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## Forensic Investigation in Anaphylactic Deaths

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### 1. Introduction

Deaths anaphylaxis related have always been very difficult in objectification in autopsies. So they are object of study for pathologists and legal doctors. In this work we want to propose a methodological protocol based on the various available diagnostic tools to use when an anaphylaxis related death is suspected.

### 2. Pathogenesis

The anaphylaxis is an allergic reaction. An allergic reaction is a spontaneous and exaggerate reaction of the body to a particular substance. These substances, called allergens, cause production of antibodies when enter the body. The exposition with the substance happens by inhalation, ingestion, contact or inoculation of the allergen. Every substance can act as allergen. Among the more frequent substances we remember the heterologous proteins (hormone like insulin, vasopressin, parathormon; enzymes like trypsin, chemotrypsin, penicillinases; pollens, food like eggs, fish, hazel-nuts, cereals, beans, chocolate; antiserums, hymenoptera venom); polysaccharides (iron dextran); drugs (antibiotics like penicillins, cephalosporins, Amphotericin B, nitrofurantoin, local anesthetics like procaine and lidocaine; vitamins like thiamine and folic acid); diagnostic substances (iodated means of contrast, sodium dehydrocoled, sulfobromoftaleine); industrial chemical products (ethylene oxide). (Fauci et al., 2009)

The concept of anaphylaxis comes from the study of the actinotoxins on the dogs' arterial blood pressure (Richet, 1902).

It is well known that the anaphylactic shock is an example of the immediate type of hypersensitivity reaction inducing a diffuse organ hypoperfusion. It has been defined (Delage & Irely, 1972) as the failure of the peripheral circulation induced by an antigen (allergen)-antibody reaction in already sensitized subjects for a foreign substance. Whenever the hypoperfusion is complicated by increased capillary permeability, a rapidly irreversible circulatory fatal damage occurs (anaphylactic death).

Delage and Irely (Delage & Irely, 1972), in their clinico-pathological study of 43 validated cases of drug-induced fatal anaphylactic shock, the predominant role of penicillin, subsequently confirmed (Di Maio & Di Maio 2001; Menchel et al., 1987; Weeden, 1988), is

reported. In these as well as in other cases immunoglobulin E (IgE) antibodies have been tested to various allergens, present in contrast media (Di Maio & Di Maio 2001; Lang et al., 1995; Pumphrey & Roberts, 2000; Risgaard et al., 2008), sera (Vance & Strassmann, 1942; Johann-Liang et al., 2011), insect venom (Pumphrey, 2000; Riches et al., 2001; Yunginger et al., 1991), and food (Di Maio & Di Maio 2001; Pumphrey, 2000; Pumphrey & Roberts, 2000; Yunginger et al., 1991) are thought to initiate anaphylactic reaction in patients previously sensitized towards that allergen (often unknowingly).

A register including all fatal anaphylactic reactions in the UK is operative since 1992 (Pumphrey, 2008). In France and Belgium since 2001 a university research team has founded the Allergy Vigilance Network, that in addition to reporting cases of severe anaphylaxis, to determine the prevalence of sensitization to risk allergens and screening and long-term monitoring of dangers related to new foods, ingredients and adjuvant sensitizing factors, with the French National Institute for Food Safety (AFSSA) and the Ministry of Consumer Affairs (DGCCRF) and various patient associations, also analyzes dangers related to the allergenicity of natural and modified food proteins (Moneret-Vautrin et al., 2002; Moneret-Vautrin, 2007).

Allergy depends on the individual "predisposition". In certain people the contact between the allergen and the human body causes an abnormal immune reaction that clinically appears with the wide spectrum of manifestations of the allergic reaction (Crane, 2006; Liccardi et al., 2006)

Hypersensitivity reaction can be classified according the four type of immuno-pathological reaction of Gell and Coombs (Fauci, 2009):

- type I: they are the result of an IgE-mediated reaction that leads to an immediate hypersensitivity
- type II: IgG or IgM mediated. These antibodies are directed against cellular surface's antigens altered by the drug that provoke a complement-mediated cytotoxicity.
- type III: immuno-complexes mediated. The immunocomplexes' dimensions determine the site of deposition and the consequent immunological damage.
- type IV: retarded hypersensitivity. They come out by the interaction of the antigen with T lymphocyte and determine a cell-mediated reaction.

