathetic ganglia. It is one of the most important malignant tumors of childhood, accounting for up to 10% of all childhood cancers and 15% of cancer deaths among children. The peak incidence is in the first 3 years of life.

Neuroblastomas range in size from minute, barely discernable nodules to tumors readily palpable through the abdominal wall. The cut surface is soft and friable, with a variegated maroon color. Areas of necrosis, hemorrhage, calcification, and cystic change are frequently found. In the case of small neuroblastomas, a yellow rim of compressed adrenal cortex may be noted. Microscopically, the tumor is composed of dense sheets of small, round to fusiform cells with hyperchromatic nuclei and scanty cytoplasm. Mitoses are frequent. Characteristic rosettes are defined by a rim of dark tumor cells in a circumferential arrangement around a central pale fibrillar core – Homer Wright rosettes.

Neuroblastomas readily infiltrate the surrounding structures and metastazise to regional lymph nodes, the liver, lungs, bones.

VIII. BONES, JOINTS and SKELETAL MUSCLES DISORDERS

BONE TUMORS are rare tumors but important because many of them occur in children and young persons and have a poor prognosis.

Bone tumors are generally classified to the normal cell or tissue they recapitulate:

- bone-forming tumors (osteoma, osteoblastoma, osteosarcoma);
- cartilage-forming tumors (chondroma, chondroblastoma, chondromy-xoid fibroma, chondrosarcoma)
- fibrous and fibro-osseous tumors (nonossifying fibroma, fibrosarcoma);
- tumors that do not have normal tissue counterparts (giant cell tumor, Ewing's sarcoma).

Metastatic tumors are the most common form of skeletal malignancy; more than 75% of bone metastases originate from cancers of breast, prostate, kidney and lung.

BONE-FORMING TUMORS

Osteoma is a slow-growing tumor, usually solitary, most often arising on or inside the skull and facial bones. Osteomas are bosselated, sessile, round-to-oval tumors, composed of woven and lamellar bone deposited in a cortical pattern, with Haversian-like systems; some variants contain a component of trabecular bone in which the intertrabecular spaces are filled with hematopoietic marrow.

Osteosarcoma is defined as a malignant mesenchymal tumor in which the malignant cells produce bone matrix. Is the most common primary malignant bone tumor and is most frequent in adolescents.

Osteosarcomas often arise adjacent to the knee (lower femur, upper tibia or fibula) or shoulder (proximal humerus). Grossly, they are bulky tumors with hemorrhagic, cystic, soft and bony hard areas. The tumors frequently destroy the overlying cortex, spread into the marrow cavity, elevate or perforate the periosteum; infrequently, they penetrate the epiphyseal plate or enter the joint.

Histologically, osteosarcoma is composed of malignant osteoblasts which vary in size and shape and have large, hyperchromatic nuclei; tumor giant cells are common, as are atypical mitoses. The neoplastic bone is usually woven, with a coarse, lace-like architecture or deposited in broad sheets. Other matrices, including malignant cartilage and fibrous tissue, may be present.

Osteosarcoma spreads through the bloodstream to the lungs. Currently, with the complex treatment, the long-term survival rate has been increased to 60%.

CARTILAGE-FORMING TUMORS

Chondroma. Chondromas are benign tumors of hyaline cartilage; they may arise within the medullary cavity (enchondromas) or on the surface of the bone (subperiosteal or juxtacortical chondromas). They are usually solitary, located in the metaphyseal region of tubular bones, and the favored sites are the short tubular bones of the hands and feet. Grossly, chondromas are smaller than 3 cm, gray-blue, translucent, with a nodular configuration. Microscopically, they are composed of well circumscribed nodules of cartilage, with cytologically benign chondrocytes not as pairs, but irregular number (3 – 6 cells) within small lacunae and cartilaginous (hyaline) matrix.

