Retroperitoneal, mesenteric and multifocal fibrosis : review of their aetiopathogenesis. A possible role of adipocytes as in Crohn's disease ?

E. Jacobs[1], J.P. Cosyns[2], R. Fiasse[3]

(1) Université Libre de Bruxelles ; (2) Department of Pathology, (3) Department of Gastroenterology, University Hospital St. Luc, Université Catholique de Louvain, Brussels.

Abstract

First observed during an autopsy by Simpson in 1867 as a cause of hydronephrosis, retroperitoneal fibrosis became a medical topic after the detailed report of two cases by Ormond in 1948. Initially considered to be chiefly an urological disease, it appeared progressively that it could possibly be a systemic disease because of its occasional association with inflammatory fibrosing processes in other sites of the body or with clinical and biological manifestations of hypersensitivity or autoimmunity. Mesenteric panniculitis and mesenteric fibrosis may occur independently or, occasionally, in association with retroperitoneal fibrosis. One third of the cases of retroperitoneal fibrosis can be attributed to specific causes. That the other cases (idiopathic retroperitoneal fibrosis) could be manifestations of an immunological (systemic) process with vasculitis is generally accepted. The authors present a survey of the various possible morphological aspects of the disease and a review of its aetiopathogenesis. Idiopathic retroperitoneal fibrosis is usually characterized by an overproduction of fibro-inflammatory tissue ; however in few cases as well as in mesenteric panniculitis, extensive development of fatty tissue may also occur. The authors suggest that an initial proliferation of adipocytes, considered to account for the fat hyperplasia adjacent to Crohn's ileitis, could also play a role in the pathogenesis of the inflammatory fibrosing process in some cases of mesenteric and retroperitoneal fibrosis. (Acta gastroenterol. belg., **2010**, 73, **252-260**).

Key words : retroperitoneal fibrosis, mesenteric panniculitis, fibrosis, Crohn's disease, adipocytes.

Introduction

Retroperitoneal fibrosis (RPF) was first observed in 1867, at autopsy by A.R. Simpson (1) as quoted by von Hoffman *et al.* (2), then clinically in 1905 by Albarran (3). Very few cases were reported in the French and German literature (4) before the description in 1948, by Ormond (5) of two cases who aroused interest and led to an increased awareness of the disease and of its variants and associations. Several reviews, some of them extensive, have been published on the subject (6-22).

In 1958, Barrett (23) drew attention to the histological similarities between mediastinal and retroperitoneal fibrosis. Thereafter, several authors reported on the possible development in some individuals, of one or more fibro-inflammatory processes associated, either simultaneously or not, with retroperitoneal fibrosis (systemic, multifocal, multisystem fibrosis) (24,25,26). Moreover, the occasional association of features similar to those observed in generalized vasculitis, hyperallergic states, collagen diseases and of biological or systemic clinical autoimmune manifestations, led to the suggestion that idiopathic retroperitoneal fibrosis could be part of a more systemic disease (27) of chronic (auto) immune origin (28,29) with vasculitis, like in collagen diseases. Consequently, initially considered as an urologic disease, due to the frequent involvement of the urinary tract, RPF extended progressively to additional medical disciplines like internal medicine, immunology, gastro-enterology, hepato-pancreatology and cardiovascular pathology.

Definition

Among a rather profuse terminology (30-32), the term "retroperitoneal fibrosis" is most commonly used. It corresponds to a chronic, non-suppurative inflammation leading to the progressive replacement of the normal adipose retroperitoneal tissue by fibrous tissue. Primary and secondary RPF represent two and one third of the cases, respectively. Similar fibroinflammatory processes (mesenteric panniculitis, lipodystrophy, mesenteric fibrosis) may involve the mesenteries which are considered as an intraabdominal extension of the retroperitoneal tissular area.

The prevalence of the disease (1.4 per 100,000 inhabitants) (21-22) is probably underestimated if one takes into account the great number of fibrous reactions around abdominal aneurysms (5 to 10 per cent of all of them). The disease usually affects middle aged male patients but it may occasionally occur in children and even in the fetus. Rarely fibroinflammatory processes have been observed in members of the patient's family. There is no evidence of racial predisposition. Possible predisposing factors include HLA B27 (33,34), the presence of HLA-B1*03 (35), an allele linked to a wide range of autoimmune condition, alpha 1 antitrypsin deficiency (26) and an elevated IgG4 blood level (36-38).

Correspondence to : Dr. E. Jacobs, 421, avenue Louise, Box 15, B-1050 Brussels. Belgium. E-mail : jacobs.edouard@scarlet.be

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Histopathology (12,21,22,24,39-43)

Gross findings

In secondary retroperitoneal fibrosis, the fibro-inflammatory process usually develops near the site of the triggering cause, e.g. chronic infection, malignant involvement of the retroperitoneal space, extravasation of blood. In most drug-induced and idiopathic cases of retroperitoneal fibrosis, it originates near the lower abdominal aorta and common iliac arteries at the level of the anterior surface of the fourth and fifth lumbar vertebrae. Its lateral extension may involve one or both ureters ; bilateralization of unilateral lesions is observed in more than two third of the cases. The process may progress continuously or as separate foci along the aorta and major aortic branches and sometimes extend into the pelvis or upwards to the level of the renal vessels and even into the mediastinum. It may encase or even sometimes obstruct the retroperitoneal vessels, notably the vena cava and iliac vein. Involvement or occasional invasion of various structures or organs in the retroperitoneum and abdominal cavity (12,44-46) have also been reported together with varied possible clinical consequences, e.g. duodenal or rectosigmoid subocclusion, portal hypertension (47), obstruction of the biliary tract (48). The lesion presents as a $\geq$ 2 to 6 cm or sometimes even more thick plaque or mass (49, 50). In up to 15% of the cases, additional fibro-inflammatory masses or processes may be found outside the retroperitoneal area, in the abdominal cavity or in various sites or organs of the body (15) : pericardium, pleura, lung, liver, kidney, scrotal region, pituitary fossa, suprasellar region, brain surface, epidural space and even the subcutaneous area (personal case). Several other specific fibroinflammatory processes, have occasionally been reported in association with retroperitoneal fibrosis e.g. mediastinal fibrosis, Riedel's thyroiditis, orbital pseudotumour, cervical fibrosis, chronic sialodenitis and, in the abdomen, sclerosing cholangitis, autoimmune pancreatitis, mesenteric fibrosis, pelvic fibrosis and likewise other autoimmune diseases such as systemic lupus erythematosus, periarteritis nodosa.