Type I reaction is characterized by a rapid activation (in few minutes) of vasoactive and spasmogen substances by antibodies that are on the surface of the mastcells and basophils. It's composed of three phases:

1. sensitization, when the immune system come into contact with the allergen for the first time and stimulates IgE antibodies by B cells (the IgE production is under the control of TH2 CD4+ that increases its production and under the control of TH1 that reduces the production). The IgE bind mastcells' and basophils' receptors making them sensible to a next exposition to the antigen.
2. initial reaction: Immune system has a memory; so at the second exposition to the allergen there's a binding between the antigen and the IgE antibodies localized on the mast-cells and basophils (sensitized). High affinity receptors (IgE) are almost exclusively on the mast-cells and on the basophils while low affinity receptors are also in other cytotypes (eosinophils, macrophages, platelets).

When the allergen binds to the high affinity receptor there's the activation of the mastcells that leads to the degranulation of the mastcells and release of primary mediators (preformed) such as histamine, adenosine, chemiotactic mediators (e.g. the ones for the eosinophils), enzyme (tryptases, kynases), proteoglicans. There's also the

release of secondary mediators of 'de novo' synthesis such as leucotrienes, prostaglandines, platelets' aggregation stimulation factors, cytokines, chemokines. In the first 30-60 minutes after exposition symptoms happen. Histamine is characterized by a very short half-life in the circulation, tryptase and chymase, are stable post-mortem (Edston et al., 2007; Nishio et al., 2005) and respectively used in post-mortem diagnosis of acute anaphylaxis (Edston, 2007; Nishio, 2005; Pumphrey, 2000; Riches et al., 2001; Schwartz, 1987; Yunginger et al., 1991). Tryptase is a serine protease stored mainly in mast cell granules, not found in circulating basophils, eosinophils, platelets or any other cell, represented by two varieties: an active free form ( $\beta$ ) and an inactive tetramere ( $\alpha$ ) (Ansari et al., 1993; Schwartz et al. 1995).

The former is a protein released from mast cell granules during anaphylactic reactions, the latter is a similar protein secreted by resting mast cells and raised in mastocytosis (Pumphrey & Roberts, 2000; Schwartz et al. 1995).

Chymase is a mast cell-derived serine protease, characterized as an angiotensin II-generating enzyme (Nishio, 2005) and used to determine mast cells and thus to assess the timing of wounds after deaths (Bonelli et al., 2003; Urata et al., 1990).

It is quite stable in serum and a significant positive correlation between serum chymase and tryptase levels was found in post-mortem diagnosis of anaphylaxis (Nishio, 2005). Heterogeneity of human mast cells is known (Irani & Schwartz, 1994; Weidner & Austen, 1993) and recently different subsets of mast cells (MC) are distinguished by immunohistochemistry (Perskvist & Edston, 2007), as follows:

MC-TCs (formerly connective tissue mast cells) mainly composed of histamine, heparin, tryptase, chymase, cathepsin G and carboxypeptidase, preformed and stored in granules.

- MC-T (formerly mucosal mast cells) lacking or containing only small amounts of chymase, carboxypeptidase and cathepsin.
  - MC-C lacking tryptase and not further characterized
3. Late phase: after 2 hours from the initial response the presence of antigen is not necessary and the tissue infiltration begins by inflammatory cells (neutrophils, eosinophils, basophils, monocytes) with consequent tissue lesions (in particular epithelia and mucosas).

This is the typical allergic reaction that usually brings to vasodilatation, skin rash, edema, itching; but the clinical spectrum is very wide and the allergic disturbs can be poor or get the death for anaphylactic shock.

Anaphylaxis is the most dangerous among the allergic reaction and it is a severe systemic reaction, with an often sudden and important beginning, with an acute response that happens in a variable time from few seconds to few minutes after the antigen exposition.

Anaphylaxis can be elicited for every concentration of the antigen (also minimal, sometimes it happens during skin test for drugs, etc.) (Bernstein et al., 2004; Blanton & Sutphin, 1949; Eleuterio González et al., 1997; Harris & Sure, 1950; Liccardi et al., 2006; Lockey et al., 1987; Riezzo, 2010; Weber-Mani & Pichler, 2008).

The typical anaphylaxis consists of sudden weakness, itching and urticaria, chest oppression, respiratory distress (wheezing) followed by cardio-circulatory collapse. Symptoms maybe very variable and could be involved almost all the functions/apparatus.