Chondrosarcoma is a malignant tumor that originates from cartilage cells and produces neoplastic cartilage. It commonly arises in the central portions of the skeleton, including the pelvis, shoulder and ribs. Macroscopically, chondrosarcomas are bulky tumors, composed of nodules of gray-white, translucent, glistening tissue, with spotty calcifications; areas of necrosis, cystic change, and hemorrhage are present.

Histologically, chondrosarcomas are composed of malignant cartilage cells in various stages of maturity. They vary in degree of cellularity, cytologic atypia, and mitotic activity from low-grade tumors (mild hypercellularity, sparse binucleate cells, few mitotic figures) to high-grade chondrosarcomas which exhibit marked hypercellularity, extreme pleomorphism with bizarre tumor giant cells, high mitotic activity.

MISCELLANEOUS TUMORS

Ewing's Sarcoma is a primary malignant small round cell tumor of bone and is the second most common bone sarcoma in children. Ewing's sarcoma usually arise in the diaphysis of long tubular bones, especially the femur, and in the flat bones of the pelvis. It presents as a painful enlarging mass, and the affected site is tender, warm and swollen.

Ewing's sarcoma arises in the medullar cavity and invades the cortex and periosteum, producing a soft tissue mass. The tumor is tan-white and frequently contains areas of necrosis and hemorrhage. Histologically, it is composed of sheets of uniform small, round cells that are variably arrayed in rosettes, with neurofibrillary cores (Homer Wright) or central lumens (Flexner-Wintersteiner). They are slightly larger than lymphocytes with scant cytoplasm, which may appear clear because of its glycogen content. Although the tumor contains fibrous septae, there is generally little stroma. Necrosis may be prominent, and there are relatively few mitotic figures despite the dense cellularity of the tumor.

Giant Cell Tumor. Giant cell tumor of bone is a locally aggressive, potentially malignant neoplasm (pulmonary metastasis in ~2% of cases) characterized by the presence of multinucleated, osteoclast-type giant cells (synonym – "osteoclastoma"). It usually arises during the third to fifth decades, with a slight female predominance. Giant cell tumors in adults originate at the junction of the metaphysis and the epiphysis of a long bone, but in adolescents they are confined proximally by the growth plate and are limited to metaphysis. The majority of them arise around the knee (distal femur and proximal tibia), but virtually any bone may be involved.

On gross examination, giant cell tumors are large, clearly circumscribed; on cut section, is soft, without bone or calcification, light brown with hemorrhagic areas. Microscopically, giant cell tumors exhibit two types of cells. The mononuclear cells are oval, uniform, with large nuclei, scanty cytoplasm and indistinct cell membranes. They represent the proliferating component of the tumor, and mitoses are easily identified. The second cellular type is represented by large osteoclast-like giant cells having 100 or more nuclei. The stroma is richly vascularised, with hemorrhage areas and hemosiderin deposition.

ARTHRITIS

INFECTIOUS ARTHRITIS. Articular structures can become infected by direct inoculation, by contiguous spread from a soft tissue abscess or focus of osteomyelitis or by hematogenous dissemination during an episode of bacteremia. The most common organisms are gonococcus, Staphylococcus, Streptococcus, Haemophilus influenzae, Mycobacterium tuberculosis, and gram-negative bacili.

Bacterial infections usually cause an acute suppurative arthritis. The classic presentation is the sudden development of an acutely painful and swollen infected joint that has a restricted range of motion. Involved synovium shows hyperemia, edema and is covered by purulent exudate; the joint space is filled with an inflammatory exudate rich in fibrin and leukocytes. The articular cartilage is partially destroyed by suppuration and largely detached from the bone.

Infectious arthritis heals with sequelae; large alterations of synovium and cartilage produce permanent deformities of the joint.

Tuberculous arthritis develops following hematogenous dissemination from a visceral site of infection (usually pulmonary) or as a complication of adjoining osteomyelitis. It usually affects the weight-bearing joint, especially the hips, knees and ankles.

