Endocrine Organs

16

Endocrine organ dysfunction can explain sudden and unexpected death, although this is rarely the case in forensic practice (Püschel 2004). Nevertheless, there is a wide range of possible endocrine diseases which may be relevant at forensic autopsy (Table 16.1).

Examples of findings include:

- Type 1 and type 2 diabetes: lethal hypoglycemia and diabetic coma
- Addison's disease: acute adrenocortical insufficiency
- Lethal and often clinically unrecognized pheochromocytoma
- Thyroid and parathyroid dysfunctions
- Acute hypophyseal dysfunction or necrosis (e.g., Sheehan's syndrome)

Distinct histopathological findings cannot be seen in all cases of endocrine dysfunction; however, less pronounced findings can also be included in forensic evaluation and may explain clinical symptoms.

16.1 Diabetes

Sudden and unexpected death as a result of diabetic metabolism disturbances occurs occasionally due to infection, acute pancreatitis, in cases of islet cell involvement, sometimes accidentally in cases of incorrect dosage of antidiabetics or insulin, in rare cases as homicide with insulin administration, and also rarely as suicide (Banaschak et al. 2000; Kernbach-Wighton and Püschel 1998; Valenzuela 1988; DiMaio et al. 1977). In the case of insulin injection, the dermal and subepidermal injection site should be investigated immunohistochemically using an antibody against insulin (Wehner et al. 1997). In all cases, a rapid urine glucose test at autopsy can provide the crucial hint. Thereafter, postmortem biochemical findings are of prime importance (Osuna et al. 1999, 2005; Karlovsek

Table 16.1 Lethal endocrine dysfunctions

Organ or organ structure	Dysfunction
Hypophysis	Hypopituitarism/Sheehan's syndrome
Parathyroid gland	Hypo- and hyperparathyroidism (adenomas, carcinomas)
Thyroid gland	Underactive thyroid (e.g., thyroiditis)
	Thyrotoxicosis (e.g., Graves' disease, autonomous adenoma, rarely struma ovarii)
Adrenal malfunction	Acute and chronic organic destruction
Adrenal cortex	Hyperfunction: endocrinologically active tumors/Addison's disease
Adrenal medulla	Endocrinologically active tumors (pheochromocytoma)
Pancreatic islet cells	Insulitis, diabetic coma, hypoglycemic coma
Thymus	Myasthenia gravis
Endocrinologically active tumors	For example, serotonin-producing carcinoid

R. B. Dettmeyer, *Forensic Histopathology*, https://doi.org/10.1007/978-3-319-77997-3_16

2004; Kernbach and Brinkmann 1983). The combined findings of glucose and lactate in the cerebrospinal fluid and vitreous humor of the eyes are particularly significant, as are the findings of blood sugar and HbA1c concentration in the blood (Sippel and Möttönen 1992; Ritz and Kaatsch 1990).

Histologically, a hyperglycemic metabolic disturbance can lead to glycogen nephrosis; the correlation of which with biochemical postmortem parameters has been investigated (Lasczkowski and Püschel 1991). After diabetes of long-standing, accompanying diseases (e.g., arterio-arteriolosclerosis) and sometimes even the clinical picture of diabetic glomerulosclerosis (Kimmelstiel–Wilson type) (Fig. 16.1) can be seen histopathologically. This disease must be differentiated from lobular forms of glomerulonephritis in any differential diagnostics (Wehner and Haag 1980).

While acute hypoglycemia will not necessarily show diagnostically relevant findings, a long-lasting hyperglycemia with lethal diabetic coma leads to a resorption of glycogen via epithelial cells, primarily in the main parts of the renal tubules. Vacuolated epithelial cells of the renal tubules can be seen histologically (Fig. 16.2). However, vacuoles do not necessarily contain glycogen, and lipid determination is also

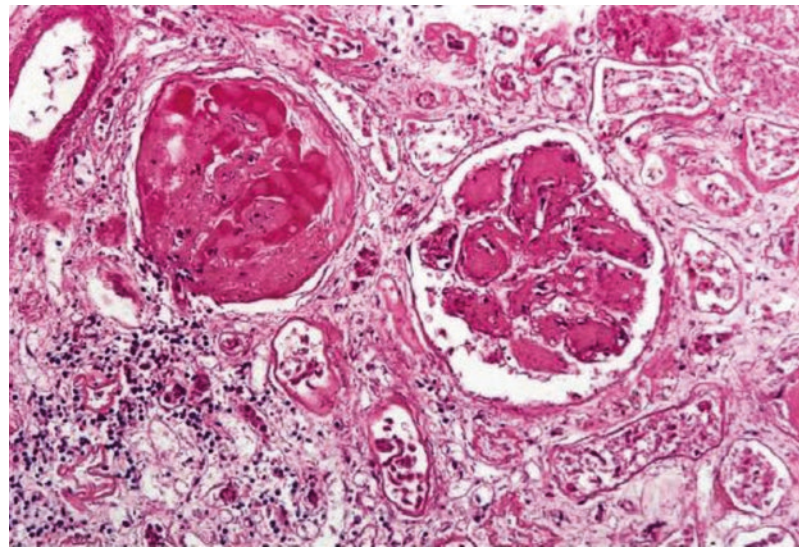

Fig. 16.1 Known dialysis-dependent renal failure in a case of diabetic glomerulosclerosis of Kimmelstiel–Wilson type in a 53-year-old woman with lethal diabetic coma (Elastica van Gieson ×400)

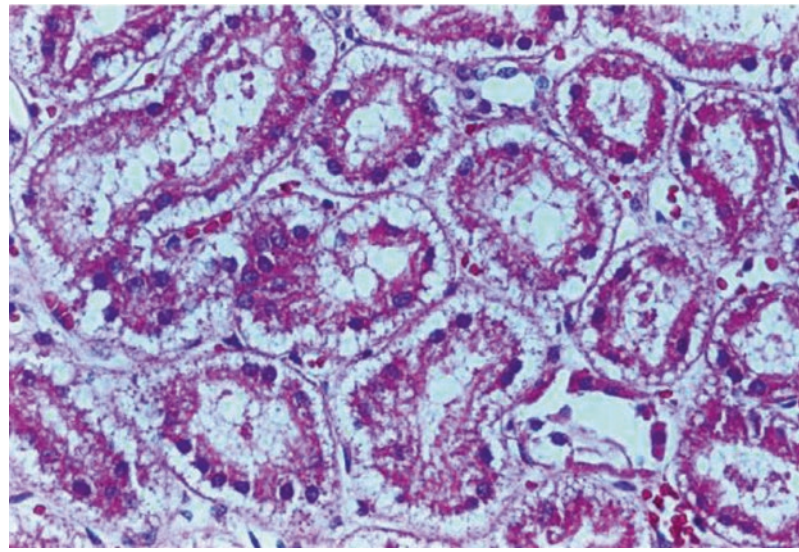

Fig. 16.2 Lethal diabetic coma (postmortem blood sugar level 869 mg/dl) with vacuolated epithelial cells of the renal tubules (H&E ×200)

positive in cases of death due to diabetic coma (Zhou et al. 2015; Thomsen et al. 2006).

If glycogen sediments of this sort are found in epithelial cells of the renal tubules, these cells are then called Armanni–Ebstein cells (Zhou et al. 2010; Ritchie and Waugh 1957). The Armanni–Ebstein lesion was first reported in 1877 and has been associated with deaths due to diabetic ketoacidosis. Meanwhile Armanni–Ebstein cells were also found in cases of nondiabetic individuals who died due to starvation (Milroy and Parai 2011). The glycogen sediments in Armanni–Ebstein cells can be determined in comparatively autolytic kidney tissue (Fig. 16.3), and glycogen drops can be seen in PAS staining (Fig. 16.3). Conventional hematoxylin and eosin staining initially reveals only Armanni–Ebstein cells; however, in addition to glycogen, these can also contain lipids and are found in cases of death due to hypothermia (Byard and Zhou 2010; Zhou and Byard 2011).

In rare cases, impaired sugar metabolism can be caused by an acute dysfunction in insulin production, such as insulitis (Fig. 16.4).

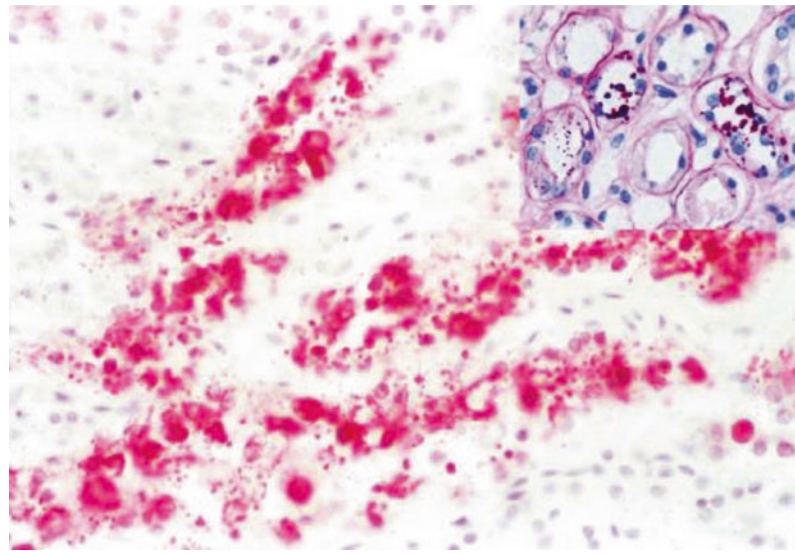

Fig. 16.3 Lethal diabetic coma with glycogenic vacuoles in the cytoplasm of epithelial cells of the renal tubules, referred to as Armanni–Ebstein cells (Best's carmine ×200), and glycogen drops in the lemen of the renal tubules (PAS v200)

