ABSTRACT

Although there are very frequent in animals, the hepatic diseases, regardless of their etiology (degenerative, inflammatory, tumoral), primary or secondary, specific or non-specific, due to their discrete clinical signs and to the difficulties in establishing a certain paraclinical diagnostic, can only be revealed in the most advanced stages or after necropsy.

The PhD thesis includes 252 pages and 190 colour photographs and is divided into two distinct parts: Part I, which contains bibliographic data on the theme and Part II, contains the personal research performed during the preparation of this thesis.

In the first part of the thesis, extended on 36 pages, one can fiind the stage of knowledge regarding the normal and pathological morphophysiology in mammalian liver. This part is structured in two chapters in which is systematized the information collected from 166 bibliographical sources, forming the needed database for the orientation and interpretation of the personal observation and their evaluation.

The original part of the thesis, developed on 181 pages, contains material and methods of work, the obtained results and their interpretation and general conclusions.

The investigations regarding the morphopathology of the swine liver were performed following the methods of morphological diagnostic recommended by OMS and IISPV (IDSA) for the specific laboratories from our country.

The studied material was represented by liver and gallbladder harvested from 500 slaughtered pigs from a swine farm from Iasi county, 39 pig cadavers brought to DSVSA Iasi for the diagnostic of leptospirosis and 150 cadavers brought to the necropsy chamber of the morphopathology department of FMV Iasi. Out of the 689 cases, 160 presented morphopathological changes of various intensity.

The harvested organs were photographed and listed, and then, 3 fragments of liver and gallbladder were selected and sampled from each slaughtered pig, for the histological examination.

The examination method was adapted to the anatomophysiological systems of the organism (Abricosov) and consist of preliminary inspection of the topography and the relation between the organs inside the body, followed by separate evisceration of each apparatus and detailed examination of each organ.

In the first part of the necropsy, the following were of interrest: the identification of the body (species, race, sex, age, colour, stature, body weight), condition and the post-mortem modifications (in order to establish the time of death). The second part of the necropsy consists of the exterior examination and the interior examination after the opening of the natural cavities.

By inspection, the colour, the volume, the shape of the liver, the lobe proportion, the pathological deposits, the surface alterations and the prominence of the lobulation (which is normal in pigs) were examined. For example, in carnivores, the liver has an homogenous surface; the macroscopic prominence of the lobulation indicates a pathological state.

The usual technique for the histological processing of the samples consisted of the analysis of the harvested tissues, in order to obtain microsections subjected to histological/histochemical coloration methods for the cytohistochemical or cytohistopathological examinations.

The tissue samples are processed following the next steps: fixation, molding, refixation, sample transfering, paraffin embedding and microtomy.

The results of the research revealed the presence of numerous pathological processes of the organ, produced by viruses, bacteria and parasites.

The liver, as a parenchimatous organ, rich in specific morphofunctional tissue and poor in vasculo-conjunctive sustaining stroma is exposed relatively quickly after death to cadaveric tisular changes. The early instalation of the post-mortem modifications make more difficult the macroscopic and the microscopic morphopathological diagnostic.

Among the sinusoidal cellular reactions, the *erythrophagocytosis* is highly frequent in swine, is intense in the Kupfer cells, but is also present in the hepatocytes and the histiocytes from the portal space; associated with lymphoplasmocytary infiltrations and miliar necrosis leads to the diagnostic of hemophagocytic syndrome which is associated to some viral diseaseswith hepatic tropism, shock or immune reactions started by the alteration of the erythrocytary membrane.

The epithelioid cells and the giant cells were identified in the panarteritis nodosa, which has an immune fusion mechanism; in piglets with acute or chronic salmonellosis were present small cells with multiple nuclei derived from the fusion between monocytes and macrophages and in the chronic cholangiohepatitis, multinucleated cells formed by the fusion or plasmodiation of the hepatocytes. *For the differential diagnosis are considered the epithelioid and the giant*

cells present in the lesions of tuberculosis produced by the avian type, in hepatoperitoneal cysticercosis and ascaridiosis.

The erythropoiesis identified in the piglets that died at 7-10 days old, can be recognised by the presence of some focal clusters of cells of the erythroid line in the sinusoidal capillaries or in the Disse spaces, adiacent to the hepatocytes, derived from the few erythrobasts and the frequent elements in intermediary or final stages of differentiation; the cells are gathered around a big macrophage or a Kupffer cell which can frequently be found performing erythrophagocytosis.

There were identified and described the *star-shaped and ground glass hepatocytes*, mono- and binucleated, asteroid, with homogenous and eosynophilic cytoplasm, as well as hepatocytes with eosinophilic and Pas positive granules, both types being associated to viral immune hepatitides from human pathology.