The thickening of the mesentery in mesenteric panniculitis or lipodystrophy by development of fat, its degeneration and the resulting infiltration by lipid laden macrophages as well as the subsequent variable degree of fibrosis is frequently observed (51). The fat infiltration tends to be thickest at the root of the mesentery and sometimes extends into the retroperitoneum as a contiguous or occasionally separate focus.

Retractile mesenteritis, which has many pathological similarities with retroperitoneal fibrosis, is a fibrotic thickening and shortening of the mesentery towards its base. Progression of the fibrosis in mesenteric panniculitis seems variable, often mild to moderate, but occasionally sufficient to account for the development of some cases of retractile mesenteritis.

Microscopic findings

According to Mitchinson (24), the earliest lesion in RPF consists of a polyclonal infiltration of lymphocytes and plasma cells in the interstitium of the adipose tissue ; the blood vessels then become abundant, with fibroblasts and collagen deposits. Later the collagen becomes progressively hyalinized with a considerable reduction of cellular activity, development of fibrosis and possibly the deposition of calcium and focal ossifications. Maturation of the lesion progresses laterally from the midline (52), the lateral edge of the mass usually remaining more inflammatory (15,16) ; however there may be a great variety in the histological aspects of biopsies taken from different sites of the retroperitoneal mass (30,52,53).

Additional cells possibly encountered in the lymphoplasmocytic infiltrate (12,21,22,24,31,52) are polymorphonuclear eosinophils, neutrophils (often rare or absent), macrophages (54), histiocytes (sometimes lipid laden or foamy), spindle-shaped fibroblasts with possible bizarre forms (50,55), mast cells, occasional smooth muscle cells (56,57) and, rarely, multinucleated giant cells (12,27). The cellular inflammatory infiltration may be diffuse with loose aggregates of cells between the collagen bands, and perivascular around and within the adventitia of small vessels with focal infiltration of their wall.

Mitchinson (24) observed adipocytes appearing to break down only after being encircled by collagen. Necrosis, mentioned in a few articles as small foci (7,30,45,58,59), was exceptionally reported as an extensive fat-necrotizing process (60).

In previous studies, perivascular infiltration by chronic inflammatory cells was considered as rather common (16,27,61,62), but actual vasculitis as inconstant (10% of the cases of whom one third had systemic vasculitis) (16,61,63). In a recent study on 24 patients (43) with idiopathic RPF, an ongoing vasculitic process was present in 11 cases (46%). Vasculitis is more frequent in the initial active inflammatory period than in the mature stage or at autopsy, and of various types (24,61,64-74). It usually involves small and medium-sized arteries (27,62,75,76) and occasionally larger vessels (66, 67). The possible importance of venulitis of small veins with sclerosis and obliteration has been emphasized by Hywel Jones (77) and Meyer (78).

Information concerning the state of the adipose tissue is often neglected in reported cases of retroperitoneal fibrosis as well as in the most recent extensive reviews of the disease (21,22,43).

Between 1955 and 1987, few papers were published reporting several cases presenting with an important development of fat in the mesentery and occasionally in the retroperitoneum. Degeneration of fat was observed with a possible leakage of fatty material and subsequent lymphocytic and monocytic infiltration with collagen deposits.

Two personal cases illustrate the histopathological aspects of the disease and suggest that necrosis of

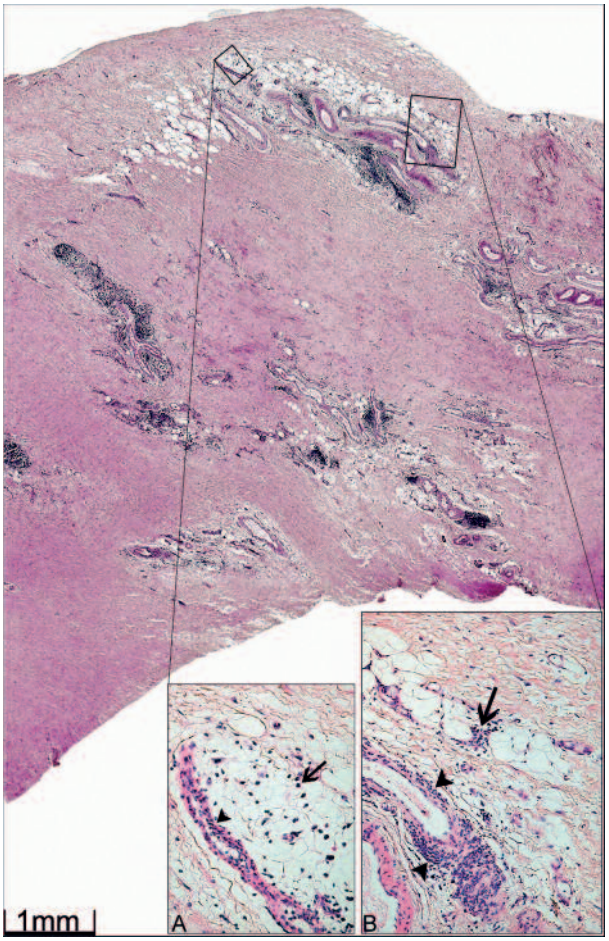

Fig. 1. — Extensive dense fibrous tissue removed from a patient with idiopathic retroperitoneal fibrosis containing numerous inflamed vessels and areas of entrapped preexisting adipose tissue. HE. Insert A : Transmural infiltration of a vessel wall (arrowhead) by chronic inflammatory cells and polymorphonuclear leukocytes. Chronic inflammatory cells adjacent to residual adipocytes (arrow). HE. Obj. ×20. Insert B : Chronic inflammatory cells aggregated in the adventitia of a vessel wall (arrowheads) as well as close to residual entrapped adipocytes (arrow). HE. Obj. ×10.