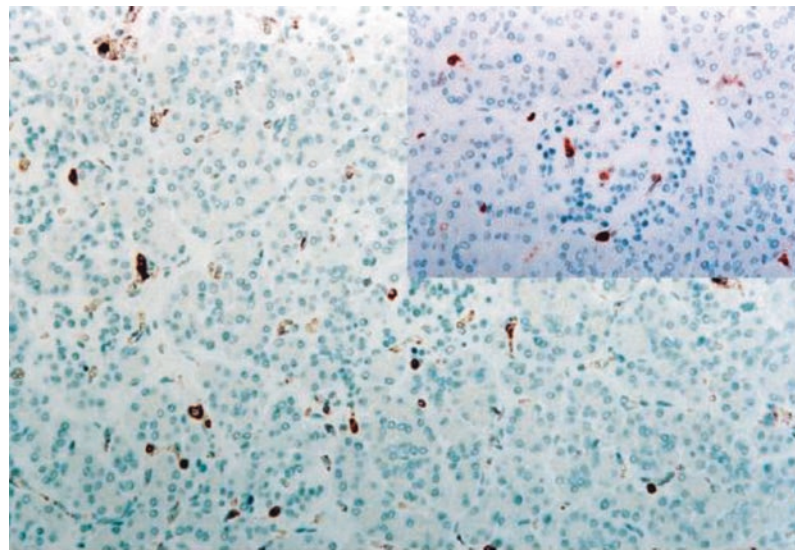

Fig. 16.4 Pancreatic tissue with acute lymphocytic insulitis and an increase in the number of leukocytes in pancreatic islet cells (both LCA ×400)

In cases of hyperglycemia with lethal diabetic coma, extensive infections can often be seen, in particular in the respiratory and genitourinary tract and in rare cases, such as fungal infections, in several organ systems. Vacuoles with a ground-glass appearance in the cell nuclei of hepatocytes are said to indicate a diabetic metabolic state. However, additional causes should be considered, and intoxication should be excluded.

If blood sugar levels remain inadequately controlled in insulin-dependent diabetes over a prolonged period of time, abnormally pronounced *nonalcoholic hepatic steatosis* may develop. As part of this process, mostly small to at most medium-sized vacuoles predominate in the hepatocytes, presenting a relatively uniform picture (Fig. 16.5).

While diabetic metabolic disturbances can only be diagnosed chemically as hypoglycemia or hyperglycemia (determination of glucose concentration and HbA1c value, particularly in blood, serum, liquor, and vitreous humor), indications of underlying diseases can be seen histomorphologically (Table 16.2).

Table 16.2 Histomorphological indications of long-term diabetes mellitus

Organ or organ system	Histomorphological findings
Arterial vascular system	Atherosclerosis at an advanced stage compared to the age of the patient, also arteriolosclerosis
Liver	Microvesicular steatosis of the liver with optically empty vacuoles in the cell nuclei of hepatocytes—nonspecific
Kidneys: glomeruli	Diabetic glomerulosclerosis (Kimmelstiel–Wilson type) of varying severity
Kidneys: arterioles	Relatively pronounced arteriosclerosis
Kidneys: tubules	Vacuolar brightening of the distal tubular cells with Armanni–Ebstein cells, PAS-positive cytoplasm (alternatively, Best's carmine stain)
Pancreas	No pathological findings with conventional histological methods; in some cases, possible insulitis
Infections	Chronic and acute exacerbated infections, including mycoses (pneumonias, infections of the genitourinary tract, etc.)

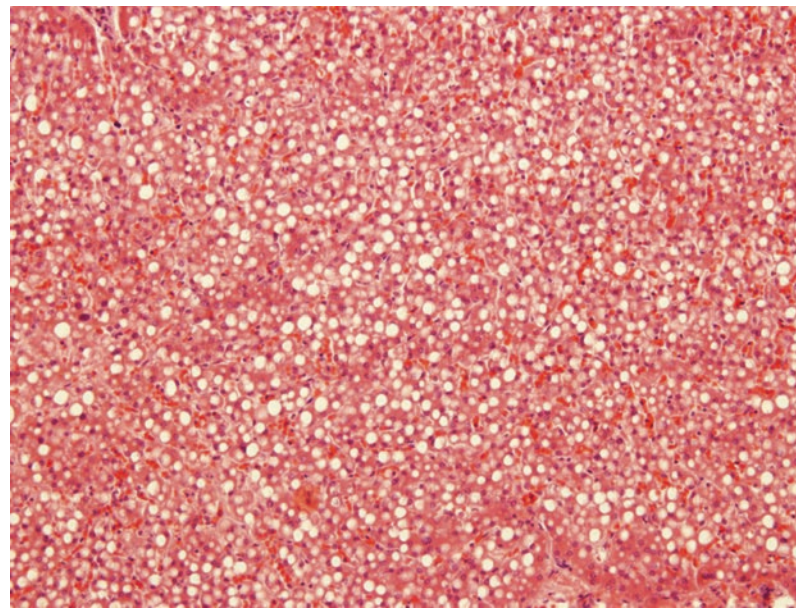

Fig. 16.5 Pronounced nonalcoholic hepatic steatosis in insulin-dependent type 1 diabetes inadequately controlled over a prolonged period of time (H&E ×100)

Hypoglycemia

In cases of hypoglycemia (blood sugar <50 mg%), only scant histological findings can be seen. Nerve cell damage with pyknotic nuclei in nerve and glial cells is described in particular in the central nervous system. Extensive elective parenchymal necrosis occurs, frequently along the sulcal depths. Granular cell necrosis and homogenization of Purkinje cells can occur, in particular in cases of a sudden change from diabetic coma to hypoglycemic coma (Roggendorf 1995). In a case of insulin suicide or homicide, insulin is detectable in routinely formalin-fixed and paraffin-embedded subcutaneous injection marks, in spite of a postmortem interval of day up to weeks. Around birefringent crystalline material, probably zinc phosphate, immunohistochemistry can reveal granular insulin depots as well as an insulin staining along the lipocyte membranes (Lutz et al. 1997).

16.2 Loss of Adrenocortical Lipids

Some authors report that morphological changes in the adrenal cortex are completely absent in acute deaths (Uotila and Pekkarinen 1951). It is only after a prolonged survival time that loss of adrenocortical lipids can be seen (Fig. 16.6; Symington et al. 1956; Spann 1954). Investigations on acute lipid mobilization in cases of very short posttraumatic survival times have been conducted. In these investigations, lipid accumulation in the sinusoids of the adrenal cortex has been found in cases in which death did not occur suddenly, in particular in the middle cortical layer (the fasciculate zone). Scarlet red staining was performed; other staining methods (Nile blue sulfate, Sudan III, osmium IV) did not lead to better differentiation. However, findings were not equally distributed within the fasciculate zone of the adrenal cortex (Heinrichs et al. 1969). The authors interpreted this lipid mobilization as a vital reaction that would also allow for a conclusion as to how rapidly death occurred. However, histological findings should be interpreted with

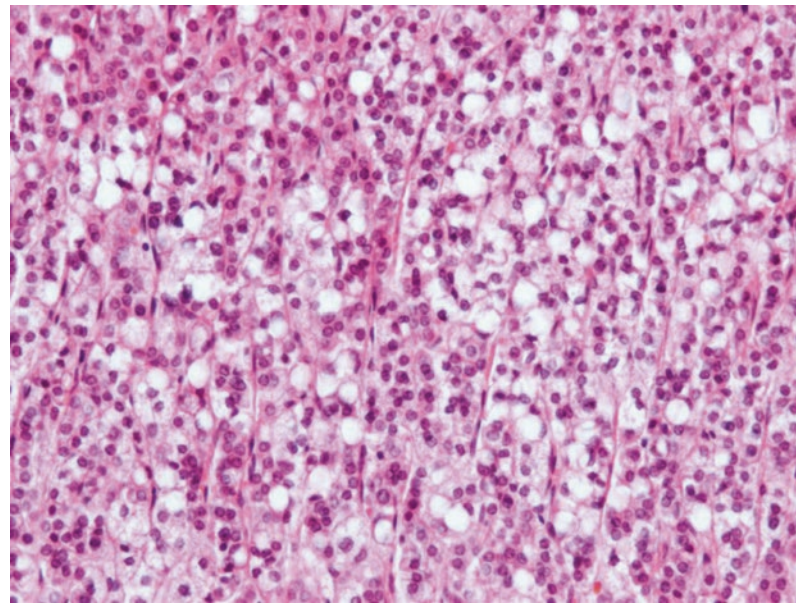

Fig. 16.6 Partial lipid depletion of cells in the zona fasciculata of the adrenal cortex (H&E ×200)

caution. On the one hand, a single histological tissue section cannot be sufficiently representative of the entire adrenal cortex, while on the other there can be various causes for vacuolated lipid depletion in the cells of the zona fasciculata of the adrenal cortex.

16.3 Acute Primary Adrenal Insufficiency (Addison's Disease)

Circulatory lesions, inflammation, and tumors of the adrenal glands can affect the secretion of hormones and may cause lethal metabolic crises (Palmiere et al. 2014; Hecht et al. 2009b; Burke and Opeskin 1999; Al Sabri et al. 1997). Only in very rare cases does adrenocortical carcinoma cause sudden death (Marshall et al. 2007). Even if such cases are quite rare, the primary and secondary morphological findings and symptoms of an acute disease should be known by all forensic medical examiners. Addison's disease is primary adrenal insufficiency due to bilateral destruction of, or damage to, the adrenal cortex, for example, in the setting of tuberculosis (Ward and Evans 1985), due to malignant disease, or in the case of autoimmune adrenalitis. In addition to advanced myasthenia, cachexia and brownish pigmentation of the skin and mucosa (bronze skin disease) can be seen.

An infection (Woenkhaus et al. 2005) or Waterhouse–Friderichsen syndrome can trigger acute adrenal insufficiency with a lethal course. This results in a shock-like condition due to electrolyte deficit with acidosis, vomiting, diarrhea, hemorrhage, and numbness. The disease peaks at between 40 and 50 years of age. In 80% of cases, an autoimmune adrenalitis can be assumed (Fig.16.7), which occurs in isolation in approximately 40% of cases and in connection with an autoimmune polyendocrine process in approximately 60% of cases (Woenkhaus et al. 2005).