The cytomegalia or the *megalocytosis* also known as *large cell change* or *hepatocitary dysplasia* is a form of extreme hypertrophy characterized by nucleo-cytoplasmic gigantism associated with a variable degree of atypia. In the etiopathogeny of theese changes are involved the biliary diseases wich cause the accumulation of the biliary pigments inside hepatocytes in viral hepatitidis, the mycotoxins (especially the aflatoxins), the pyrrolizidine alkaloids, nitrosamins, phytotoxins and alkilant agents, the chronic copper intoxication.

The compensatory hepatocytary hyperplasia, the nodulary hyperplasia of the hepatocytes and the regenerative nodular hyperplasia in cirrhosis are presented together with their significance and histological elements of differentiation.

The hyperplasia of the bile ducts is caused by biliary obstructions, parasitary invasions, the prolongued action of some toxic substances (alpha-tyo-cyans, pyrrolizidine alkaloids, di-metil-nitrosamins, aflatoxins), viral or immune agressions. The differential diagnostic involves biliary adenoma and adenocarcinoma.

The glycogenolyses, far more frequent and of higher pathological interest than the glycogenoses, are severe lesions caused by metabolic diseases, toxic substances, infectious or parasitary diseases, due to the decrease of the glycogenogenesis. In the hypoglycemia of piglets, the predisposal factor for this disease is the very low deposit of glycogen which insures the minimum necessary.

From the pathogenic point of view, the *hepatic steatosis* identified in only 4% of the cases, may be *primary*, generated by mithocondrial toxins and hypoxia, with the decrease of the fat acid oxidation, and *secundary*, determined by infectious hepatotoxic agents, immunological, enzymatic, circulatory and nutritional agents etc.; from the point of view of the intensity of the steatosic process, in mammals can be observed *fatty overloads* and *fatty degenerations*.

The hydroprotidic hepatosis, surprisingly frequent, diagnosed in different patological states, were identified and described in both forms with their multiple variety and patogenic mechanisms.

The *intracellular hyalinosis,* present as spherical PAS+ and diastasoresistant inclusions may be the expression of an hereditary enzymatic defect, of autophagia, phagogitation of the apoptotic bodies, erythrophagocytosis, the storage of the immune complexes or some plasmatic glycoproteins, viral aggregates.

The hepatic fibrosis represents the increase of the quantity of extracellular matrix and a modification of the collagen types and of the deposit areas ; in fibrosis, the quantity of collagen, proteglycans, fibronectin and hialuronic acid may be 6 times higher than in the normal liver. The varieties of intralobular fibrosis (centrolobular, exolobular and diffuse), forced, postnecrotic scarring, multilobular and the fibrosis between the vascular units are presented.

The identified circulatory disorders were: active and passive hyperemia, ischemia, hemorrhage, macro- and microthrombosis, telangiectasia and edema.

The periportal and subcapsular telangiectasia, present in 2 pigs, is characterized by multiple *sinusoidal dilatations* limited by endothelium, filled with blood, scattered throughout the parenchyma, with no zonal distribution. In *peliosis*, this spaces are limited by hepatocytes instead of the endothelial cells and, in the surrounding parenchima produces by compression, the herniation of some groups of hepatocytes in the cavernous spaces.

The apoptotic hepatocytes have concave shape, deformed cellular membrane, condensed acidophilic cytoplasm, nuclei in cortical hyperchromatosis ; the apoptotic bodies lacking the chromatin blocks, rounded, acidophilic and PAS+, present in the cytoplasm of the hepatocytes are known as Councilman bodies, having a diagnostic value in the viral hepatitides.

The hepatic necrosis or the local mortification, relatively circumscribed, of the hepatic parenchyma is caused by the brutal action of some necrotizing agents from the extracellular medium and by multiple mechanisms, being expressed as: *dry necrosis* or *coagulation necrosis*, which is the most frequent, and the *coliquative necrosis*, also known as *liquefactive, humid* or *lytic necrosis*.

The hepatitides were present in 127 of our cases and were expressed by almost all the morphological types of the inflammatory process.

The necrotic hepatitis was diagnosed as *miliar necrotic hepatitis* with salmonellic etiology, as well as *necrotizing hepatitis*, with big foci, caused by *Clostridium perfringens* and *Fusobacterium necrophorum*.

The purulent hepatitis caused by different pyogenic bacteria, among which the most frequent involving in swine pathology is attributed to *Arcanobacterium pyogenes*, was observed

in our cases as an *infiltrative (flegmonous)* type, as well as *localized* (abscesses) inflammation. The matured hepatic abscesses have the classical structure, being formed of the puss cavity and the wall structured on three layers: I. The internal layer, formed of macrophages and histiocytary cells adapted to the phagocytosis function; II. The intermediary or reparatory layer of the abscess, formed of lymphocytes, histiocytes, fibroblasts, fibrocytes and conjunctive fibres; III. The external sequestrational layer, constituted of fibrous connective tissue; the abscesses situated superficially may induce the inflammation of the hepatic capsule – *fibrinous or fibrous perihepatitis*.