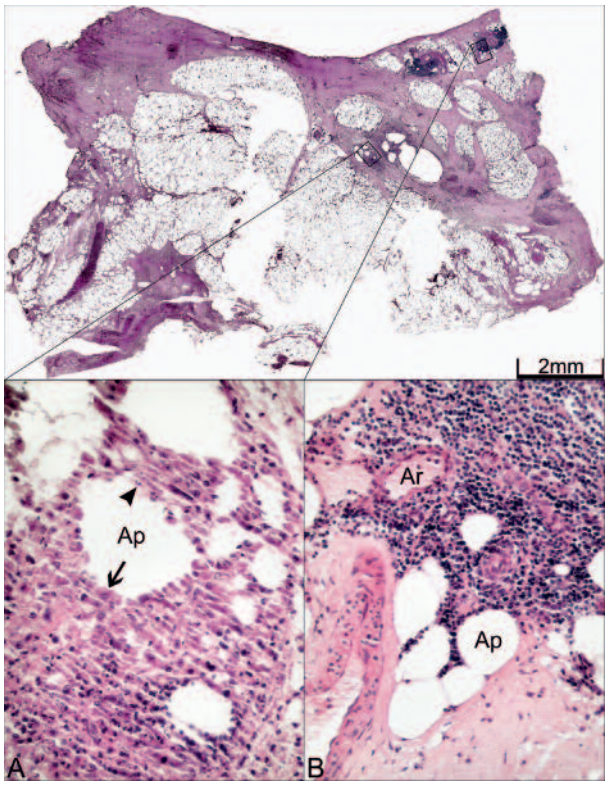

Fig. 2. — Retroperitoneal fibrosis presumably due to the consumption of Cafergot®. Extensive replacement of fat tissue by dense fibrous tissue. HE. Insert A : Area of necrotic adipocytes (Ap) surrounded by macrophages (arrow) admixed with chronic inflammatory cells and polymorphonuclear leukocytes (arrowhead). HE. Obj ×20. Insert B : Mature adipocytes (Ap) in contact with a cluster of chronic inflammatory cells embedding small arteries (Ar) showing diapedesis. HE. Obj. ×20.

adipocytes is inconstant and that a polymorphous inflammatory infiltrate may be found in close contact with focal necrotic adipocytes.

In the first case, a 54-year old woman, who underwent a resection of a left retroperitoneal mass presumably due to retroperitoneal fibrosis, pathological examination revealed extensive bundles of collagen fibrils in association with spindle-shaped cells. Several vessel walls contained chronic inflammatory cells consisting of small lymphocytes, macrophages and plasma cells either focally aggregated within and around the adventitia or diffusely distributed in association with polymorphonuclear leukocytes within the whole vessel wall. The pre-existing adipose tissue was entrapped in the collagenous tissue and not well demarcated from it. Mild chronic inflammatory infiltrates were found in close contact with the residual adipocytes (Fig. 1).

In the second case, a 58 year-old woman, who underwent a resection of a retroperitoneal mass, due to retroperitoneal fibrosis attributed to chronic use of Cafergot® (ergotamine + caffeine), pathological examination revealed extensive replacement of fat by dense fibrous tissue with focal areas of infiltration by chronic inflammatory cells located around mature adipocytes and around small arteries displaying diapedesis. In a few areas, the adipose tissue was necrotic showing extensive accumulation of macrophages admixed with chronic inflammatory cells and polymorphonuclear neutrophils in close contact with necrotic adipocytes (Fig. 2).

Aetiopathogenesis

The aetiopathogenesis of secondary and primary retroperitoneal fibrosis has been extensively reviewed (6, 12,15,18,19,21,22,24,29,79,80).

A large number of aetiological factors have been considered. For many of them, the causal relationship is

obvious or probable (Table 1A). For some, however, it is questionable, and their coexistence with retroperitoneal fibrosis may be purely coincidental (Table 1B).

Secondary (non-idiopathic) retroperitoneal fibrosis

Desmoplastic reaction to the development of a primary or metastatic neoplasm represents 8% of all cases, for example cancer of the breast, lung, thyroid, colon, pancreas, prostate, ureter, Hodgkin's disease, lymphoma, sarcoma. A few malignant cells may be disseminated in an extensive fibrous reaction, and the diagnosis of malignancy in biopsies may be difficult or even easily missed.

Retroperitoneal fibrosis induced by carcinoids is probably linked to the serotonin secreted by the tumour, to its derivatives or to another incretin.

Of note, some cases developed after radiotherapy.

Fibrosis may arise near a focus of local or metastatic infection in the retroperitoneal space e.g. diverticulitis (79), Crohn's disease (81,82) retrocaecal appendicitis, abscesses (79), active chronic phlebitis (77,83), ascending lymphangitis and adenitis originating notably from infection of the lower urogenital tract (30,84,85).

Fibrosis may result from a chronic irritation : e.g. presence of an aortic prosthesis, starch from surgical gloves, microfibrillar collagen - Avitene®, extravasated barium, asbestosis.

It may follow extravasation of blood, lymph, pancreatic juice (86), e.g. after surgery, trauma, or of urine from an ureteropyelic tract damaged by surgery, ischaemia or acutely blocked (87,88). As opposed to what was initially considered, the fibro-inflammatory reaction that surrounds some abdominal aortic aneurysms is exceptionally due to leakage of blood.

The chronic use of certain drugs may lead to the development, in a small percentage of patients, of a fibrous process possibly involving the ureters (89-92). Regression of the lesion usually occurs after withdrawal of the medication. Several drugs have been incriminated : ergotamine, dihydroergotamine and some of their derivatives (methysergide, bromocriptine, pergolide, lysergic acid). A causal relationship has been suggested but not demonstrated with the use of analgesics, beta-blockers, methyldopa or hydralazine.

Idiopathic (primary) retroperitoneal fibrosis

Among various previous hypotheses, it has been suggested that idiopathic RPF could actually be the sequelae of an unrecognized or forgotten traumatism, or the result of the perpetuation of an infection, not suppressed by the repeated use of antibiotics.

For more than 50 years, several authors have emphasized its possible link with vasculitis (27,61,62,65,66,75, 93,94), collagen diseases (28,94,96-98), hypersensitivity or immunologically mediated processes (7,27-29,75,97, 98).