Decedents are typically very slim and cachectic, such that anorexia nervosa may also be considered (Arlt and Allolio 2003; Adams et al. 1998). Atrophied adrenal glands are frequently difficult to differentiate during autopsy, and thyroid glands are frequently reduced in size. Histologically, adrenal glands show a significant reduction of the parenchyma in the cortical region and lymphocytic infiltration (almost exclusively in the cortical region), which can be seen as a consequence of an autoimmune process (Palmiere 2015; Govi et al. 2015; Martín Martorell et al. 2002). Inflammation is accompanied by a tendency toward fibrosis of varying degrees. Increased corticotropin (ACTH)-releasing cells

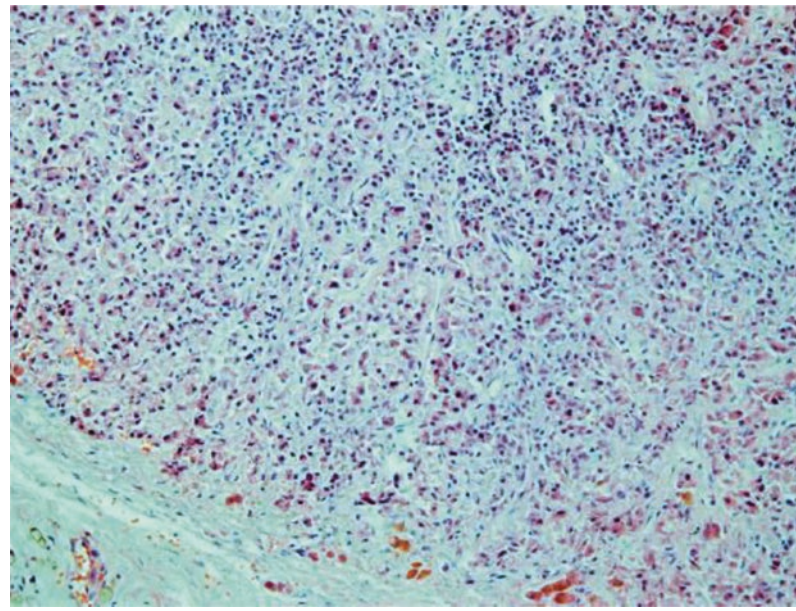

Fig. 16.7 Lymphocytic adrenalitis with clinical symptoms of Addison's disease (H&E ×100)

in the adenohypophysis (apparently reactive) have been reported (Schröder et al. 2009). Medical examinations of the thyroid gland sometimes show chronic thyroiditis with atrophic thyroid follicles.

16.4 Fatal Pheochromocytoma

Pheochromocytomas, tumors of the adrenal gland marrow, are well known as rare causes of sudden death, although they often result in a confusing array of clinical symptoms (Cardesi et al. 1994; Kniseley et al. 1988; James 1976). Pheochromocytomas occur both hereditarily and sporadically (Primhak et al. 1986; Vallance 1957). The biochemical hallmark and characteristic clinical sign of this tumor are secretion of catecholamines, causing dramatic elevations in blood pressure (Badui et al. 1982).

Only a few individual cases describe pheochromocytomas as a cause of sudden death (D'Errico et al. 2009; Preuß et al. 2006; Türk et al. 2004; Vallance 1957). Some authors suggest that pheochromocytomas have been misdiagnosed more often than previously assumed (Lo et al. 2000). Earlier studies showed that <50% of pheochromocytomas found at autopsy were already diagnosed, while the patient was still alive (Benowitz 1990).

Pheochromocytomas are generally found unilaterally (80%) and seldom bilaterally (10%) in the adrenal glands; about 10% are found outside the adrenal glands, but less than 10% are malignant (Preuß et al. 2006). They present as well-circumscribed encapsulated tumors of varying size and show a bright brown carnose color. Relicts of the yellow cortex of the suprarenal gland may be visible at the margin of the tumor. In addition, these tumors have large eosinophilic cells with granular cytoplasm as well as prominent and partly bizarre nuclei with PAS-positive small inclusions (Fig. 16.8). If there is any doubt as to the diagnosis, immunohistochemical investigations using antibodies against neuroendocrine-specific enolase (NSE) will help to demonstrate neuroendocrine granules such as chromogranin A and synaptophysin (Fig. 16.9). Additionally, the so-called sustentacular cells surrounding the tumor can be positive for S-100, a neuroectodermal marker (Preuß et al. 2006). In cases of acute cardiac failure, coagulative myocytolysis or contraction band necrosis can be found, termed catecholamine necrosis. Using confocal laser scanning microscopy, myocardial cells with ruptured myofibrils

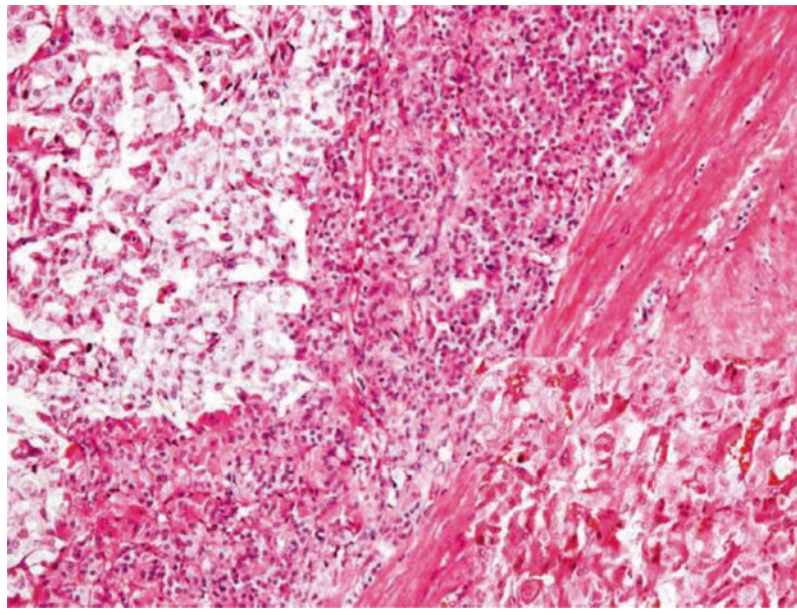

Fig. 16.8 Pheochromocytoma with tumor cells presenting nuclear pleomorphism, round or oval but also some polymorph nuclei, and rare mitoses (H&E ×100, Insert: H&E ×200)

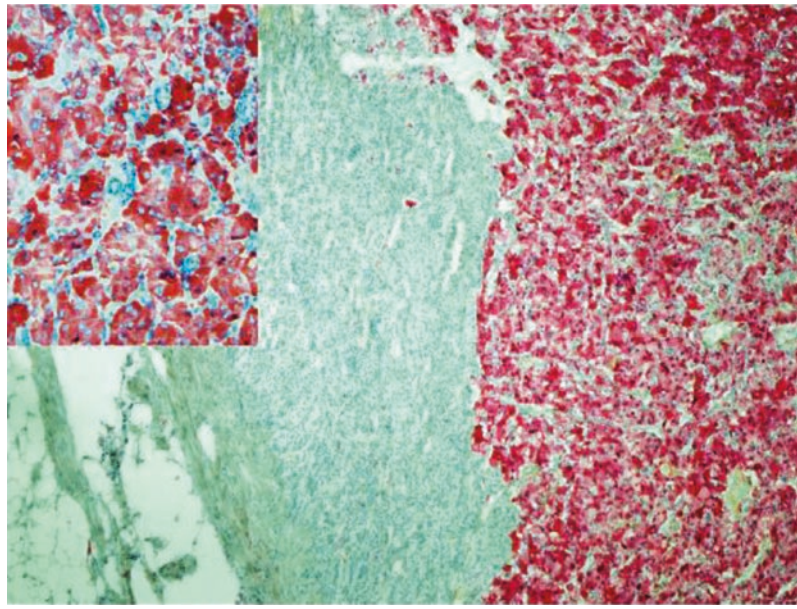

Fig. 16.9 Pheochromocytoma with positive immunohistochemical evidence of expression of synaptophysin (×40) and chromogranin A (Insert: ×200)

are described, characterized by hypereosinophilic bands of hypercontracted sarcomeres demonstrated by granular cytoplasm (D'Errico et al. 2009).

Extra-adrenal Paraganglioma

These tumors seldom occur in adult patients and resemble pheochromocytomas in morphology, functional behavior, and symptoms. They can be found in the region of the para-aortic paraganglia (organ of Zuckerkandl), duodenum, and bladder wall. They predominantly secrete noradrenaline and show a malignant degeneration more frequently than pheochromocytomas. Only a few cases of sudden death due to paragangliomas have been reported (Sperry and Smialek 1986; Isaacson et al. 1960). Causes of death in cases of pheochromocytoma or extra-adrenal paraganglioma are often the result of severe paroxysmal hypertension, such as cerebral vascular accidents, abrupt hemorrhage into the tumor, or acute left ventricular failure (Preuß et al. 2006; James 1976).

16.5 Thyroid and Parathyroid Dysfunction

Sudden death in association with metabolic crises due to dysfunction of the thyroid and parathyroid glands, e.g., thyrotoxicosis, parathyrotoxic crisis, myxedema, and acute hypoparathyroidism, is rarely seen in forensic practice (Hostiuc et al. 2015). Dysfunction can be seen in inflammatory, hyperplastic, and neoplastic processes. Inflammation of the thyroid gland accounts for approximately 20% of all thyroid diseases. According to its clinical course, thyroiditis has been subdivided into acute, subacute, and chronic forms. Classifications are based on the fact that the majority of thyroiditis cases have an autoimmune background. The most common form of this disease is autoimmune thyroiditis, with or without subclinical or manifest hypothyroidism. Thyroiditis is both clinically and morphologically distinct from thyroid tumors. Therefore, a careful examination of organs can provide useful information.

Thyroid and parathyroid dysfunctions do not necessarily show macroscopic findings.

However, appropriate histological findings can often be seen, sometimes in connection with the determination of laboratory parameters (hormone level, calcium level, etc.). Frequently, thyroid dys-

function remains undiscovered without histological controls (Liu and Lin 2015; Edston et al. 2001; Edston 1996). In particular, chronic inflammatory thyroiditises with a reduction in hormone-producing parenchyma can lead to severe dysfunction and may explain sudden death in some cases.