Tuberculous arthritis has an insidious onset and causes gradual progressive pain. Mycobacterial seeding of the joint induces the formation of confluent tuberculous granulomas with central caseous necrosis. The affected synovium may grow as a pannus over the articular cartilage and erode into bone along the joint margins. Chronic disease results in severe destruction with fibrous ankylosis and obliteration of the joint space.

RHEUMATIC ARTHRITIS

Rheumatic fever is an acute, often recurrent, inflammatory disease principally of children that generally follows a pharyngeal infection with group A beta-hemolytic streptococci. It seems that rheumatic fever is the result of an immune response to streptococcal antigens inciting a cross-reaction to tissue antigens.

In rheumatic fever, the onset of the articular lesions is insidious or acute and the clinical course is characterized by remission and exacerbation periods. They have migratory character and large joints, such as the knees, are most often afflicted.

The affected joint is painful and swollen. Synovium shows hyperemia, edema and slight leukocyte infiltrate. The synovial fluid is turbid, with more inflammatory cells than normal.

The changes are transitory and resolve without sequelae in a period of days. Occasionally, the articular pain and disability may persist for a time; synovium and the connective tissue may present a slight inflammatory infiltrate composed of lymphocytes, plasma cells and macrophages.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic systemic inflammatory disease, with unknown pathogenesis, that may affect many tissues and organs (skin, heart, blood vessels, lungs, and muscles) but principally attacks the diarthrodial joints, producing a nonsuppurative proliferative synovitis. Women are afflicted three to five times more often than men and the onset is usually in the third or fourth decade. The proximal interphalangeal and metacarpophalangeal joints, elbows, knees, ankles and spine are commonly affected; usually, the joints of extremities are afflicted simultaneously and in a symmetric pattern. The clinical course of the disease is variable, punctuated by remissions and exacerbations. The spectrum of clinical manifestations ranges from mild signs and symptoms to severe, destructive and mutilating disease.

Morphologically, the most severe alterations are manifested in the joints. Initially, the synovium becomes edematous, thickened and hyperplastic, covered by delicate and bulbous fronds. The stroma is infiltrated by lymphocytes, plasma cells, macrophages, and giant cells. The vascularity is increased with superficial hemosiderin deposits. Aggregates of organizing fibrin cover portions of synovium and float in the joint space as “rice bodies”. The inflamed synovium creeps over the articular surface forming a pannus with erosions of the underlying cartilage. Changes in the synovial fluid include a massive increase in volume, an abundant protein and polymorphonuclear leukocytes content, and increase turbidity. In time, after the cartilage has been destroyed, the fibrocellular pannus bridges the apposing bones forming a fibrous ankylosis that eventually ossifies. Tendino-ligamentous involvement frequently accompanies the arthritis, with irreversible damage or even ruptures of the tendons and ligaments. Occasionally the inflammation extends into the adjacent muscles.

OSTEOARTHRITIS

Osteoarthritis, also called degenerative joint disease, is characterized by the progressive erosion of articular cartilage. It appears insidiously, without apparent initiating cause, in the sixth decade, as an aging phenomenon. Rarely, osteoarthritis may appear in younger individuals having some predisposing condition, such as previous traumatic injuries to a joint, a congenital developmental deformity of a joint or a systemic disease.

Characteristic symptoms of osteoarthritis include deep, achy pain that worsens in time, morning stiffness, crepitus and limitation of range of movement. Impingement on spinal foramina by osteophytes results in cervical and lumbar nerve root compression with radicular pain, muscle spasms, muscle atrophy and neurologic deficits.

In the early stage of osteoarthritis, gross examination reveals a granular articular surface that is softer than normal. Eventually full-thickness portion of the cartilage are sloughed, and the exposed subchondral bone plate become the new articular surface. Later on, friction burnishes the bone, giving it the appearance of polished ivory (eburnated bone). Small fractures through the articulating bone are common, and the dislodged pieces of cartilage and bone tumble into the joint forming loose bodies (joint “mice”). The fracture gaps allow synovial fluid to enter into the subchondral regions, forming fibrous walled cysts. Synovium is congested and fibrotic, with some chronic inflammatory cells. Mushroom-shaped osteophytes develop at the margins of the articular surface.