Although idiopathic fibrosis and systemic vasculitis are most likely associated, it is not yet clearly established whether the fibrosis is due to the vasculitis, or if both lesions are independently due to the same cause (62,76). The usual location of the inflammatory process around the large vessels of the retroperitoneal area and the frequent occurrence of a fibro-inflammatory reaction around aortic or aorto-iliac aneurysms (99) led Mitchinson (100-102) and Parums *et al.* (103-105) to consider that idiopathic RPF could be a chronic periarteritis (periaortitis). This might result from an allergic or

Table 1A. — **Secondary (non-idiopathic) retroperitoneal fibrosis : aetiologies**

CANCER	Primary or metastatic Carcinoid (serotonin or derivative)
RADIOTHERAPY	
INFECTION	(local or metastatic) e.g. :
	• Crohn's disease - Diverticulitis - Ulcerative colitis (?) - Appendicitis - Abscess - Proctitis
	• Pyelonephritis
	• Ascending lymphangitis and adenitis (notably from an infection of the lower urogenital tract)
	• Thrombophlebitis
	• Chronic infection (perpetuated by use of antibiotics) - Actinomycosis
CHRONIC IRRITATION	
	• Aortic prosthesis
	• Starch (surgical gloves) – Microfibullar collagen – Avitene® (surgery) – Alcohol (infiltrations) – Sclerosing injections – Formol (bladder instillation) - Extravasated barium - Asbestosis.
FLUID EXTRAVASATION	
Blood, lymph	
	• Trauma, surgery – Disorder of haemostasis – Henoch-Schönlein purpura – Endometriosis – Aneurysm ?
	• Stasis or blockage of lymph vessels
Pancreatic juice	
	• Pancreatitis, pancreatic cyst, tumor
Urine	
	• Damage to the ureteral wall (surgery, ischaemia) – Acute blockage of ureter
Liquor folliculi	
	• Ruptured ovarian follicle
DRUG ADMINISTRATION	
	• Ergotamine - Dihydroergotamine
	• Methysergide, bromocriptine, pergolide, lysergic acid.
	• Analgesics ? – Betablockers ? – Methyldopa ? – Hydralazine ?

Table 1b. — **Rare or questionable causes of retroperitoneal fibrosis**

Syphilis – Brucellosis – Toxoplasmosis – Lymphopathia venereum – Tuberculosis.
Hepatitis B – Hepatitis B with periarteritis nodosa.
Hepatitis C (with cryoglobulin)
Hanta virus infection
History of rheumatic fever
Histoplasmosis (mediastinal fibrosis)
Schsistosomiasis (immunomediated)
Guinea worm infestation
Echinococcal cyst (ruptured)
Smoking habits – Hypercholesterolemia – Diabetes (?)
Marfan's syndrome
Ehlers-Danlos syndrome
Coarctation of aorta
Sickle-cell trait
Gardner syndrome
Low grade T cell lymphoma – Lymphoid dysplasia (predisposition to β cell lymphoma)
Sarcoidosis
Presence in the retroperitoneal tissue of
Uric acid crystals (hyperuricemia) – rheumatoid nodules
In animals :
Rabbits : vitamin E deficiency
Macaque : simian acquired immunodeficiency ; retrovirus (retroperitoenal fibromatosis)

immune reaction to an oxidized low-density lipoprotein such as ceroid (insoluble polymer of oxidized lipoproteins) elaborated within atherosclerotic plaques and leaking from the damaged aortic wall where a plaque of atheroma has breached into the media. Instead of retroperitoneal fibrosis, Mitchinson (101,102) suggested the new term of "periaortitis" which also included inflammatory aneurysms and perianeurysmal fibrosis with the possible involvement of the ureters (106).

More recently, considering the rather frequent observation of concomitant constitutional symptoms, raised acute phase-reactant levels, clinical and biological autoimmune manifestations and the positive antibody tests, Vaglio *et al.* (21,22) suggested that, rather than being an exaggerated local reaction to atherosclerosis, RPF could be a local manifestation of a systemic autoimmune process, an hypothesis previously proposed by Hoffman *et al.* (27) ; Ormond (29) and Zabetakis (97). For Vaglio *et al.* (21,22), the vasculitis involves the adventitial vasa vasorum of large vessels (107), the abdominal aorta, and sometimes the thoracic aorta, as well as the periaortic retroperitoneal small vessels. According to these authors, this could promote both the fibroinflammatory reaction typical of periaortitis and the medial thinning with aneurysmal distension. This is on line with the histological studies of Nezelof *et al.* (39) for whom RPF is a disease of the adventitia. However, whether the multifocal fibrosis represents a scattered but histologically uniform reaction in susceptible individuals to a variety of antigenic stimuli or, more probably, a manifestation of the same disease in different organ systems awaits further elucidation (108-110). In addition, it is not yet clearly established why the lesions are located in the lower part of the retroperitoneal area in most cases of idiopathic retroperitoneal fibrosis.

Table 2. — **Idiopathic retroperitoneal fibrosis : aetiopathogenic hypotheses**

• Systemic Weber Christian's disease.
• Ignored or forgotten traumatism or infection.
• Variable individual degrees of reparative inflammatory reaction and fibrosis for comparable degrees of injury in different persons.
• Collagen disease
• Vasculitis – Hypersensitivity vasculitis
• Immunomediated, autoimmune process.
• **Periaortitis - periarteritis**
– **Immune reaction to ceroid (from atherosclerotic plaques)**
Atherosclerosis
Aneurysm
– Aortitis
– Takayasu's arteritis.
• **Local manifestation of a systemic autoimmune process**.
• Genetic factor : HLA B 27 ? - HLA-DRB* 03 ? - alpha 1 antitrypsin deficiency ?
• Hyper IgG 4 disease ?

The two most classic theories are typed in bold.

Sometimes extensive fibrous tissue may occur in other diseases possibly involving the retroperitoneal area. This must be considered in the differential diagnosis (43) including e.g. Erdheim Chester's disease, inflammatory myofibroblastic pseudotumour (plasma cell pseudotumour), lymphomatoid granulomatosis, xanthogranulomatofibrosis, fibromatosis, inflammatory malignant histiocytosis, inflammatory fibrosarcoma and inflammatory fibrosing liposarcoma.