The eosinophilic hepatitis was identified both in parasitary hepatitides with interlobular localization, as trajectories in the hepatic tissue or abscesses and eosinophilic granulomas and in the leukocytoclastic phase of the poliarteritis nodosa.

The lymphohistiocytary hepatitis, as a predominantly proliferative non-suppurative type of inflammation, can be classified from the evolutive point of view as acute, subacute and chronic, and from the topographical point of view, as intralobular and interlobular, nodular and diffuse ; the extralobular form may be portal as a conglomeration of 28-30 lymphocytes or interlobular or polinodular. The association of the lymphocytes with the monocytes-macrophages suggests infections with viruses or Gram- germs, and the association of the lymphocytes with plasmocytes suggests immune or autoimmune hepatopathies. The lymphohistiocytary hepatitis with necrosis and lymphohistiocytary inflammatory infiltrate is characteristic to salmonelic infections.

In the chronic lymphohistiocytary hepatitis with supraunitary fraction between the round cell inflammatory infiltrate and the fibrocellular connective component, can be differentiated the persistent variety limited between the terminal plates and the aggresive variety, with the invasion of the inflammatory infiltrate in the lobule, *piece meal necrosis* and hepatocytary lesions. The presence of the granulocytes in the inflammatory infiltrate suggests chronic cholangiohepatitis.

In 2 cadavers of young pigs and in 7 adult animals slaughtered for consumption was identified the *hepatic cirrhosis* or *chronic hepatitis in the final stage*, a chronic, diffuse and irreversible scarring of some slow necrotic lesions by the proliferation of the connective tissue, sometimes of the bile ducts also, in prejudice of the parenchyma and the severe alteration of the lobulary architecture of the organ, associated with the reshuffling of the parenchyma by regenerative activity. From the etiopathogenic point of view, there are metabolic or toxic cirrhoses, posthepatic, postnecrotic, congestive, billiary and cryptogenic cirrhosis. Morphologically, in *the atrophic cirrhosis*, the hepatic capsule is thickened and connected to the thick septa which limit the unequal prominent lobules. In the *hypertrophic cirrhosis*, almost

every cell is surrounded by connective tissue by the excesive development of the collagen fibres and the compactization of the reticulin network in the Disse spaces.

The *multiple interstitial hepatitis* is caused by the migration of the larval stages of the nematode *Ascaris suum*, trematodes and by the localization of the parasites; the lesions caused by the larval migration consist of necrotic and hemorrhagico-necrotic tunnels, eosinophilic trajectories and finally fibrous, of scarring, and the localization ones, by abscesses and eosinophilic granulomas and angiocholitis.

The hepatitides with giant cells were identified as *diffuse* inflammations and also as infectious pyogranulomas and hydatic granulomas with characteristic structure.

In a few cases were observed star-shaped and ground glass hepatocytes, adjacent glycogenosis, apoptotic cells as acidophilic Councilman bodies, lymphoplasmocytary inflammatory infiltrate, especially in the portal spaces, ballooning degeneration, cytolysis and lytic micronecrosis due to some cytotoxic immune reactions, phagocytosis in the Kupffer cells, inclusions, observations that impose further investigations regarding some hepadnavirosis in swine.

The lesions of the bile ducts included *epithelial metaplasia*, steatosis, hyperplasia of the billiary ducts, extra- and intrahepatic cholestasis and chataral, suppurative, lymphohistiocytary, lymphoplasmocitary, sclerosing, distructive and parasitary inflammations.

The trematodosic parasitary cholangitis identified in 2 bodies with lesions of interstitial parasitary hepatitis was characterized by highly dilatated billiary ducts, adult parasites and eggs and an abundent cathar consisting of mucus, necrotic detritus, polymorphic inflammatory cells, scarce eosinophils and germs, limited by fibrosis.

In *the chronic cholecystitis*, identified in an adult pig, slaughtered for consumption, the gallbladder was slightly enlarged, with a smooth and shiny serous, covered with fibrine pellicles, dry yellowish mucosa, erosions and ulcerations. Microscopically, the folds of the mucosa appear necrotized, astructured, with bacterial collonies, rare groups of nucleated epitheliocytes and caliciform cells. The chorion is thickened due to a polymorphicdiffuse cellular infiltrate, the lymphoid noduli being rarefied by the lymphocytolysis or replaced by serofibrinous and leucocytary exudate.

The liver, which from the point of view of the necropsy findings is a cardinal organ in all animal species, in swine has a variety of lesions, including all the types of the fundamental pathological processes: disorders of cellular adaptation, tissular growth disorders, circulatory disorders, inflammations. The research we performed deeply explains the morphopathogenesis of the identified hepatopathies and solves the most part of their etiology.

Even if the swine pathology from the big and medium farms of our country is plainly dominated by the mycoplasmic syndromes (especially enzootic pneumonia) and by the specific viral syndromes, the opportunistic bacteria and the parasitary invasions with hepatic localization produce supplementary health and economic issues, because of the partial or total confiscations that are necessary in the slaughter-houses.