SKELETAL MUSCLES DISORDERS

MUSCULAR DYSTROPHIES

Muscular dystrophies are a heterogeneous group of inherited disorders characterized clinically by progressive weakness of the voluntary muscles, caused by primary muscular degeneration.

Duchenne muscular dystrophy (Progressive Muscular Dystrophy). It is a severe, progressive, noninflammatory myopathy, X-linked inherited condition. Duchenne muscular dystrophy is caused by the deletion of a gene on the short arm of the X chromosome encoding a protein termed dystrophin. This probably plays a role in maintaining the integrity of the myocyte membrane during the shape changes associated with contraction.

Boys with Duchenne dystrophy are normal at birth and early motor milestones are met on time. Walking, however, is often delayed. Weakness begins in the pelvic girdle muscles and then extends to the shoulder girdle. The weak muscles become atrophic and are replaced by fibrofatty tissue; eventually, "pseudohypertrophy" of the calf muscles develops.

The patients are usually wheelchair-bound by the age of 10 years and bedridden by 15. The common causes of death are complications of respiratory insufficiency caused by muscular weakness or cardiac arrhythmia owing to myocardial involvement. The disease's process in Duchenne dystrophy consists of a relentless degeneration of muscle fibers, a prolonged effort at repair and regeneration, and progressive fibrosis. The earliest pathologic changes in the muscle consist of irregularly distributed foci of degenerating and regenerating muscle fibers, with variation in fiber diameter (due to the presence of both small and giant fibers) together with scattered, large hyalinized fibers that have lost their normal cross-striations, believed to be hypercontracted fibers. In later stages, the muscles become almost totally replaced by fat and connective tissue.

Myotonic dystrophy. Is the most common form of adult muscular dystrophy and is characterized by sustained muscle contractions and rigidity (myotonia) and progressive muscle weakness. The disease is inherited as an autosomal dominant trait and the age at onset and severity of symptoms show extreme variations. Pathologically, skeletal muscle may show features of a dystrophy similar to Duchenne dystrophy. In addition, there is an increase in the number of internalized nuclei and the presence of ring fibers, with a subsarcolemmal band of cytoplasm that appear distinct from the center of the fiber. Also, fiber splitting, necrosis, and regeneration processes are present.

INFLAMMATORY MYOPATHIES

There are a variety of inflammatory diseases involving muscle: noninfectious inflammatory muscle disease (polymiositis, dermato-myositis, inclusion body myositis); infectious myositis; inflammatory processes associated with diffuse systemic inflammatory disease.

Noninfectious inflammatory myopathies comprise an uncommon, heterogeneous group of disorders characterized by possible immunologically mediated injury and inflammation of skeletal muscle. Three relatively distinct disorders – dermatomyositis, polymyositis and inclusion-body myositis – are included in this category. They are thought to have an autoimmune origin because of: (1) their association with other autoimmune diseases; (2) the fact that they sometimes seem to follow viral infections; (3) the detection of autoantibodies; (4) evidence of muscle cell injury mediated by cytotoxic T-cells. The morphological aspects of these entities are: the presence of inflammatory cells; necrosis and phagocytosis of muscle fibers; mixture of regenerating and atrophic fibers; fibrosis.

Dermatomyositis may occur in children or adults and implies the involvement of skin as well as the skeletal muscle. It is characterized by a distinctive skin rash which takes the form of a heliotrope discoloration of the upper eyelids with periorbital edema, often accompanied by a scalling erythematous eruption on the knuckles, elbows and knees. Bilateral symmetric slow of muscle contraction which typically affects the proximal muscles first. The inflammatory infiltrates are located especially around small blood vessels and in the perimysial connective tissue. Characteristic, a few layers of atrophic fibers are present at the periphery of fascicles, sufficient for diagnosis even the inflammation is mild or absent. In addition, a dramatic reduction in the intramuscular capillaries can be observed.