Role of adipocytes – Similarities to Crohn's disease

We acknowledge that idiopathic retroperitoneal fibrosis is now usually considered as a local manifestation of a systemic autoimmune process with vasculitis. However, as already suggested in several articles pub-

lished from 1955 to 1987, we think that other processes, notably a "primary" proliferation of fat (111-118) could in some cases precede and apparently initiate a fibro-inflammatory reaction in the mesentery and occasionally in the retroperitoneal area. In such cases, the mesenteric or retroperitoneal lesion is a mass of relatively normal and structurally altered adipocytes constituting large nodules centred on a lymph node or vessel (59,112, 116,118). The adipocytes vary considerably in size, most of them being much smaller than normal fat cells ; they are found mainly at the periphery of large nodules or in small nodules (112). Degenerative changes of fat cells may occur, with occasional disruption, fatty cyst formation by coalescence (60,116,118) and release of fatty material, with subsequent interstitial infiltration by lymphocytes and monocytes and development of fibrous tissue (59,77,112,118) probably regulated by moderators produced by cells of the immune system. According to Kipfer (51), in a majority of patients with mesenteric panniculitis, the lesions exhibit varying degrees of inflammatory infiltration of the mesentery with lipid-laden macrophages and fibrosis occurring in a limited number of them.

Information concerning the amount and state of fat has generally been neglected by the authors reporting new cases of retroperitoneal fibrosis and in the recent reviews of the disease. Even in the detailed study of Corradi *et al.* (43), the involvement of fat is merely characterized by "absence of necrosis, poorly demarcated surface between idiopathic retroperitoneal fibrosis and the pre-existing adipose tissue".

In one patient with retroperitoneal fibrosis, reported by Ormond in his first article on the disease (5), the perireteral fibrosis had progressed during four years and the tissue was dense, almost without fat and with little cellular infiltration. However, in the second patient in whom the process was evidently younger and of much shorter duration, there were alternating areas of dense, fibrous, connective tissue and of considerable fat with throughout the entire sections examined a diffuse infiltration by inflammatory cells and considerable fibroblastic activity. Twelve years later, in a review of retroperitoneal fibrosis, Ormond (6) concludes as follows : "Any difference which existed in the microscopic appearances consisted in the relative amount of fat, the types of fibrous tissue and the cellular infiltration".

The two aforementioned personal cases illustrated the variability of the amount of fat, of necrosis and of the adjacent inflammatory infiltrate.

We have been impressed by the similarities, as outlined in Table 3, between the fatty reaction of the mesentery in ileal Crohn's disease and the pathological features observed in mesenteric panniculitis, lipodystrophy and in some cases of retroperitoneal fibrosis.

The thickening of the mesentery adjacent to regional enteritis was reported in 1932 by Crohn *et al.* (119), although without identification of the nature of the hypertrophied tissue. The currently well known accumulation of mesenteric fat has apparently been neglected by most pathologists or authors reporting further cases, even by Block *et al.* (81) in their review of 27 patients with obstructive uropathy due to Crohn's disease. Although focusing on the urological complication, one of us (120) reported in the resected specimen of one of two such cases inflammatory tissue with enlarged adenopathies at the level of the ileo-colic junction, and a "lipomatous" mass with a slight degree of fibrosis and lymphoid infiltration.

Actually, the importance of the fat hypertrophy and of the fatty wrapping was first recognized by surgeons (121), and later emphasized by Sheehan (122). The search for its mechanism increased the attention drawn to a possible pathogenic role played by the adipocytes. Peroxisome proliferators-activated receptor gamma (PPAR-γ), an important regulator of the proliferation and differentiation of adipocytes, is over-expressed in mesenteric adipocytes of patients with Crohn's disease compared to controls (123) together with a proliferation of small adipocytes (124,125) and a marked hyperplasia of mesenteric fat. The intraabdominal fat is an important source of tumor necrosis factor (TNF-α) possibly contributing to the mucosal inflammation in regional ileo(colitis) and of adiponectin presumably involved in the regulation of intestinal inflammation.

Table 3. — **Histopathological analogies of mesenteric and some retroperitoneal fibro-inflammatory processes with Crohn's disease**

Crohn's disease	**Mesenteric panniculitis** **Retroperitoneal fibrosis** (some cases)
DEVELOPMENT OF FAT IN THE ADJOINING MESENTERY (119,122-125,127).	INITIAL FAT PROLIFERATION (112,118) THICKENING of mesenteric or retroperitoneal tissue or nodular masses (46,50,112,114-116).
PROLIFERATION OF SMALL ADIPOCYTES (124,125).	Relatively NORMAL FAT CELLS (114) and ABNORMAL FAT CELLS (112,118), notably at the periphery of the large nodules (45,46,112) and in small nodules (112).
LYMPH NODE CLOSE TO REACTIVE ADIPOCYTES (127)	LYMPH NODE or blood vessel IN THE CENTER OF FAT NODULES (112) *OR* SCATTERED IN THE TISSUE (116).
MICROBES IN THE TISSUE (126)	MICROBES IN THE TISSUE (occasionally) (6,84,128-130) CHRONIC INFECTION (77,111,129,131) PAST TRAUMA, SURGERY (116) or INFECTION (51,111,129)

The proliferation of mesenteric fat tissue in Crohn's disease could possibly result from the colonisation of adipocytes by bacteria, following bacterial translocation, with increased expression of PPARγ and inflammatory mediators (126). According to Pond (127), it could also be due, as in HIV (Human Immunodeficiency Virus) infected individuals, to a bidirectional interaction between immuno-activated lymphocytes of mesenteric lymph nodes and perinodal adipocytes. This makes polyunsaturated fatty acids selectively and almost instantly available to the immune cells when required. The hyperplasia of the mesenteric fat in HIV patients probably represents the establishment of successful coexistence of the virus and its host, with or without the aid of drugs (127). It seems to us reasonable to think that a similar process may occur, but with microbes, in patients with chronic Crohn's ileitis.

The presence of microbes by culture or histological examination has occasionally been reported in the pathological tissue of retroperitoneal and mesenteric fibrosis (60,84,128-130).

A past history of infection, a chronic persisting or repeated infection (131), a trauma and various fluid extravasations (blood, urine, pancreatic juice ...) have been incriminated as triggering factors (51,116). In animals, mesenteric fibrosis (retractile mesenteritis) has been experimentally induced by surgical trauma or injection of bacteria into the mesentery (51). This favours the hypothesis of the triggering role of bacteria (or viruses) also in the development of some cases of mesenteric or retroperitoneal fibrosis as outlined in our comparative study (Table 3).

In their recent (2009) review of the role of adiponectin in inflammatory gastro-intestinal diseases, Shäffler and Schölmerich (132) suggest that it could be involved in the aetiopathogenesis of mesenteric panniculitis, although no clinical or basic study is currently available.