Less common forms of autoimmune thyroiditis include subacute granulomatous (de Quervain's) thyroiditis, postpartum thyroiditis, silent ("painless") thyroiditis, and invasive-sclerosing thyroiditis (Riedel's thyroiditis). Non-autoimmune thyroiditis is very rare (e.g., acute suppurative thyroiditis, radiation thyroiditis).

The following histological diagnoses can only be considered as indications of sudden endocrine-related death, rather than definitive evidence. Comparison with additional findings and hormone analysis to confirm the histomorphological diagnosis are both necessary. If possible, hormone analysis should be performed in the early postmortem interval (Edston et al. 2001; de Letter et al. 2000; Risse et al. 1986).

16.5.1 The Thyroid Gland

Inflammation and, in particular, hyperthyroidism can cause sudden death (Lynch and Woodford 2014; Siegler 1998; Edston 1996). Histological findings may be seen in thyroid tissue, such as papillary formations of the follicular epithelium and increased intracolloidal resorption vacuoles, which can be interpreted as a morphological sign of increased functional activity. Histomorphological findings alone can sometimes indicate that functional disorders are likely but do not provide definitive evidence. In addition, medication can affect the histological picture of the thyroid gland. A goiter develops in 5–15% of patients with chronic lithium intake. Histologically, diffuse hyperplasia can be seen. Anticonvulsants (e.g., phenytoin, carbamazepine) can also cause unspecific thyroiditis (Sheu and Schmid 2003).

Lymphomatous Goiter (Hashimoto's Goiter)
This autoimmune thyroiditis mainly affects women between 40 and 60 years of age. It is a chronic lymphatic thyroiditis with gradual formation of a goiter and hyperthyreosis. Histological findings show destructive inflammation of the thyroid parenchyma. In addition to lymphatic tissue with pronounced germinal centers, a lymphoplasmacellular inflammatory infiltrate can be seen, which moves between the cells of the follicular epithelium (Fig. 16.10). Giant cells can also occur (Schmid and Böcker 1997b), as well as oxyphil metaplasia with eosinophil follicular epithelia.

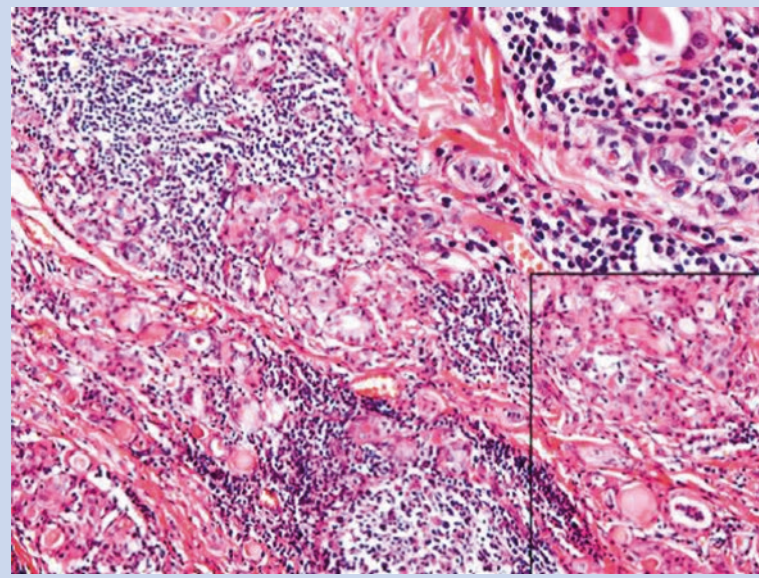

Fig. 16.10 (**a**, **b**) Hashimoto's goiter with lymphatic germinal centers and a lymphoplasmacellular inflammatory infiltrate invading and partly destroying the follicular epithelium (insert) (H&E ×100, ×400)

Atrophic Autoimmune Thyroiditis

In the case of atrophic autoimmune thyroiditis, clinical signs of hypothyroidism can be seen. Histologically, pronounced fibrosis with macroscopically diminished thyroid glands is evident, while functionally active thyroid tissue is rare, and a loose lymphoplasmacellular inflammatory infiltrate can be seen. Infrequently, dense fibrosis (Riedel's thyroiditis) can be seen, typically in connection with euthyreosis.

De Quervain's Thyroiditis

This is a granulomatous thyroiditis that does not usually lead to severe dysfunction in hormone production. Histologically, both lymphoplasmacellular inflammation and polynuclear giant cells can be seen (Fig. 16.11).

Diffuse Hyperthyroid Goiter (Graves' Disease)

This form of thyroid dysfunction is also an autoimmune disease, typically occurring between 30 and 40 years of age; females are more frequently affected than males. The thyroid gland is enlarged and appears dark red macroscopically. Histologically, a cubic to highly prismatic follicular epithelium can be seen. This epithelium is situated on papillary cell buds which protrude into the follicular epithelium (Fig. 16.12). Adjacent intracolloidal resorption vacuoles can be seen when thyroid colloid is present. A certain fibrotization can be observed subepithelially, along with loosely spread lymphocytes. Autoimmune diseases of the thyroid gland can be accompanied by a myxomatous mitral valve prolapse; the embedded hydrophilic glycosaminoglycans can be detected with Alcian Blue staining. In the case of a thickened mitral valve, valve insufficiency may occur (Kahaly et al. 1995). Cases of sudden unexpected death in undiagnosed Graves' disease have been described (Lynch and Woodford 2014).

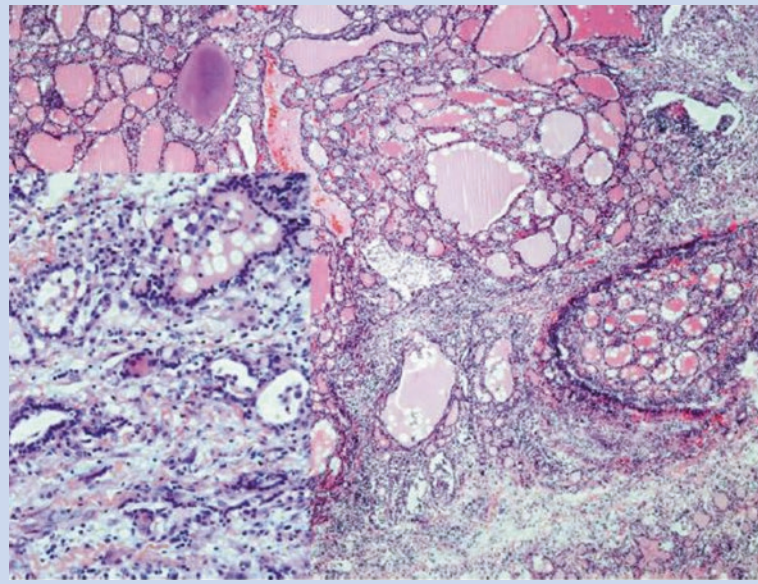

Fig. 16.11 (**a**, **b**) Granulomatous de Quervain's thyroiditis with lymphocytic inflammatory infiltrate, slight interstitial fibrosis, and increased intracolloidal resorption vacuoles as a histological sign of increased functional activity; hyperthyroid phase (H&E ×40, Insert: H&E ×200)

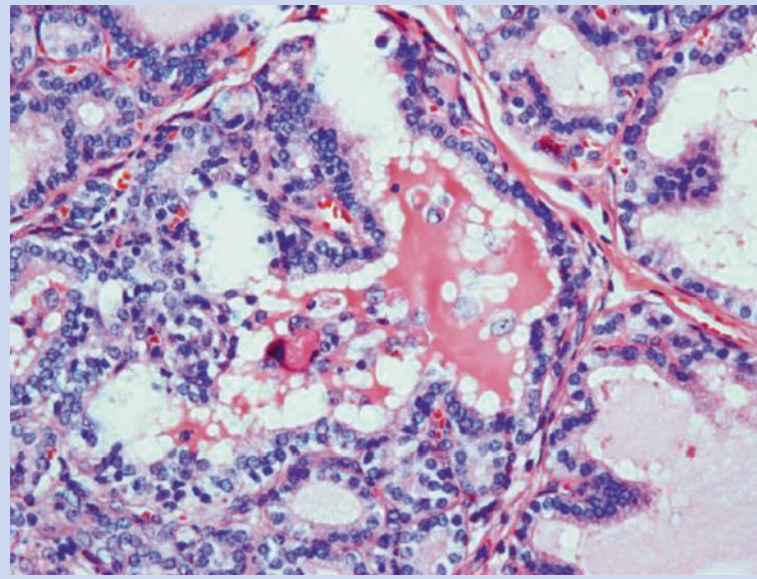

Fig. 16.12 Graves' disease: hyperthyroid goiter with micropapillary formations of the follicular epithelium and intracolloidal resorption vacuoles as a sign of increased functional activity of the thyroid gland (H&E ×200)

Amiodarone-Induced Thyroiditis

Long-term medication with amiodarone or propylthiouracil can promote both hypothyroidism and a thyrotoxic crisis (Sheu et al. 2006; Gough and Gough 2002; Mulligan et al. 1993; Smyrk et al. 1987). Amiodarone, an iodine-containing antiarrhythmic, can lead to severe thyroid dysfunction. Histologically, destructive chronic inflammation with lymphocytes and formation of foam cells from macrophages can be seen; intracolloidal resorption vacuoles as a sign of increased functional activity may also occur. The follicular epithelium will be gradually destroyed, and post-inflammatory fibrosis forms.