Polymyositis. The pattern of muscle involvement is similar to that seen in dermatomyositis but cutaneous involvement is lacking. Histologically, the inflammatory cells are present in the endomysium;

lymphoid cells surround and invade healthy muscle fibers. Both necrotic and regenerating fibers are present, without evidence of vascular injury.

Inclusion-body myositis begins with the involvement of distal muscles, especially extensors of the foot and flexors of fingers. Muscle weakness may be asymmetric and typically affects individuals over the age of 50 years. The diagnostic finding in this form of myositis is the presence of rimmed vacuoles in the myocytes, seen only in frozen section. The pattern of the inflammatory cell infiltrate is similar to that seen in polymyositis.

Infectious myositis. Any pyogenic infection of the soft tissue may affect the muscle producing acute suppurative inflammation.

Clostridial infections of the muscle cause the clostridial gas gangrene which is characterized by marked edema and enzymatic necrosis of involved muscle cells. The affected region is swollen and the overlying skin forms large, bullous vesicles that rupture. Gas bubbles caused by bacterial inflammation appear within the gangrenous tissues. The inflamed muscle is soft, blue-black, friable and semifluid as a result of the proteolytic action of the released bacterial enzymes. Microscopically, there is severe myonecrosis, extensive hemolysis, and marked vascular injury, with thrombosis.

There are some **systemic inflammatory conditions** in which muscle is secondarily affected.

In *scleroderma* (systemic sclerosis), inflammatory myositis indistinguishable from polymyositis may develop. Also, in *rheumatoid arthritis*, the muscles adjacent to affected joints present inflammatory lesions.

IX. CENTRAL NERVOUS SYSTEM TUMORS

The nervous system is the most complex organ system in the body. Diseases of the nervous system are common throughout the human life span and contribute substantially to mortality and morbidity: stroke, dementia, mental retardation, traumatic brain and spinal cord injury, meningitis and tumors.

Primary CNS tumors of the central nervous system constitute only 2% of all "aggressive" neoplasms of the adults, and 20% of all cancers of childhood (being second only to leukemia as the most common childhood malignancy, and are the most common pediatric solid tumors). For adults, metastatic tumors to the CNS are far more common than are primary tumors and are a major problem in clinical management.

They have several characteristics that set them apart from neoplastic processes elsewhere in the body. First, the distinction between benign and malignant tumors is less evident than in other sites; some glial tumors with the histologic features of a benign neoplasm may infiltrate entire regions of the brain, leading to clinically malignant behavior. Conversely, grossly (imagistic + intra-operative) well-define tumors, which apparently could be excised completely bear the highest malignancy grade (and poor prognosis)

In the brain, the surgical procedures are restricted by functional considerations, and some benign lesions may have lethal consequences because of their location.

For nearly a century, the classification of CNS tumours has been based on concepts of histogenesis, depending entirely on the idea that tumours can be classified according to their microscopic similarities with presumed cells of origin and their developmental differentiation states. Nowadays, the WHO classification (2016) breaks with this old tradition and incoporates well-establish molecular parameters into charaterization of CNS tumors, in order to stratify prognosis and to individualize therapy. But because this new paradigma implies genotyping, implementation of phenotypic-genotypic diagnosis and availability of immunohistochemical surrogates for molecular genetic alterations, the light microscopic appearance of H&E-stained sections is still in charge to provide some basic approach.

A much simplified classification of the CNS tumors according to their histogenesis is used for the purpose of this teaching course:

- neuroepithelial tumors: gliomas,
- embryonal tumors: medulloblastoma, neuroblastoma, atypical teratoid/rhabdoid tumor;
- mesenchymal tumors: meningiomas, schwannomas;
- germ cell tumors: germinoma, teratoma;

….

- metastases / secondary involvement of CNS from primary extraneuraxial malignancies (mainly lung, breast and skin cancers).