Conclusions

The analysis of fat in retroperitoneal fibrosis has been usually neglected when compared to detailed studies of the inflammatory infiltration and of the blood vessels. Other fibroinflammatory processes with a significant development of fat, reported in the past, occur in some cases of so-called idiopathic" fibrosis", and quite frequently when the mesentery is involved. These subtypes of inflammatory fibrosis show pathological similarities with the reaction observed in the mesentery adjacent to Crohn's disease, suggesting an active role of adipocytes. Microbial or viral infection may possibly play a role.

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References

1. SIMPSON A. Hydronephrosis. Description of a congenital case and remarks on the etiology of the disease. *Glasgow Med. J.*, 1867-NS2 : 332-342.
2. VON HOFFMAN E., FRIEDRICH M., KUHN M.W. Ungewöhnliche Formen der retroperitonealen Fibrose (M. Ormond). *Fortschr. Röntgenstr.*, 1989 , **151** : 627-629.
3. ALBARRAN J. Rétention rénale par périurétérite. Libération externe de l'uretère. *C.R. Assoc. Franç. Urologie*, 1905, **9** : 511-517.
4. KAUDE J. Retroperitoneal fibrosis., *Acta Radiol . (Diagn).*, 1966, **4** : 331-343.
5. ORMOND J.K. Bilateral ureteral obstruction due to envelopment and compression by an inflammatory retroperitoneal process. *J. Urol.*, 1948, **59** : 1072-1079.
6. ORMOND J.K. Idiopathic retroperitoneal fibrosis. *JAMA*, 1960, **174** : 1561-1568.
7. UTZ D.C., HENRY J.D. Retroperitoneal fibrosis. *Med. Clin. North America*, 1966, **50** : 1091-1099.
8. DUCROT H., GRUNFELD J.P., WATCHI J.M. Les fibroses retropéritonéales (dix observations personnelles et revue de la littérature). *La Presse Médicale*, 1967, **75** : 2661-2666.
9. HARDY J.C., JACOBS E. La fibrose rétropéritonéale. Essai de synthèse et diagnostic différentiel. *Acta Urol. Belg.*, 1974, **42** : 113-276.
10. KOEP L., ZUIDEMA G.D. The clinical significance of retroperitoneal fibrosis. *Surgery*, 1977, **81** : 250-257.
11. WAGENKNECHT L.V., HARDY J.C. Retroperitoneale Fibrosen. 1st Ed. Stuttgart. Georg Thieme Verlag 1978.
12. LEPOR H., WALSH P.C. Idiopathic retroperitoneal fibrosis. *J. Urol.*, 1979, **122** : 1-6.
13. JACOBS E. In Bockus Gastroenterology 4th Edition. Vol. 7. Retroperitoneal diseases : 4214-4249. W.B. Saunders Company 1985.
14. HIGGINS P.M., ABER G.M. Idiopathic retroperitoneal fibrosis. An update. *Dig. Dis.*, 1990, **8** : 206-222.
15. AMIS E.S. Retroperitoneal fibrosis. *Am. J. Roentgenol.*, 1991, **157** : 321-329.
16. GILKESON G.S., ALLEN N.B. Retroperitoneal fibrosis. A true connective tissue disease. *Rheum.Dis.Clin. North America*, 1996, **22** : 23-38.
17. KOTTRA J.J., DUNNICK N.R. Retroperitoneal fibrosis. *Radiol. Clin. North America*, 1996, **34** : 1259-1275.
18. VAN BOMMEL E.F.H. Retroperitoneal fibrosis. *Netherl. J. Med.*, 2002, **60** : 231-242.
19. MEIER P., GILABERT C., BURNIER M., BLANC E. La fibrose rétropéritonéale, une maladie inflammatoire méconnue. Observations cliniques et revue de la littérature. *Néphrologie*, 2003, **24** : 173-180.
20. ESTRADE V., TRAXER O., SIBONY M., HAAB F. Fibrose rétropéritonéale. *Ann. Urol.*, 2004, ***38*** : 3-13.
21. VAGLIO A., SALVARINI C., BUZIO C. Retroperitoneal fibrosis. *Lancet*, 2006, **367** : 241-252.
22. VAGLIO A., PALMASINO A., CORRADI D., SALVARINI C.,BUZIO C. Retroperitoneal fibrosis : evolving concepts. *Rheum. Dis. Clin. North America*, 2007, **33** : 803-817.
23. BARRETT N.R. Idiopathic mediastinal fibrosis. *Brit. J. Surg.*, 1958, **46** : 207-218.
24 . MITCHINSON M.J. The pathology of idiopathic retroperitoneal fibrosis. *J. Clin. Pathol.*, 1970, **23** : 681-689.
25. COMINGS D.E., SKUBI K.B., VAN EYES J., MOTULSKI AG. Familial multifocal fibrosclerosis. Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis and pseudotumor of the orbit may be different manifestations of a single disease. *Ann. Int. Med.*, 1967, **66** : 884-892.
26. PALMER P.E., WOLFE H.J., KOSTAS Cl. Multisystem fibrosis in alpha-1-antitrypsin deficiency. *Lancet*, 1978, I *:* 221-222.
27. HOFFMAN W.W., TRIPPEL O.H. Retroperitoneal fibrosis : etiologic considerations. *J. Urol.*, 1961, **86** : 222-231.
28. QUE G.S., MANDEMA E. A case of idiopathic retroperitoneal fibrosis presenting as a systemic collagen disease. *Am. J. Med.*, 1964, **30** : 320-329.
29. ORMOND J.K. Idiopathic retroperitoneal fibrosis : a discussion of the etiology. *J. Urol.*, 1965 : **94** : 385-390.
30. HACHE L., UTZ D.C., WOOLNER L.B. Idiopathic fibrous retroperitonitis. *SGO.*, 1962, **115** : 737-744.
31. WEBB A.J., DAWSON-EDWARDS P. Non-malignant retroperitoneal fibrosis. *Br. J. Surg.*, 1967, **54** : 508-518.
32. ALBERTI C., SACCHINI P., CORETELLINI P., ROSSI P. Fibroses retroperitoneale : alcune nuove acquasizioni su patogénesis e diagnostica. *Arch. It. Urol. Nephrol. Androl.*, 1991, **63** : 23-25.