Could be involved: cardio-vascular system (tachycardia, hypotension, arrhythmias, ischemia/ myocardial infarction, heart arrest, symptoms from hypoperfusion are constant), nervous system (vertigo, asthenia, syncope, convulsions), eye (conjunctival injection,

lachrymation), upper airway (nasal congestion, sneezing, hoarseness, stridor, pharyngeal or laryngeal edema, cough, obstruction, laryngospasm), lower airway (dyspnea, bronchospasm, tachypnea, involvement of the accessory respiratory muscles, cyanosis, respiratory arrest), skin (rash, erythema, itching, urticaria or urticarial reaction, edema, maculo-papular rash), gastrointestinal apparatus (nausea, vomiting, abdominal pain, diarrhea)(Crane et al. 2006; Fauci, 2009; Rovere-Querini, 2010).

Lethal cases are mainly due to: acute respiratory distress derived by the glottis edema or by bronchial obstruction/bronchospasm; cardio-vascular collapse also without an important respiratory distress.

In the lethal cases between the contact with the allergen and the anaphylaxis there's a very short time. The anaphylaxis shows immediately or in few minutes after the exposition; in the most of the cases by 15-20 minutes. Reactions after 60 minutes from the exposition are very rare. As soon the reaction occurs as easier the death is; sometimes death can be immediate and, however by 1-2 hours. More rarely death occurs by 24 hours.

### 3. Proposal of a methodological protocol

In most of the cases the diagnosis of anaphylactic death represents a challenging deal. So it's very important that the anatomo-pathological and/or medico-legal investigations must be very scrupulous and must analyze:

- medical history of the deceased and eventual investigations on the spot;
- necropsy with:
- lab tests, for which it's better to use peripheral blood sample and not central ones;
- histological tests
- histochemical and immuno-histochemical tests.

#### 3.1 Medical history and investigations on the spot

To make diagnosis of anaphylactic death it's important to make a correlation between the symptoms and an insect bite, the ingestion of food, drugs or other substances.

So we should collect anamnesis by family and general practitioner, especially if related to a history of allergy. Some patients, however, doesn't know to have allergies and anaphylaxis is the first (and last) allergic reaction they have in their life.

Especially in the cases with medical history negative for past allergic reaction it's important, when possible, going on the spot where the death occurred to get the eventual syringes used for injection and/ or to evaluate the presence of nests of wasps. It's important hearing to witnesses that could tell the symptoms of the victim. Sudden weakness, itching and urticaria, chest oppression and respiratory distress (wheezing) followed by cardio-circulatory collapse may occur. Symptoms maybe very variable and could be involved almost all the functions/apparatus as we remembered before.

#### 3.2 Complete necroscopic exam

It's very important beginning with an accurate external exam to verify the presence of signs such as rash, urticaria or angioedema; to verify the skin integrity finding out eventual site of inoculation: it's important to investigate also the sites covered by hair. If there a positive finding it's opportune to proceed, during the successive autopsy, also to get a skin sample after the examination of the route in the case of subcutaneous or intramuscular injection. During the autopsy the pathological findings are often aspecific.

Usually we find multivisceral congestion, aspecific finding in various different types of death. (Barnard, 1967; Da Broi & Moreschi, 2011; Delage & Irej, 1972; Di Maio & Di Maio, 2001; Edston & van Hage-Hamsten, 2005; James & Austen, 1964; Low & Stables, 2006; Lu et al., 2006; Menchel et al, 1987; Pumphrey & Roberts, 2000; Shen et al.,2009; Yilmaz et al., 2009).

You can find:

- glottis edema and/or of the pharyngo-laryngeal districts;
- congestion and/or pulmonary edema;
- hyperinflation of the alveoli with acute emphysema;
- endo-luminal bronchial secretions- this finding is more frequent if there's an asthmatic factor and it's usually related to a almost immediate death;
- hemorrhagic petechiae: it's suggestive of an asphyxial component of the death and it's usually associated with an almost immediate death.

These findings can change according to the allergen type, to the way of administration and to the time passed between the exposition and the death (Edston & van Hage-Hamsten, 2005; Low & Stables, 2006; Pumphrey & Roberts, 2000). If the death is very fast the only macroscopic finding is an important multivisceral congestion associated or not with the petechial hemorrhages (Edston & van Hage-Hamsten, 2005; Low & Stables, 2006; Pumphrey & Roberts, 2000; Roberts & Pumphrey, 2001).