Autonomous Thyroid Adenoma

Autonomous or toxic thyroid adenoma is said to be responsible for approximately one third of cases of hyperthyroidism (Hecht et al. 2009b). Histologically, the adenoma is completely surrounded by a modest fibrous fiber capsule. The follicular epithelium shows, as in Graves' disease, micropapillary formations and is relatively bright and high. Abundant intracolloidal resorption vacuoles are visible. Frequently, regressive changes, as can be seen in a goiter, occur, including fibrosis, hemorrhage, calcium deposits, and siderophages. In the case of autonomous adenoma, the remaining thyroid tissue might be atrophic (Schmid and Böcker 1997b). Multiple toxic or autonomous adenoma with a similar histological picture is referred to as toxic multinodular goiter (Plummer's disease). In cases of autonomous adenoma or toxic multinodular goiter, a thyrotoxic crisis may occur on administration of iodine-containing contrast agents (Sheu et al. 2003). The development of thyrogenic cardiomyopathy may be considered, depending on the duration of hyperthyreosis.

Thyrotoxic Crisis

A thyrotoxic crisis is a rare endocrinological emergency with a mortality rate of up to 50% (Burch and Wartofsky 1993). The main clinical symptoms include tachycardia, hyperthermia, and central nervous system disorders. Psychotic states and cramping, as in epileptic seizures, occur (Hecht et al. 2009a; Safe et al. 1990). At autopsy, signs of right heart failure with upper venous congestion, peripheral edemas, and vascular congestion in the internal organs can be seen (Safe et al. 1990; Zierhut and Girlich 2004). Despite inconspicuous findings in the coronary arteries, cardiac arrhythmias and acute myocardial infarctions have been described (Cheah et al. 1971; Kotler et al. 1973), as well as cardiac arrhythmias attributed to coronary spasms (Wei et al. 1979). Typically, a preexisting hyperthyreosis is assumed that may lead to a thyrotoxic crisis when triggering factors occur, such as iodine ingestion or discontinuing thyrostatic therapy (Reschke and Lehnert 2003). In rare cases, accidental or suicidal administration of thyroid hormones should be considered (Hartung et al. 2010; Bhasin et al. 1981). Uncontrolled intake of liothyronine can cause lethal thyroid storm in an euthyroid patient without manifest cardiac disease. Histological findings in such cases include a thyroid gland with plump follicles and a flattened epithelial layer, while the myocardium may present multiple fresh cell necroses (Hartung et al. 2010). Evident uncontrolled intake of liothyronine can cause thyrotoxic crisis and even lethal thyroid storm. In principle, trauma or surgery can also trigger a thyrotoxic crisis.

Hypothyroidism

In the case of a severely underactive thyroid, myxedema and additional symptoms may occur, including ptosis, macroglossia, pasty swelling in the face, cool and dry skin, bradycardia, hypotonia, and even shock (Wall 2000). Hypothyroidism has a mortality rate of up to 20% (Hecht et al. 2009a). There is no morphological correlate for the clinical diagnosis of hypothyroidism.

Radiation-Induced Thyroiditis

External radiation and radioiodide therapy leads to a destruction of thyroid follicles with inflammatory infiltrates, proliferation of fibroblasts, and subsequent fibrosis. Cell nuclei of follicular epithelia may show pronounced pleomorphism and hyperchromasia.

Black Thyroid

A distinctive but very rare side effect of exposure to minocycline, a tetracycline derivate, is black pigmentation of the thyroid gland. Histology findings present clumps of black-brown pigment, visible in epithelial cells and in the colloid (Bell et al. 2001). Also, a granular precipitate of black-brown pigment has been noted in the apical portions of follicular epithelial cells (Tsokos and Schröder 2006). These pigments are also PAS-, Ziehl–Neelsen-, and Sudan IV-positive. Hypothyroidism is occasionally associated with minocycline-related black thyroid, and the development of depressive disorders is possible. No definitive correlation can be drawn

between sudden death and black thyroid, which can develop due to chronic intake of high doses of minocycline. The macroscopic picture of "black thyroid" can also form in the setting of *ochronosis* (*alkaptonuria*). Again in this clinical picture, one sees microscopic (partially dustlike, partially fine-grained) deposits of blackish pigment in the thyroid follicles, particularly in the follicular epithelial cells (Fig. 16.13). These deposits are homogentisic acid, which also accumulates especially in bradytrophic tissue (cartilage, intervertebral discs, scar tissue), as well as in the vessel intima of larger vessels. Microscopic analysis reveals partially dustlike blackish pigment. Disorders such as hematochromatosis, chronic arsenic poisoning, porphyrinuria, Addison's disease, and argyrosis need to be considered in the differential diagnosis. Ochronotic changes have been observed following long-term treatment with antimalarial medications (quinacrine, hydroquinone), antibiotic use (tetracyclines such as minocycline), as well as phenothiazine and phenacetin abuse (Klein et al. 2008).

In the event of protracted stress, the thyroid can react to activation, e.g., in gradual hypothermia or malignant hyperthermia (Fig. 16.14). Several thyroid samples need to be analyzed in order to diagnose this type of thyroid function activation; each sample should show increased intracolloidal resorption vacuoles as a sign of increased functional activity.

In the case of severe trauma involving fractures, chest compression, and marked blood congestion in the head and neck area, it is also possible to detect ruptured vessels and hemorrhage in the thyroid follicles (Byard 2013).

Table 16.3 summarizes the histological criteria for the various thyroid disorders (modified from Hostiuc et al. 2015)

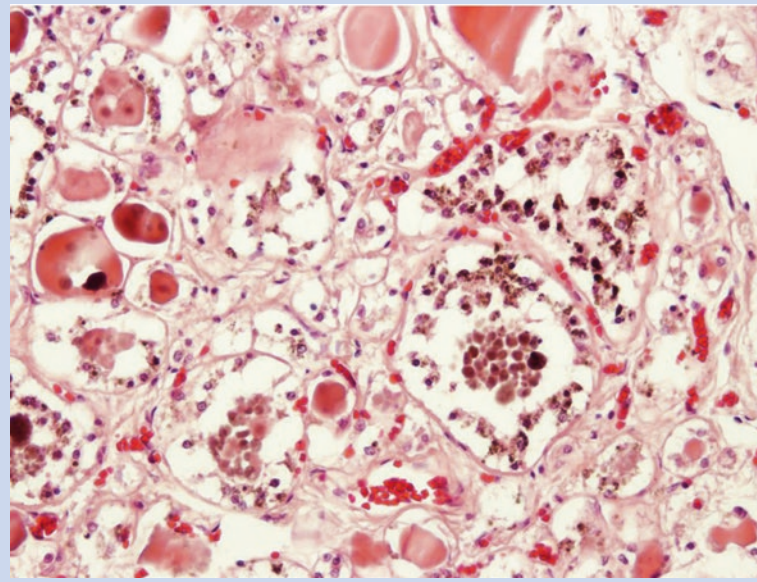

Fig. 16.13 Marked colloid depletion in the thyroid follicles with blackish pigment in the follicular epithelium and follicular spaces, occasionally also in the apical region of the follicular epithelium; "black thyroid" in ochronosis (H&E ×100)

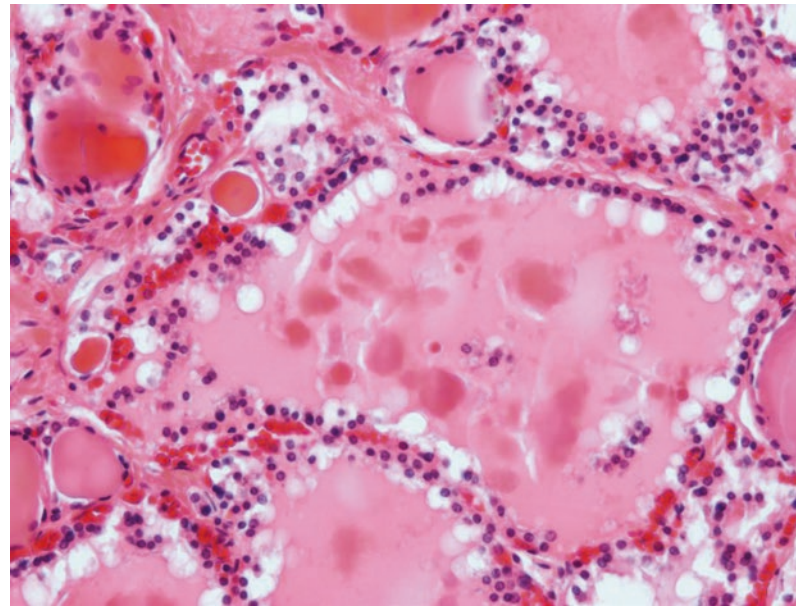

Fig. 16.14 Increased intracolloidal resorption vacuoles as a sign of increased functional thyroid activity (H&E ×200)

Table 16.3 Histological findings in the various thyroid disorders

Diagnosis	Histology
Partially diffuse, partially nodular colloid goiter	Varying thyroid follicle size with a flat, cubic epithelium, no loss of colloid, no inflammation, and no increase in intracolloidal resorption vacuoles Nodular structures, microhemorrhages, interstitial fibrosis with calcifications, ossification, and necrosis are possible
Graves' disease	To some degree small, but also larger thyroid follicles with a high, prominent, and partially pseudopapillary epithelium, lymphocytic infiltrates (generally $CD4^+$-T-lymphocytes), and abundant intracolloidal resorption vacuoles (Fig. 16.12)
Subacute thyroiditis (de Quervain) (Fig. 16.10)	*Hyperthyroid phase:* thyroid colloid depletion, follicle wall rupture, multinucleated giant cells, signs of acute inflammation *Hypothyroid phase:* loss of follicular epithelium, mixed inflammatory cell infiltrates, granulomas surrounding the ruptured follicle *Regenerative phase:* increasing fibrosis and regenerating follicles
Chronic thyroiditis	Buildup of lymphocytic cells in thyroid tissue, some with fully formed germinal centers between the thyroid follicles No histological criteria for increased thyroid function
Riedel's thyroiditis	Cell-poor, strongly fibrosed tissue involving adjacent thyroid tissue, small atrophic residual thyroid follicles with flat epithelium, scant thyroid colloid
Amiodarone thyroiditis	Partially fibrosed, partially chronic inflammatory areas in thyroid tissue as well as tissue that has undergone degenerative change, to an extent involving foam cells in irregularly and diffusely enlarged follicles
"Black thyroid"	Deposits of blackish pigment in apical areas of the follicular epithelium and in the thyroid colloid, e.g., due to tetracycline treatment (ochronosis should be considered in the differential diagnosis; Fig. 16.13)
Autoimmune (Hashimoto) thyroiditis	Atrophic thyroid follicles and oncocytic metaplasia of the follicular epithelium (Hurthle cells), differently sized nuclei, nodular areas, lymphocytic infiltrates with T-cells ($CD4^+$, $CD8^+$) and B-cells of varying density and composition infiltrating the follicular epithelium in places. Frequently enlarged lymph nodes and reactive follicular hyperplasia in adjacent areas (Fig. 16.10)
Increased intracolloidal resorption vacuoles	Uncharacteristic signs of elevated functional activity of varying etiology (Fig. 16.14)
Traumatic crush asphyxia	Congestion-related vessel wall rupture and hemorrhage in thyroid tissue, as well as in thyroid follicles