33. DE LUCA S., TERRONE C., MANASSERO A., ROCA ROSSETTI S. Aetiopathogenesis and treatment of idiopathic retroperitoneal fibrosis. *Ann. Urol.*, 1998, **32** : 153-159.
34 . CHEVET D., RIVALAN J., REBIBOU J.M., MICHEL F., GUIGNIER F. Idiopathic retroperitoneal fibrosis and HLA antigens. *Nephron*, 1996, **73** : 495.
35. MARTORONA D., VAGLIO A., GRECO P. Chronic periarteritis and HLA-DRBI*03). Another clue to an autoimmune origin. *Arthr. Rheumat*., 2006, **55** : 126-130.
36. HAMANO H., KAWA S., OCHI Y., UNNO H., SHIBA N., WAJIKI M., NAKAZAWA K., SHIMOJO H., KIYOSAWA K. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet*, 2002, **359** : 1403-1404.
37. NEILD G.H., RODRIGUEZ-JUSTO M., WALL C., CONNOLLY J.O. Hyper IgG 4 disease : report and characterization of a new disease : *BMC*, 2006, **4** : 23 (available from http://biomedcentral.com/1741-7015/4/23.
38. ZEN Y., SAWAZAKI A., MIYAYMA S., NOTSUMATA K., TANAKA N., NAKANUMA Y. A case of retroperitoneal and mediastinal fibrosis exhibiting elevated levels of IgG4 in the absence of sclerosing pancreatitis (autoimmune pancreatitis). *Human Pathol.*, 2006, **37** : 239-243.
39. NEZELOF C., WATCHI I.M., AUVERT J., XERRI A., COUVELAIRE R. Sur l'incidence urétérale de la fibrose rétropéritonéale idiopathique extensive (à propos de 15 cas). *J.Urol. et Nephrol.*, 1967, **73** : 193-229.
40. SAXTON H.M., KILPATRICK F.R., KINDER Ch., LESSOF M.H., MC HARDY-YOUNG S., WARDLE D.F.H. Retroperitoneal fibrosis. A radiological and follow-up study of fourteen cases. With an appendix on the electron microscopic appearances by Williams P.L. *Quart. J. Med. New Series*, 1969, **38** : 159-181.
41. SCHNITZLER L., VERRET J.L., CAWRON C., TUCHAIS E., SORET J.Y., SALAUN Y. Fibrosclérose multifocale (médiastinale, rétropéritonéale, pelvienne avec mésentérite rétractile) associée à une vascularite et révélée par un livedo. *Ann. Dermatol. Vénéreol (Paris)*, 1978, **105** : 943-956.
42. CHOMETTE G., TRANBALOC P., DELCOURT A., AURIOL M. Anatomie pathologique de la fibrose rétropéritonéale idiopathique. Le concept de fibrose systémique multifocale. *Chirurgie (Mémoires Acad. Chir.)*, 1986, **112** : 343-348.
43. CORRADI D., MAESTRI R., PALMISANO A., BOSIO S., GRECO P., MANENTI L., COBELLI R., MORONI G. DEI TOS A.P., BUZIO C., VAGLIO A. Idiopathic retroperitoneal fibrosis : clinicopathologic features and differential diagnosis. *Kidney Int.*, 2007, **72** : 742-753.
44. INKLEY S.R., ABBOTT G..R. Unilateral pulmonary arteriosclerosis. *Arch. Int. Med.*, 1961, **108** : 903-915.
45. LEFFALL L.D., WHITE J.E., MANN M. Retroperitoneal fibrosis. Two unusual cases. *Arch. Surg.*, 1964, **89** : 1070-1076.
46. BINDER S.C., DETERLING R.A., MAHONEY S.A., PATTERSON J.F., WOLFE H.J. Systemic idiopathic fibrosis. Report of a case of the concomitant occurrence of retractile mesenteritis and retroperitoneal fibrosis. *Am. J. Surg.*, 1972, **124** : 422-430.
47. WEBB J., SHERLOCK S. The aetiology, presentation and natural history of extra-hepatic portal venous obstruction. *Quart. J. Med.*, 1979, **192** : 627-639.
48. DE JACO C., FERENCI P., SCHOBER E.,KASERER K., FÜGGER R., NOVACEK G., GANGL A. Stenosis of the common bile duct due to Ormond's disease : case report and review of the literature. *J. Hépatol.*, 1999, **31** : 156-159.
49. DINEEN J., ASCH T.H., PEARCE J.M. Retroperitoneal fibrosis. Anatomic and radiologic review with a report of four new cases and an explanation of pathogenesis. *Radiology*, 1960, **75** : 380-390.
50. BUCKBERG G.D., LONGMIRE W.P., DILLEY R.B. The protean manifestation of sclerosing fibrosis. *Surg. Gynecol. Obstet.*, 1966, **123** : 729-736.
51. KIPFER R.E. Mesenteric panniculitis and retractile mesenteritis. In Bockus Gastroenterology 5th Ed. Vol. 4. Chapter 164. 3106-3109 W.B. Saunders Company. Philadelphia 1995.
52. DEHNER L.P., COFFIN C.M. Idiopathic fibrosclerotic disorders and other inflammatory pseudotumors. *Seminars Diagn. Pathol*., 1998, **15** : 161-173.
53. ANONYMOUS. Periureteric fibrosis. *Lancet*, 1957, **273** : 780-781.
54. HUGHES D., BUCKLEY P.J. Idiopathic retroperitoneal fibrosis is a macrophage rich process. *Am. J. Surg. Pathol.*, 1993, **17** : 482-490.
55. HAWK W.A., HAARD J.B. Sclerosing retroperitonitis and sclerosing mediastinitis. *J. Clin. Pathol.*, 1959, **32** : 321-334.
56. SHIRLEY H., GUP A.K., SPANO J. Idiopathic pelvic fibrosis. Report of a case with unusual histologic and radiographic features. *Ann. Int. Med.*, 1967, **67** : 1248-1254.
57. HUTCH J.A., ATKINSON R.C., LOQUAM G. Perirenal (Gerota's) fasciitis. *J. Urol.*, 1959, **81** : 76-95.
58. MARGOLES J.S., Mc QUEENEY A.J.. Ormond's syndrome. A discussion of the problem and a presentation of three cases. *Arch. Surg.*, 1960, **81** : 660-667.