In the table n. 1 there are the results of different studies present in literature (Barnard, 1967; Delage & Irej, 1972; Greenberger et al, 2007; James & Austen, 1964; Low & Stables, 2006; Pumphrey & Roberts, 2000; Shen et al.,2009; Yilmaz et al., 2009).

Autopsy findings	Study		
	Delage & Irej (1972)	James & Austen (1964)	Barnard (1967)
Number of cases	40	6	50
		3 cases penicillin, 1 case guinea-pig haemoglobin; 1 case bee venom; 1 case ragweed extract	Insect-Stings
Erythematous skin rash/cutaneous edema			35
Pulmonary congestion and edema	36	5	35
Upper airway edema	15	4	14
Hyperinflation of the lungs and/or mucous plugging of airways	18	5	16
Petechial hemorrhages			10

Autopsy findings	Study						
	Pumphrey & Roberts (2000)			Low & Stables (2006)			
Number of cases	56			18			
	Venom (19)	Food (16)	Drugs (21)	Venom (4)	Food (2)	Drugs (10)	Undetermined (2)
Erythematous skin rash/cutaneous edema	1	2	0	0	0	0	2
Pulmonary congestion and edema	14	9	18	3	0	5	2
Upper airway oedema	6	10	7	3	0	0	1
Hyperinflation of the lungs and/or mucous plugging of airways	7	5	3				
Petechial hemorrhages	4	5	1				

Autopsy findings	Study		
	Greenberger et al. (2007)	Shen et al. (2009)	Yilmaz et al. (2009)
Number of cases	25	28	36
Erythematous skin rash/cutaneous edema	3	4	2
Pulmonary congestion and edema	18	28	29
Upper airway edema	16	15	11
Hyperinflation of the lungs and/or mucous plugging of airways	3	11	5
Petechial hemorrhages	6		3

Table 1. Autopsy findings.

A complete autopsy, with histo-pathological and chemical-toxicological investigations, is mandatory in every case.

### 3.3 Laboratory tests

A very useful first investigation is the research of the total and specific IgE for specific substances: The Igs are very stable also after death (Hieda et al, 1991).

The finding of total IgE doesn't demonstrate the anaphylaxis but indicates that the subject was sensible for particular substances (e.g. insect venom, antibiotics, etc.). However, in there's a positive history or suspect for allergies for specific substances, every suspected substance must be tested with specific IgE. If there isn't an accurate anamnesis or an history of allergy it's a good idea testing the most common allergens. (Calvani et al., 2007; Hamilton & Adkinson, 2003; Horn et al., 2004).

A second investigation on the cadaverous blood sample is the dosage of beta-tryptase. As we already said, the degranulation of the mast-cells releases powerful chemical mediators (histamine, tryptase, etc.) (Ansari et al., 1993, Carson et al., 2009; Way & Baxendine 2002).

The tryptases, instead, are relatively stable post-mortem (values can remain high for some days in a serum sample kept at room temperature and for some months if freezed) (Joint Task Force on Practice Parameters et al., 1998; Horn, 2004) and their dosage is very useful in the diagnostics of acute anaphylaxis. As already said, in addition to mast cells also the basophiles produce tryptases but fewer than 300-700 times compared to skin and lung mast cells. So the serum concentration of tryptase is considered an index of mast cells activation. In particular we must determine the beta-tryptases that are usually released by mast cell degranulation (while the alfa-tryptase is secreted constitutively by mast cells and represent an index of the mast cells mass and so it is present in the mastocytosis) (Kanthawatana et al, 1999; Schwartz 2004).

For this reason the ratio between total tryptase (alfa + beta) and beta-tryptase is important to distinguish between an episode of anaphylaxis and patients with systemic mastocytosis: a ratio less than 10 is usually indicative of an anaphylactic reaction while a ratio <20 suggests a systemic mastocytosis (Joint Task Force on Practice Parameters et al., 2005; Lieberman et al, 2010; Schwartz et al., 1995, Schwartz & Irani, 2000). Serum levels of tryptase quickly increase and are detectable by 30 minutes (the concentration peak is reached in the first 2-3 hours) and remain high for about 5 hours (Joint Task Force on Practice Parameters et al., 2005; Lieberman et al, 2010). High levels of beta-tryptase point out a degranulation and, so, support the diagnosis of anaphylaxis.