The location of a single tumor lesion is particularly relevant in the diagnosis of primary CNS tumors. For metastases (more common in the brain than in the spinal cord), the common presentation is in the form of multiple, well-delineated spherical nodules randomly distributed.

NEUROEPITHELIAL TUMORS are represented by the tumors of glial cells (termed gliomas) and by other non-glial cells found in different stages of maturation, some being at their earliest step of development (medulloblastoma).

Gliomas are derived from astrocytes (astrocytoma), oligodendrocytes (oligodendroglioma) and ependymal cells (ependymoma).

Astrocytoma is a glioma composed of astrocytes. It develops in the cerebral hemispheres in adults, in the midbrain, pons and cerebellum in the first 2 decades of life and in the spinal cord, predominantly in the thoracic and cervical segments, in young adults. The most common presenting symptoms are seizures, headaches, and focal neurological deficits related to the anatomic site of the tumor. The life expectancy of patients with astrocytoma is variable, but approximates 5 years; transformation to a higher degree of anaplasia, often to glioblastoma multiforme occurs in 10% of cases and shortens life expectancy.

On gross examination, astrocytomas are poorly defined, gray-white, and infiltrate the brain with an indistinct margin. They range from a few centimeters in diameter to enormous lesions that replace a cerebral hemisphere and extend into the opposite hemisphere. They often contain microcysts and occasionally, calcospherites. The highest grade lesions are characterized by a mixture of firm, white areas and softer, yellow foci of necrosis as well as cystic change and hemorrhage.

Microscopically, astrocytoma is distinguished by a matrix of slender glial cytoplasmatic processes, in which the nuclei are dispersed randomly. This network of intermingled cell processes replaces or displaces the normal background and gives the tumor a distinctly "fibrillary" appearance. There are some morphologic variations of astrocytoma:

- *Fibrillary astrocytoma* – has intermediately dense glial processes;
- *Gemistocytic astrocytoma* – the tumor cells have abundant, eosinophilic cytoplasm;
- *Pilocytic astrocytoma* – it typically occurs in children and is often cystic; microscopically, the tumor is composed of bipolar cells with long, thin "hair-like" processes and contains Rosenthal fibers and microcysts;
- *Anaplastic astrocytoma* is a less differentiated tumor which is distinguished from the other astrocytomas by much denser cellularity, and greater cellular pleomorphism (histological anaplasia). The topographic distribution parallels that of astrocytoma. The growth of the tumor is rapid, and patients do not survive more than 3 years.
- *Glioblastoma multiforme* is the extreme expression of aggressiveness (biological) and anaplasia (histopathological) among the glial neoplasms and accounts for 40% of all primary intracranial tumors. Most glioblastomas have constituent cells with recognizable astrocytic properties but they display marked pleomorphism, frequent mitoses, areas of necrosis, and endothelial proliferation. The last feature is a manifestation of cellular hyperplasia induced by vascular endothelial cell growth factor (VEGF) which is produced by malignant astrocytes, perhaps in response to hypoxia. A similar hyperplasia of fibroblasts is also initiated by the presence of glioblastoma near the dura. Hyperplasia of fibroblasts may actually attain malignant proportions, in which case, the growth intermingles fibrosarcoma with glioma, resulting in a *gliosarcoma*.

Glioblastoma typically infiltrates extensively, frequently crossing the corpus callosum and producing a bilateral lesion likened to a butterfly in its gross configuration. It is a mixture of firm, white areas and softer, yellow foci of necrosis and remote hemorrhage, as well as cystic change and red areas of recent hemorrhage; it is this appearance that gives its appellation: "multiforme".

The cardinal histopathological features of glioblastoma multiforme are:

- marked cellularity, with variable degrees of cellular pleomorphism and multinucleated cells, frequent mitoses = the extreme expression of **anaplasia** among the glial neoplasms;
- serpentine areas of **tumor necrosis** which occurs in areas of hipercellularity with highly anaplastic tumor cells crowded along the edges of the necrotic regions, producing so-called **"pseudopalisading necrosis"**;
- **endothelial cell proliferation**, which creates clusters of small vessels, referred to as **"glomeruloid"** formations.