16.5.2 Parathyroid Glands

As a rule, four parathyroid glands can be seen at autopsy. They lie in pairs and should not normally weigh more than 60 mg. The parathyroid glands in children are somewhat red-brown, while in older people, due to fatty tissue deposits, they appear yellowish-brown. Histologically, a distinction is drawn between clear parathyroid principal cells rich in glycogen (PAS staining) and oxyphil cells. Parathyroid principal cells are solid and situated in small groups, in part with small colloid-containing follicles. Parathyroid dysfunction with increased activity is divided into primary, secondary, and tertiary hyperparathyroidism. These various dysfunctions can result in a hypercalcemic crisis. Reduced activity may lead to lethal hypocalcemia. Here too, histological findings alone cannot verify hyper- or hypocalcemia. However, if further secondary changes are present, particularly in the bones, blood vessels, and soft tissues, it is very likely that chronic hypercalcemia can be verified.

Hyperparathyroidism

The various forms of hyperparathyroidism can lead to a lethal hypercalcemic crisis. In some cases, the underlying cause is a malignant tumor disease with symptoms such as vomiting, renal failure, and coma (Edelson and Kleerekoper 1995). Chronic hyperparathyroidism can lead to calcifications in internal organs, such as the myocardium (Fig. 16.15), kidneys (Fig. 16.16), and lungs (Fig. 16.17), as well as osteomalacia and further vessel and soft tissue calcifications (Schmid and Böcker 1997a).

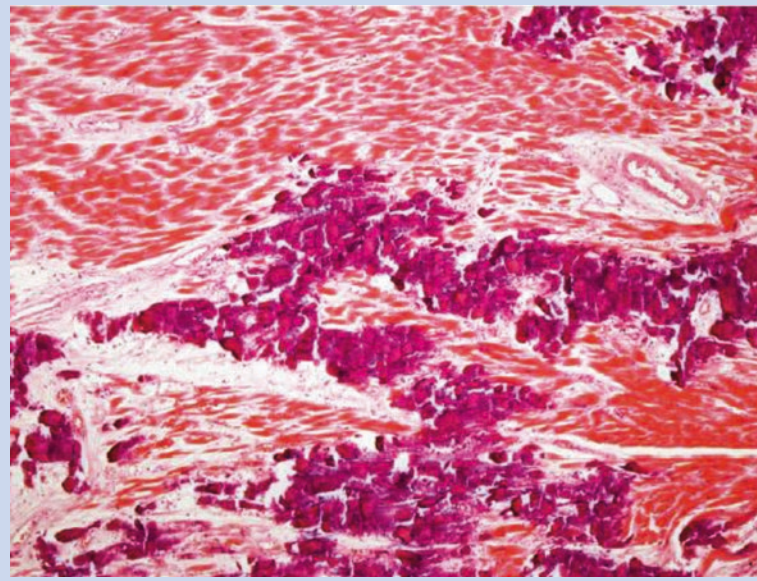

Fig. 16.15 Secondary hyperparathyroidism with severe basophilic calcium salt deposits in the myocardium (H&E ×100)

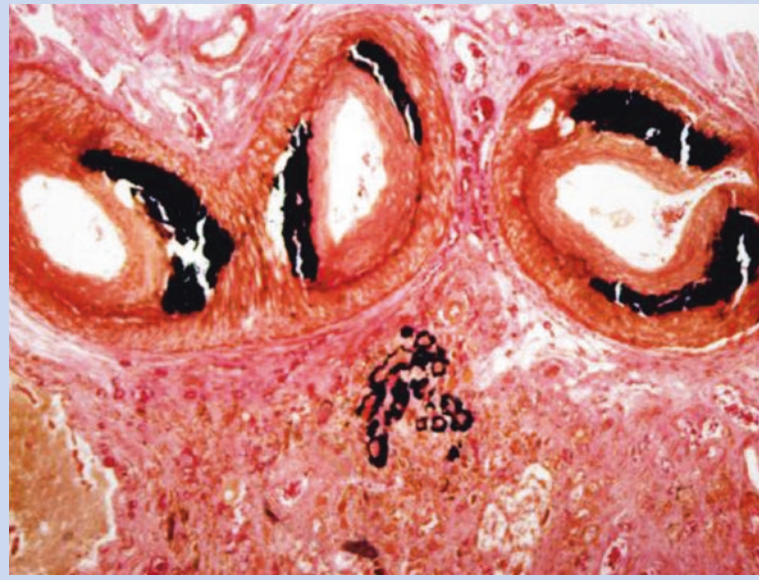

Fig. 16.16 Pronounced nephrocalcinosis with severe calcium deposits in peripheral vascular walls in the case of secondary hyperparathyroidism in a 58-year-old patient with dialysis-dependent renal failure found dead in his home (Kossa ×40)

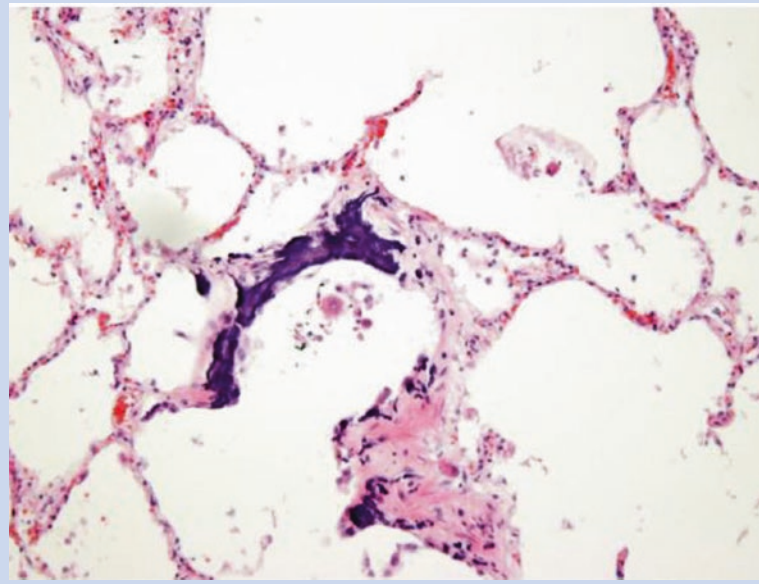

Fig. 16.17 Semicircular streaky basophilic calcifications of a bronchiolar wall in the lung tissue in a case of secondary hyperparathyroidism (H&E ×100)

Hyperplasia of the parathyroid principal cells can be the cause of hyperparathyroidism (Sheu et al. 2003), although not in all parathyroid glands. Histologically, densely situated parathyroid principal cells with fine fibrous septa can usually be found; adipose cells are rarely seen. A complete connective tissue capsule does not need to be present (Hecht et al. 2009b). Additional causes for hyperparathyroidism include parathyroid adenomas (>80% of cases) or parathyroid carcinomas (<3% of cases). In adenoma, a capsule of connective tissue can typically be seen (Sheu et al. 2003). Parathyroid carcinoma mostly affects patients of at least 50 years of age with particularly high calcium levels in their serum. Macroscopically, parathyroid carcinomas are gray-white; histologically, infiltrative growth, regressive changes, and atypical cells can be found.

Hypoparathyroidism/Hypocalcemia

Clinically, acute tetany is known to occur in cases of inadvertent total parathyroidectomy following parathyroid surgery; hypocalcemia can lead to death. Other causes may include autoimmune processes with involvement of parathyroid glands (Schmid and Böcker 1997a, b). Cases of acute heart failure due to hypocalcemia following sodium EDTA therapy for lead poisoning have also been described (Brown et al. 2006).

16.6 Pituitary Gland and Hypophyseal Dysfunction

Pituitary Gland

The pituitary gland (anterior pituitary) contains different cell populations: acidophils, containing prolactin (PRL) and growth hormone (GH), and basophils, containing *luteinizing hormone* (*LH*), *thyroid-stimulating hormone* (*TSH*), and *adrenocorticotropic hormone* (*ACTH*). It should be possible to detect these pituitary hormones immunohistochemically for up to 15 days postmortem—not, however, after longer than 20 days (Ishikawa et al. 2006a). The neurohypophysis (posterior pituitary) is primarily made up of glial cells and nerve fibers, with no glandular structures. During pregnancy, it is possible to visualize the activation of hormone production in the anterior pituitary (Fig. 16.18).

An increased number of vacuoles in the hormone-producing cells of the anterior pituitary have been reported in fatal hypothermia (Ishikawa et al. 2004). Individual studies report increased expression of *clusterin* in the anterior pituitary depending on age (Ishikawa et al. 2006b). Partial or complete hypopituitarism may progress to pituitary coma, resulting in secondary hypothyrosis and/or secondary adrenal insufficiency (Matschke et al. 2000). Hypophyseal dysfunction can lead to sudden death (Bauer et al. 2001; Blisard et al. 1992). Hypophyseal necrosis is typically seen with circulatory shock.