Usually the increase of the serum level of tryptase is bigger as much as the anaphylaxis has been severe. It's important underline that the negativity of this test doesn't exclude an anaphylactic death. In fact Sampson has demonstrated that the rise of this enzyme could be absent in the anaphylaxis by food, maybe because of the involvement of other cells such as basophils or monocytes/macrophages (Sampson et al., 1992).

Therefore tryptase concentrations in femoral blood (not influenced by position at death or resuscitation efforts) (Edston et al., 2007) and serum chymase and tryptase levels (Nishio et al., 2005; Shen et al., 2002) have been suggested in postmortem cases to validate the diagnosis of anaphylactic deaths.

The histamine is another product of mast cell degranulation. This mediator, even if is very valid in vivo (it's an index of mast cell activation even though not specific of the mastcells alone), isn't an effective indicator after death because has a very short half-life (2 minutes).

So the N-methylhistamine, that is a product of histamine degradation and is stable in the urine, but in the cases of anaphylactic death the time is too short to find it into the urine (Sthephan et al. 1990; Edston et al, 2005, 2007).

Among the other possible tests we remember the serum titration of a mastcell-specific chymase (Nishio et al., 2005; Osawa et al. 2008), that is a serum protein mainly kept into the mastcell granules.

It's important to note that the positivity to total IgE or of the serum tryptase cannot be considered, by the forensic profile, as a sure indication of a death by anaphylaxis because



the positivity of one or both the markers has been found also in other pathologies (Randall et al., 1995; Horn et al., 2004) such as traumatic death or the sudden infant death syndrome (Buckley et al., 2001; Edston et al., 1999; D'Errico et al., 2008; Holgate et al, 1994; Nishio & Suzuki, 2004; Schwartz, 2001) but must be integrated with the results of other investigations that must be done in every case of death.

### 3.2 Histology

Finally the histo-pathological diagnosis is very important and may show eosinophilia (Delage and Irey, 1972) especially in the upper and lower airway, in the liver and in the spleen (Voigt, 1966); the presence of glottis edema and/or pharyngo-laryngeal edema that, histologically, could be associated with a wide dissociation of collagen fibers and of the glandular elements, eosinophilic infiltration and vascular congestion (Pumphrey and Roberts, 2000).

Sometimes, using hematoxylin-eosin stain, there's lung hyperinflation with emphysema, endo-luminal mucous and peri-bronchial congestion, edema and eosinophilic infiltrate.

Another method is the mast cell count in the various organs and tissues: unfortunately specific stainings for mast-cells are based on the metachromatic properties of the cytoplasmic granules and showed limited:

1. the positivity of the mast cells varies according the technique used to fix and stain (Strobel et al., 1981);
2. the counts in the tissue 'post-mortem' after the anaphylaxis is underestimated because of the mast cells' degranulation during anaphylaxis. The staining can't put in evidence the degranulated mast cells; so, because the number of mast cells varies from each one it's impossible decide how many cells have degranulated.
3. the base -level of mast-cell concentration after death is strongly underestimated.

In literature, however, there is a case (Heard et al., 1989) where the authors compare the pulmonary concentration of mast-cells in the allergic subject pre- (biopsy) and post-mortem showing a diminution in the latter sections.

### 3.3 Auxiliary techniques: histochemical and immuno-histochemical

Since histology alone cannot give absolute results, it have been studied more complex techniques such as histochemistry and immuno-histochemistry.

In 1960 Glenner and Cohen (Glenner & Cohen, 1960) identified the proteases of mast cell granules using histo-chemical procedures. The main morphologic characteristic to distinguish mast cells is the presence, in cytoplasm, of many roundish granules, homogeneous in man, soluble in water, that stain methachromatically with basic dyes such as Toluidine blue, or with dyes for glycosaminoglycans polymerized such as Alcian blue. The granules are coated with membrane and contain heparin and histamine. In particular, the presence of heparin, an anticoagulant glycosaminoglycan, accounts for the staining of these granules. In the anaphylaxis the massive degranulation could be emphasized with this technique with the highlight of the granules next to mast cells. Furthermore it has been identified antibodies against histamine but they are not useful for post-mortem evaluation since histamine is poorly stable (Johansson et al., 1992)

Pagoda red stain is another histo-chemical procedure successfully employed for the histological demonstration of several substances with fibrillar periodical structure, like amyloids (Battaglia et al., 1985; Yanagihara et al. 1984), cellulose, siloxanes, polysiloxanes

and polyethylene polymers and more rarely to put in evidence eosinophilia in various tissues (Kyono et al, 1982). This technique displays a mixing of cytotypes, contemporaneously on the same slide, easily identifiable, since degranulated mast cells and their outside granules appear brilliant red over a pale blue background (Trani et al., 2008).