The tumor predominates in the later decades of life. The clinical course of glioblastoma multiforme rarely exceeds 18 months.

Oligodendroglioma arises in the white matter, predominantly in the cerebral hemispheres. It's most common in the middle life. Patients may have had several years of neurological complaints, often including seizures. Generally, patients with oligodendrogliomas have a better prognosis than patients with astrocytomas.

Macroscopically, oligodendrogliomas are well-circumscribed, gelatinous, gray masses, often with cysts, focal hemorrhage, and calcification. Microscopically, the tumor is composed of sheets of regular cells with spherical nuclei containing finely granular chromatin (similar to normal oligodendrocytes) surrounded by a clear halo of cytoplasm (a "fried eggs" appearance). Typically, the tumor contains a delicate network of anastomosing capillaries. The calcification, present in many of these tumors (90%), ranges from microscopic foci to massive deposition. Although the lesion is infiltrative, its slow growth permits survival for 5 to 10 years.

Ependymoma account for 6% of gliomas and is more frequent in childhood. They arise next to the ependymal-lined ventricular system, near the fourth ventricle (in the first two decades of life) or in the spinal cord (middle life). Clinically, posterior fossa ependymomas often manifest with hydrocephalus secondary to progressive obstruction of the fourth ventricle. Prognosis is poor despite the slow growth of the tumor and the usual lack of histologic evidence of anaplasia. An average survival of about 4 years following surgery and radiotherapy has been reported.

In the fourth ventricle, ependymomas are typically solid or papillary masses extending from the floor of the ventricle. Although often better demarcated from adjacent brain than astrocytomas, their proximity to the vital pontine and medullary nuclei usually makes complete extirpation impossible. Microscopically, ependymomas are composed of cells with regular, round to oval nuclei with abundant granular chromatin, disposed in a fine fibrillary background that may be very dense. Tumor cells may form gland-like structures that resemble the embryologic ependymal canal with long, delicate processes extending into a lumen, forming ependymal (true) rosettes, a pathognomonic aspect, but seldom identified. More frequent are perivascular rosettes in which tumor cells are arranged around vessels with an intervening zone consisting of thin ependymal processes directed toward the wall of the vessel.

Medulloblastoma and other **primitive neuroectodermal tumors** are composed of primitive, undifferentiated cells. *Medulloblastoma* occurs predominantly in children (the peak incidence – 7 years old) and exclusively in the cerebellum.

Childhood medulloblastomas are located in the midline of the cerebellum (vermis); lateral locations are more often found in adults. Rapid, infiltrative growth may occlude the flow of cerebrospinal fluid, leading to hydrocephalus. The tumor is often well circumscribed, gray, and friable and may be seen extending to the surface of the cerebellar folia and involving the leptomeninges. Microscopically, the tumor is usually extremely cellular, with sheets of anaplastic cells, referred to as a “blue cells tumor”. The nuclei are hyperchromatic, often rounded or elongated, arranged sometimes around a fibrillar core, forming the Homer-Wright neuroblastic rosettes. Mitoses are abundant and markers of cellular proliferation are detected in a high percentage in the cells. The cells have little cytoplasm and are often devoid of specific features of differentiation (primitive cells). At the edges of the main tumor mass, medulloblastoma cells have a propensity to form linear chains of cells extending through the neuropil, and then through the cerebellar cortex to aggregate beneath the pia, penetrate the pia, and seed into the subarachnoid space. Dissemination through the cerebrospinal fluid is a very common complication, presenting as nodular masses through the neuraxis. The tumor is higly malignant, and the prognosis for the untreated pacients is dismal; however, it is an exquisitely radiosensitive tumor.