Simmonds' syndrome describes insufficiency of the anterior pituitary gland, i.e., hypopituitarism due to a variety of causes, for example, hypophyseal tumor, hypophysitis, or Sheehan's

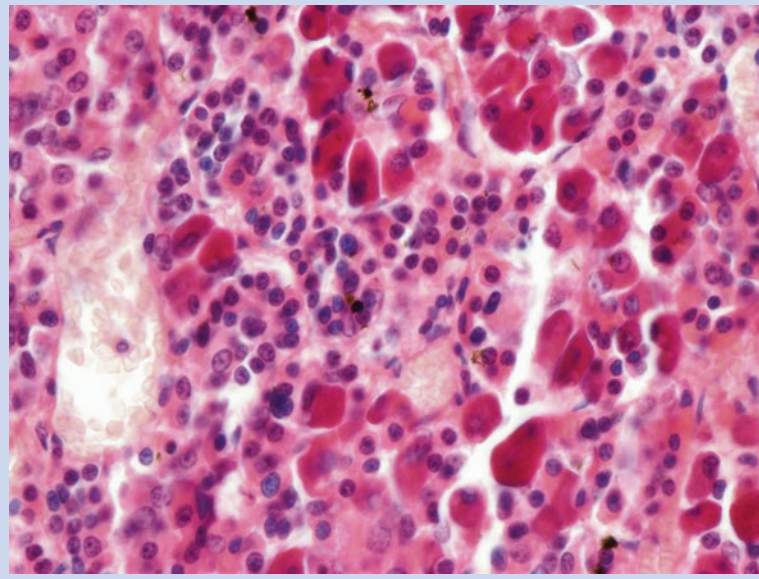

Fig. 16.18 Activated hormone production in the anterior pituitary during pregnancy (H&E ×400)

syndrome. However, these are rare diseases. The lymphocytic type of Simmonds' syndrome with diffusely spread lymphocytes is predominant among primary hypophyseal inflammations, with the possible formation of germinal centers (Hecht et al. 2009b). Inflammation can spread to the neurohypophysis. An autoimmune process is considered to be the underlying disease. Death as a direct result of primary hypophysitis is very rare (Blisard et al. 1992; Gal et al. 1986).

Sheehan's Syndrome

Sheehan's syndrome is accompanied by post-puerperal blood loss with shock symptoms and anterior pituitary insufficiency (Sheehan 1965). Its prevalence has been given in the past as 100–200 cases per 1 million women (Sheehan 1937, 1965). Progression and severity of this disease vary from partial hypopituitarism to panhypopituitarism. Clinical symptoms are variable and can occur at between 1 and 33 years postpartum (Schröder et al. 2009; Huang et al. 2002). Histologically, pronounced fibrosis or scar formation in the adenohypophysis can be found. Small tissue islets with a preserved residual parenchyma can be detected immunohistochemically as follicle-stimulating hormone (FSH) and as prolactin-secreting cells (Schröder et al. 2009; Saeger and Kühn 1984).

Hypophyseal Apoplexy

Hypophyseal adenomas are slow-growing benign tumors that may present with very few symptoms despite suprasellar growth. In some cases, this may lead to hemorrhagic infarction of tumor tissue which, in turn, may lead to the clinical picture of hypophyseal apoplexy. In rare cases, this leads to sudden and unexpected death. Histologically, tumor tissue with widespread hemorrhage and signs of infarction can be seen (Bauer et al. 2000, 2001).

References

Adams R, Hinkebein MK, McQuillen M et al (1998) Prompt differentiation of Addison's disease from anorexia nervosa during weight loss and vomiting. South Med J 91:208–211

Al Sabri AM, Smith N, Busuttil A (1997) Sudden death due to auto-immune Addison's disease in a 12-year-old girl. Int J Legal Med 110:278–280

Arlt W, Allolio B (2003) Adrenal insufficiency. Lancet 31:1881–1893

Badui E, Mancilla R, Szymanski JJ, Gardia-Rubi D, Estanol B (1982) Diverse clinical manifestations of pheochromocytomas. Angiology 33:173–182

Banaschak S, Bajanowski T, Brinkmann B (2000) Suicide of a diabetic by inducing hyperglycemic coma. Int J Legal Med 113:162–163

Bauer M, Lang C, Patzelt D (2000) Hypophysenapoplexie als Ursache eines plötzlichen unerwarteten Todeseintritts. In: 9th spring meeting of the German society of forensic medicine, Leipzig, 4–5 May 2000

Bauer M, Lang C, Patzelt D (2001) Sudden death due to pituitary apoplexy. Legal Med 3:183–186

Bell CD, Kovacs K, Horvath E, Rotondo F (2001) Histologic, immunohistochemical and ultrastructural findings in a case of minocycline-associated black thyroid. Endocr Pathol 12:443–451

Benowitz NL (1990) Pheochromocytoma. Adv Intern Med 35:195–200

Bhasin S, Wallace W, Lawrence JB, Lesch M (1981) Sudden death associated with thyroid hormone abuse. Am J Med 71:887–890

Blisard KS, Pfalzgraf RR, Balko MG (1992) Sudden death due to lymphoplasmatic hypophysitis. Am J Forensic Med Pathol 13:207–210

Brown MJ, Willis T, Omalu B, Leiker R (2006) Deaths resulting from hypocalcemia after administration of edetate disodium: 2003-2005. Pediatrics 118:534–536

Burch HB, Wartofsky L (1993) Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin N Am 22:263–277

Burke MP, Opeskin K (1999) Adrenocortical insufficieny. Am J Forensic Med Pathol 20:60–65

Byard RW (2013) Pathological changes in the thyroid gland in crush asphyxia. Forensic Sci Med Pathol 9:568–572

Byard RW, Zhou C (2010) Erosive gastritis, Armanni-Ebstein phenomenon and diabetic ketoacidosis. Forensic Sci Med Pathol 6:304–306

Cardesi E, Cera G, Gassia A (1994) Pheochromocytoma and sudden death: a case of hyperacute myocardial ischemia. Pathologica 86:670–672

Cheah JS, Lee GS, Chew LS (1971) Myocardial infarction in thyrotoxicosis. Med J Aust 1:393–395

D'Errico S, Pomara C, Riezzo I, Neri M, Turillazzi E, Fineschi V (2009) Cardiac failure due to epinephrine-secreting pheochromocytoma: clinical, laboratory and pathological findings in a sudden death. Forensic Sci Int 187:e13–e17

De Letter EA, Piette MH, Lambert WE, De Leenheer AP (2000) Medico-legal implications of hidden thy-

roid dysfunction: a study of two cases. Med Sci Law 40:251–257
DiMaio VJM, Sturner WQ, Coe JI (1977) Sudden and unexpected deaths after the acute onset of diabetes mellitus. J Forensic Sci 22:147–151
Edelson GW, Kleerekoper M (1995) Hypercalcemic crisis. Med Clin North Am 79:79–92
Edston E (1996) Three sudden deaths in men associated with undiagnosed chronic thyroiditis. Int J Legal Med 109:94–97
Edston E, Druid H, Holmgren P, Oström M (2001) Postmortem measurements of thyroid hormones in blood and vitreous humor combined with histology. Am J Forensic Med Pathol 22:78–83
Gal R, Schwartz A, Gukovsky-Oren S et al (1986) Lymphoid hypophysitis associated with sudden maternal death: report of a case and review of the literature. Obstet Gynecol Surv 41:619–621
Gough IR, Gough J (2002) Surgical management of amiodarone-associated thyrotoxicosis. Med J Aust 176:128–129
Govi A, Fersini F, Tsokos M (2015) Sudden death due to acute adrenal crisis. Forensic Sci Med Pathol 11:445–447
Hartung B, Schott M, Daldrup T, Ritz-Timme S (2010) Lethal thyroid storm after uncontrolled intake of liothyronine in order to lose weight. Int J Legal Med 124:637–640
Hecht L, Saeger W, Püschel K (2009a) Plötzlicher Tod bei Erkrankungen der Schilddrüse und der Nebenschilddrüsen. Rechtsmedizin 19:11–16
Hecht L, Saeger W, Püschel K (2009b) Plötzlicher Tod bei Erkrankungen der Hypophyse und der Nebennieren. Rechtsmedizin 19:5–10
Heinrichs L, Schulz E, Schwerd W (1969) Morphologischer Nachweis akuter Lipoidmobilisation in der Nebennierenrinde bei sehr kurzen posttraumatischen Überlebenszeiten. Arch Kriminol 143:199–203
Hostiuc S, Luca L, Iliescu DB, Dascălu MI, Drima E, Renţea I, Moldoveanu A, Ceauşu M, Pirici D (2015) Sudden thyroid death. A systematic review. Rom J Leg Med 23:233–242
Huang YY, Ting MK, Hsu BR, Tsai JS (2002) Demonstration of reserved anterior pituitary function among patients with amenorrhea after postpartum hemorrhage. Gynecol Endocrinol 14:99–104
Isaacson C, Rosenzweig D, Seftel HC (1960) Malignant pheochromocytoma of the organs of Zuckerkandl. Arch Pathol 70:725–729
Ishikawa T, Miyaishi S, Tachibana T, Ishizu H, Zhu BL, Maeda H (2004) Fatal hypothermia related vacuolization of hormone-producing cells in the anterior pituitary. Legal Med 6:157–163
Ishikawa T, Zhu BL, Li DR, Zhao D, Michiue T, Maeda H (2006a) Postmortem stability of pituitary hormones in the human adenohypophysis. Legal Med 8:34–38
Ishikawa T, Zhu BL, Li DR, Zhao D, Michiue T, Maeda H (2006b) Age-dependent increase of clusterin in the human pituitary gland. Legal Med 8:28–33
James TN (1976) On the cause of sudden death in pheochromocytoma with special reference to the pulmonary arteries, the cardiac conduction system and the aggregation of platelets. Circulation 54:348–356
Kahaly G, Mohr-Kahaly S, Beyer J, Meyer J (1995) Prevalence of myxomatous mitral valve prolaps in patients with lymphocytic thyroiditis. Am J Cardiol 76:1309–1310
Karlovsek MZ (2004) Diagnostic values of combined glucose and lactate values in cerebrospinal fluid and vitreous humour – our experiences. Forensic Sci Int 146:19–23
Kernbach G, Brinkmann B (1983) Postmortale Pathochemie für die Feststellung der Todesursache Coma diabeticum. Pathologe 4:235–240
Kernbach-Wighton G, Püschel K (1998) On the phenomenology of lethal applications of insulin. Forensic Sci Int 93:61–73
Klein A, Theile A, Körner HW, Schulz F (2008) Ochronose. Seltene Stoffwechselerkrankung mit außergewöhnlichem Sektionsbefund. Rechtsmedizin 19:25–29
Kniseley AS, Sweeney K, Ambler MW (1988) Pheochromocytoma and sudden death as a result of cerebral infarction in Turner's syndrome: report of a case. J Forensic Sci 3:1497–1502
Kotler MN, Michaelides KM, Bouchard RJ, Warbasse JE (1973) Myocardial infarction associated with thyrotoxicosis. Arch Intern Med 132:723–728
Lasczkowski GE, Püschel K (1991) Hyperglykämische Stoffwechselentgleisung: Relation zwischen Glykogennephrose und postmortalen biochemischen Parametern des Glukosestoffwechsels. Rechtsmedizin 1:41–45
Liu H, Lin F (2015) Application of immunohistochemistry in thyroid pathology. Arch Pathol Lab Med 139:67–82
Lo CY, Lam KY, Wat MS (2000) Adrenal pheochromocytoma remains a frequently overlooked diagnosis. Am J Surg 179:212–215
Lutz R, Pedal I, Wetzel C, Mattern R (1997) Insulin injection sites: morphology and immunohistochemistry. Forensic Sci Int 90:93–101
Lynch MJ, Woodford NWF (2014) Sudden unexpected death in the setting of undiagnosed Graves' disease. Forensic Sci Med Pathol 10:452–456
Marshall DT, Gilbert JD, Byard RW (2007) Adrenocortical carcinoma and sudden death. Forensic Sci Med Pathol 3:53–55
Martín Martorell P, Roep BO, Smith JW (2002) Autoimmunity in Addison's disease. Neth J Med 60:269–275
Matschke J, Sperhake J, Saeger W et al (2000) Forensische Pädopathologie – Tödliche Addison-Krise bei idiopathischem Panhypopituitarismus. Päd 6:16–20
Milroy CM, Parai JL (2011) Armanni-Ebstein lesion, ketoacidosis and starvation in a child. Forensic Sci Med Pathol 7:213–216
Mulligan DC, McHenry CR, Kinney W, Esselstyn CB Jr (1993) Amiodarone-induced thyrotoxicosis: clinical presentation and expanded indications for thyroidectomy. Surgery 114:1114–1119
Osuna E, Garcia-Villora A, Pérez-Cárceles MD, Conejero J, Abenza JM, Martinez P, Luna A (1999) Vitreous