Cytotypes	EMBP	Chymase	Tryptase	CD117	Pagoda red
<b>Eosinophils</b>	++	-	-	-	+++
<b>Mast cell</b>	-	+++	+++	-	+++

- negative reaction    ++ moderate reaction    +++ strong reaction

Table 2. Panel of identification of eosinophils and mast cells: a comparative evaluation (Trani et al. 2008).

Pagoda Red stain is a dye originally employed in the industrial field to dye clothes and occasionally carried out in cytopathology in case of nasal (Rivasi & Bergamini, 1988) or ocular (Rivasi et al., 1992) allergic processes possibly related to the presence of airborne, nonhuman elements.

Immuno-histo-chemical investigations although more expensive than histo-chemical ones allow to characterize the immuno-phenotype of the various cells in the inflammatory infiltrate associated with anaphylaxis; especially specific antibodies can bind superficial antigens in these cells such as tryptases and chymases (Akin et al. 2007; Carson & Cook, 2009; Irani et al., 1989; Perskvist & Edston, 2007).

Human mast cell tryptases comprise a family of trypsin-like neutral serine proteases that are predominantly expressed in mast cells. This antibody is useful for the identification of very atypical or immature mast cells (MC) in mast cell leukemia, and for the detection of small, even minute, dense focal MC infiltrates in staging procedures in patients with known cutaneous mastocytosis. Using an avidin-biotin enhanced immunoperoxidase procedure, with monoclonal antibodies (AA1, AA3, and AA5) directed against human mast cell tryptase, it's possible to obtain an intense staining of mast cells in paraffin-embedded tissue. It represents an highly specific and sensitive means for the detection of mast cells in routinely processed tissues.

Chymases belong to a family of serine proteases like intracellular granule and it's involved in regulating extracellular matrix proteolysis and promoting tissue remodelling (Doggrell & Wanstall, 2004). This substance is mainly found in mast cell cytoplasm but also outside the mast cells in the connective tissues surrounding vascular walls and, in less concentration, in basophils. (Hamada et al. 1999). Chymase antibodies is available for formaldehyde-fixed tissue and can be used simultaneously to tryptase by a sandwich technique applying the two antibody (Buckley et al. 1999).

The eosinophilic major basic protein, also known as MBP, PRG2, a proteoglycan 2, BMPG or bone marrow natural killer cell activator, is a constituent of the eosinophilic granules. High levels of the pro-EMBP are present in pregnancy serum and in placenta where it develops a complex with other proteins. It may influence antiparasitic defense mechanisms as cytotoxin and helminthotoxin and immune hypersensitivity reactions (Trocme et al. 1989).

The role of EMBP is to modulate inflammation and lead to tissue destruction resulting in cytotoxic effects (Butterworth & David, 1981). It has been demonstrated to be elicited in mast cell and basophil (Trocme et al. 1989) degranulation.

#### 4. Conclusions

Post-mortem diagnosis of anaphylactic death is very difficult and it's possible only excluding every other cause of death and taking into considerations the results of other exams: accurate medical history, complete necroscopic examination integrated with histological examination, lab tests, and auxiliary techniques of histochemistry and immuno-histo-chemistry. This diagnosis, in particular for the medico-legal aspect, cannot be based on the positivity of one only type of investigation (e.g. bioumoral tests) because that positivity can be found also in other pathologies (Horn, 2004) but must be integrated with the results of more investigations.

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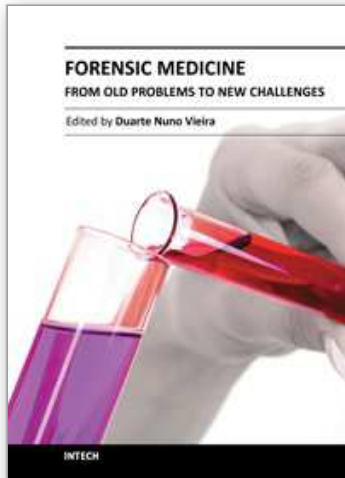
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