MESENCHYMAL TUMORS

Meningiomas are predominantly benign tumors of adults, accounting for almost 20% of all primary intracranial neoplasms. The peak frequency is in the 4^{th} to 5^{th} decades but there is a significant incidence in youthful adults.

Meningiomas arise from the meningothelial cells of the arachnoid and they may be found along any of the external surfaces of the brain, as well as within the ventricular system. Common sites of tumors include the parasagittal aspect of the convexity, dura over the lateral convexity, the wing of the sphenoid, olfactory groove, the sella turcica and foramen magnum or along the spinal cord.

On gross examination, most meningiomas appear as solitary, well-circumscribed, masses of variable sizes with a dural base that compress underlying brain but are easily separated from it. Extension into the overlying bone is not uncommon. The surface of the mass is usually encapsulated with thin, fibrous tissue and may have a bosselated or polypoid appearance. Another characteristic growth pattern is the "en plaque" variant, in which the tumor spreads in a sheet-like fashion along the surface of the dura. This form is commonly associated with hyperostotic reactive changes in the overlying bone. The lesions may have a finely gritty consistency, reflecting few calcifications, or they may be extremely calcified with psammoma bodies or even contain metaplastic bone. In the absence of these types of changes, the tumors are usually firm to fibrous and lack evidence of necrosis or extensive hemorrhage.

Several histologic patterns have been recognized, although most of these carry little prognostic significance (as a rule *typical meningiomas* that are not completely excised tend to recur, no matter the histology):

- syncytial / endotheliomatous meningioma – lobules and whorled clusters of cells which sit in tight groups, without visible cell membranes;
- fibroblastic meningioma – elongated cells and abundant collagen deposition between them;
- transitional / mixed meningioma - shares features of the syncytial and fibroblastic types;
- psammomatous meningioma – with many psammoma bodies, apparently forming from calcification of the syncytial nests of meningothelial cells.

Atypical and *anaplastic / malignant meningiomas* are extremely unusual tumors and present some particular features: single cell infiltration of underlying brain, abundant mitoses and loss of meningothelial microscopic features.

Schwannoma is a tumor derived from Schwann cells, a cell species that produce collagen as well as myelin. This tumor is also known as neurilemmoma and neurinoma. Within the cranial vault, the most common location is in the cerebellopontine angle, where they are attached to the vestibular branch of the eight nerve (acoustic neurinoma) and the patients often present with tinnitus and hearing loss. In rare instances schwannomas are derived from other cranial nerves, especially sensory nerves. Regarding the spinal cord location, 80% of these tumors arise from intradural nerve roots, especially the dorsal root. Sometimes, spinal neurinomas form across the dura mater as a result of extradural growth along the nerve roots, and as a result, form a dumbbell-shaped mass.

Grossly, they are well - circumscribed, encapsulated masses that are attached to the nerve but can be separated from it. Tumors are firm, gray masses but may also have areas of ancient hemorrhages and / or cystic change. Microscopically, tumors show a mixture of two growth patterns: Antoni A and B. Elongated cells with cytoplasmic processes are arranged in fascicles in areas of moderate to high cellularity with little stromal matrix (Antoni A); the “nuclear-free zones” of processes that lie between the regions of nuclear palisading are termed Verocay bodies. The Antoni B pattern consists of less densely cellular tissue with a loose network of cells similar to those seen in Antoni A areas along with microcysts and myxoid change of the background. A variety of degenerative changes may be found in ancient schwannomas, includes nuclear pleomorphism and vascular hyalinization, without significance of a worse prognosis.

METASTATIC TUMORS far surpass primary CNS tumors in numbers, and malignancies metastatic to the CNS rise major clinical problems. Autopsy series show that up to 25% of patients with systemic / disseminated cancers have CNS metastases. The most common site for brain metastasis is at the gray–white junction of the cerebral cortex, but any CNS region may be affected, including the choroid plexus, pineal gland and pituitary gland.

The most common primary tumors to involve the CNS are lung (most frequent for both men and women), breast, melanoma, kidney and gastrointestinal tract.