humor fructosamine concentrations in the autopsy diagnosis of diabetes mellitus. Int J Legal Med 112:275–279
Osuna E, Vivero G, Conejero J, Abenza JM, Martinez P, Luna A, Pérez-Cáceles MD (2005) Postmortem vitreous humor β-hydroxybutyrate: its utility for the postmortem interpretation of diabetes mellitus. Forensic Sci Int 153:189–195
Palmiere C (2015) Sudden death due to acute adrenal crisis. Forensic Sci Med Pathol 11:629
Palmiere C, de Froidmont S, Mangin P, Werner D, Lobrinus A (2014) Ketoacidosis and adrenocortical insufficiency. J Forensic Sci 59:1146–1152
Preuß J, Woenkhaus C, Schwesinger G, Madea B (2006) Non-diagnosed pheochromocytoma as a cause of sudden death in a 49-year-old man. A case report with medico-legal implications. Forensic Sci Int 156:223–228
Primhak RA, Spicer RS, Variend S (1986) Sudden death after minor abdominal trauma: an unusual presentation of phaeochromocytoma. Br Med J 292:95–96
Püschel K (2004) Plötzlicher Tod im Erwachsenenalter. In: Brinkmann B, Madea B (eds) Handbuch gerichtliche Medizin, vol 1. Springer, Berlin, pp 1020–1021
Reschke K, Lehnert H (2003) Die thyreotoxische Krise. Internist 4:1221–1230
Risse M, Weiler G, Benker G (1986) Comparative histologic and hormonal studies of the thyroid gland with spezial reference to sudden infant death (SIDS). Z Rechtsmed 96:31–38
Ritchie S, Waugh D (1957) The pathology of Armanni-Ebstein-diabetic nephropathie. Am J Pathol 33:1035–1057
Ritz S, Kaatsch HJ (1990) Postmortale Diagnostik von tödlichen diabetischen Stoffwechselentgleisungen: welchen Stellenwert haben Liquor- und Glaskörperflüssigkeitssummenwerte sowie der HbA1-Wert? Pathologe 11:158–165
Roggendorf W (1995) Kreislaufstörungen des zentralen Nervensystems. In: Remmele W, Peiffer J, Schröder JM (eds) Pathologie 6 – Neuropathologie, Skelettmuskulatur, Sinnesorgane, 2nd edn. Springer, Berlin, pp 62–106
Saeger W, Kühn H (1984) Sheehan-Syndrom mit letalem Ausgang. Morphologische und immunhistochemische Untersuchungen eines Falles. Pathologe 5:231–234
Safe AF, Griffiths KD, Maxwell RT (1990) Thyreotoxic crisis presenting as status epilepticus. Postgrad Med J 66:150–152
Schmid KW, Böcker W (1997a) Nebenschilddrüse. In: Remmele W (ed) Pathologie, vol 4, 2nd edn. Springer, Berlin, pp 617–628
Schmid KW, Böcker W (1997b) Schilddrüse. In: Remmele W (ed) Pathologie, vol 4, 2nd edn. Springer, Berlin, pp 579–616
Schröder AS, Hecht L, Sperhake JP, Püschel K, Saeger W (2009) Plötzlicher Tod aus endokriner Ursache. Rechtsmedizin 19:17–20
Sheehan HL (1937) Post-partum necrosis of the anterior pituitary. J Pathol Bacteriol 45:189–214
Sheehan HL (1965) The frequency of post-partum hypopituitarism. J Obstet Gynaecol Br Commonw 72:103–111
Sheu SJ, Schmid KW (2003) Entzündliche Schilddrüsenerkrankungen. Epidemiologie, Klinik und Morphologie. Pathologe 24:339–347
Sheu SY, Otterbach F, Frilling A, Schmid KW (2003) Hyperplasia and tumors of the parathyroid glands. Pathologe 24:373–381
Sheu SJ, Levin S, Schmid KW (2006) Therapy related alterations to the thyroid gland. Pathologe 27:13–18
Siegler RW (1998) Fatal heatstroke in a young woman with undiagnosed chronic thyreoiditis. J Forensic Sci 43:1237–1240
Sippel H, Möttönen M (1992) Combined Glucose and lactate values in vitreous humour for postmortem diagnosis of diabetes mellitus. Forensic Sci Int 19:217–222
Smyrk TC, Goellner JR, Brennan MD, Carney JA (1987) Pathology of the thyroid in amiodarone-associated thyrotoxicosis. Am J Surg Pathol 11:197–204
Spann W (1954) Nebennieren und Unfall. Dtsch Z Gesamte Gerichtl Med 43:103
Sperry K, Smialek JE (1986) Sudden death due to a paraganglioma of the organs of Zuckerkandl. Am J Forensic Med Pathol 7:23–29
Symington T, Duguid WP, Davidson JN (1956) Effect of exogenous corticotropin on the histochemical pattern of the human adrenal cortex and a comparison with the changes during stress. J Clin Endocrinol Metab 16:580–598
Thomsen JL, Bayer Kristensen I, Pottosen PD (2006) The histological demonstration of lipids in the proximal renal tubules of patients with diabetic coma. Forensic Sci Med Pathol 2:249252
Tsokos M, Schröder S (2006) Black thyroid: report of an autopsy case. Int J Legal Med 120:157–159
Türk EE, Sperhake JP, Saeger W, Tsokos M (2004) Phäochromozytom als Ursache des plötzlichen Todes. Z Rechtsmed 14:409–411
Uotila U, Pekkarinen A (1951) The relation of human adrenal glands to the pathological changes produced by intense continuous stress ending in death. Acta Endocrinol 6:23–50
Valenzuela A (1988) Postmortem diagnosis of diabetes mellitus. Quantitation of fructosamine and glycolated haemoglobin. Forensic Sci Int 38:202–208
Vallance WB (1957) Sudden death from an asymptomatic phaeochromocytoma. Br Med J 292:95–96
Wall CR (2000) Myxedema coma: diagnosis and treatment. Am Fam Physician 62:2485–2490
Ward S, Evans CC (1985) Sudden death due to isolated adrenal tuberculosis. Postgrad Med J 61:635–636
Wehner H, Haag G (1980) Morphologische Differentialdiagnose zwischen der nodulären diabetischen Glomerulosklerose und lobulären Glomerulonephritisformen. Pathologe 1:197–205
Wehner F, Schieffer MC, Wehner HD (1997) Immunhistochemischer Insulinnachweis an der Injektionsstelle. In: 76th Annual meeting of the German Society of Forensic Medicine, Jena, 1997

Wei JY, Genecin A, Greene HL, Achuff SC (1979) Coronary spasms with ventricular fibrillation during thyrotoxicosis: response to attaining euthyroid state. Am J Cardiol 43:335–339

Woenkhaus U, Vasold A, Bollheimer LC (2005) Akute Nebenniereninsuffizienz ("Addison-Krise"). Intensivmed 42:345–354

Zhou C, Byard RW (2011) Armanni-Ebstein phenomenon and hypothermia. Forensic Sci Int 206:e82–e84

Zhou C, Gilbert JD, Byard RW (2010) Early diagnosis of Armanni-Ebstein phenomenon at autopsy. Forensic Sci Med Pathol 6:133–134

Zhou C, Moore L, Yool A, Jaunzems A, Byard R (2015) Renal tubular epithelial vacuoles – a marker for both hyperlipidemia and ketoacidosis at autopsy. J Forensic Sci 60:638–641

Zierhut S, Girlich C (2004) Thyrotoxic crisis and myxedema. Intensivmed 41:573–582