59. CHARNOCK D.A., RIDDELL H.I., LOMBARDO L.J. Retroperitoneal fibrosis producing ureteral obstruction. *J. Urol.*, 1961, **85** : 251-257.
60. ROSS JC., PROUT G.R. Retroperitoneal fat necrosis producing ureteral obstruction. *J. Urol.*, 1976, **115** : 524-529.
61. KAY R.G. Retroperitoneal vasculitis with perivascular fibrosis. *Brit. J. Urol.*, 1963, **35** : 284-292.
62. HELLSTROM H.R., PEREZ-STABLE E.C. Retroperitoneal fibrosis with disseminated vasculitis and intrahepatic sclerosing cholangitis. *Am. J. Med.*, 1966, **40** : 184-187**.**
63. LITTLEJOHN G.O., KEYSTONE E.C. The association of retroperitoneal fibrosis with systemic vasculitis and HLA-B27 : a case report and review of the literature*. J. Rheumatol.*, 1981, **8** : 665-669.
64. PARK H., JONES I. Perirueteric fibrosis. *Lancet*, 1958, **1** : 195-196.
65. HARDMEIER Th., HEDINGER Chr. Beziehungen zwischen der retroperitoneälen Fibrose und der sogenannten Takayasuschen Arteritis. *Schweiz. Medizin. Wchschrift.*, 1964, **48** : 1669-1676.
66. JONES E.A., ALEXANDER M.K. Idiopathic retroperitoneal fibrosis associated with an arteritis. *Ann. Rheum. Dis.*, 1966, **25** : 356-360.
67. KUWANA M., WAKINO S, YOSHIDA T., HOMMA M. Retroperitoneal fibrosis associated with aortitis. *Arthr. And Rheumat.*, 1992, **35** : 1245-1247**.**
68. TER MAATEN J.C., FRANSSEN C.F.M., DAENEKINDT A.A., HOORNTJE S.J. Triple Wegener's granulomatosis in the urogenital tract. *Nephron*, 1993, **63** : 258-259.
69. KAIPIAINEN-SEPPÄNEN O., JANTUNEN E., KUUSISTO J., MARIN S. Retroperitoneal fibrosis with antineutrophil cytoplasmic antibodies. *J. Rheumatol.*, 1996, **23** : 779-781.
70. FAJAC A., GAEZOWSKI N., CORMIER J.M., DUCLOS F.M., HERREMAN G. Artérite inflammatoire type maladie de Takayasu et fibrose rétropéritonéale. *Rev. Méd. Interne*, 1998, **9** : 436-437.
71. HOUMAN H., HAQUET S., LAMLOUN M., BEN GHORBEL I., MILED M. Fibrose rétropéritonéale associée à une artérite de Takayasu. *Ann. Méd. Interne*, 1998, **149** : 1078-1080.
72. IZZEDINE H., SERVAIS A., LAUNAY VACHER V., DERAY G. Retroperitoneal fibrosis due to Wegener's granulomatosis : a misdiagnosis as tuberculosis. *Am. J. Med.*, 2002, **113** : 164-166.
73. VAGLIO A., MANENTI L., ALLEGRI L., FERROZZI F., CORRADI D., BUZIO C. ANCA-positive periaortic vasculitis : does it fall within the spectrum of vasculitis ? *J. Intern. Med.*, 2002, **251** : 268-271.
74. ASLANGUI E., RANQUE B., PAPO Th. Pseudotumoral retroperitoneal fibrosis and localized vasculitis with very high serum level of anti PR3 ANCA. *Am. J. Med*., 2003, **115** : 250-252.
75. REIDBORD H.E., HAWK W.A. Idiopathic retroperitoneal fibrosis and necrotizing vasculitis. *Cleveland Clin. Quart.*, 1965, **32** : 19-27**.**
76. CARTON R.W., WONG R. Multifocal fibrosclerosis manifested by vena caval obstruction and associated with vasculitis. *Ann. Int. Med*., 1969, **70** : 81-86..
77. HYWEL JONES J., ROSS E.J., MATZ L.R., EDWARDS D., DAVIES D.R. Retroperitoneal fibrosis. *Am. J. Med.*, 1970, **40** : 203-208.
78. MEYER S., HAUSMAN R. Occlusive phlebitis in multifocal fibrosclerosis. *Am. J. Clin. Pathol.*, 1976, **65** : 274-283.
79. CERNY J.C., SCOTT T. Non-idiopathic retroperitoneal fibrosis. *J. Urol*., 1971, **105** : 49-55.
80. MEIER P., VOGT B., BLANC. E. Rethinking the triggering inflammatory processes of chronic periaortitis. *Nephron. Exp. Nephrol.*, 2007, **105** : 17-23.
81. BLOCK G.E., ENKER W.E., KIRSNER J.B. Significance and treatment of occult obstructive uropathy complicating Crohn's disease. *Ann. Surg.*, 1973, **178** : 322-332.
82. GAUJOUX S., COUCHARD A.C., YOUSSEF J.A., PAQUET J.Ch. Obstruction urétérale et maladie de Crohn. *Gastroenterol. Clin. Biol*., 2007, **31** : 611-613.
83. SHAHEEN D.J., JOHNSTON A. Bilateral ureteral obstruction due to envelopment and compression by an inflammatory retroperitoneal process : report of two cases. *J. Urol.*, 1959, **82** : 51-57.
84. VEST S.A., BARELARE B. Periureteritis plastica : a report of four cases. *J.Urol.*, 1953, **70** : 38-50.
85. HEJTMANCIK J.H., MAJID M.A. Bilateral periureteritis plastica. *J.Urol.*, 1956, **76** : 57-61.
86. WEBB A.J., DAWSON EDWARDS P.. Retroperitoneal fibrosis associated with pancreatic disease. *Postgrad. Med. J.*, 1967, **43** : 45-50.
87. OHLSEN L. Retroperitoneal fibrosis due to leakage of urine. *Acta Soc. Med. Upsala*, 1965, **70** : 231-240.
88. MITICHINSON M.J., BIRD D.R. Urinary leakage and retroperitoneal fibrosis. *J. Urol.*, 1971, **165** : 56-58.

89. GRAHAM J.R. Methysergide for prevention of headache. Experience in five hundred patients over three years. *New Engl. J. Med.*, 1964, **270** : 67-72.
90. GRAHAM J.R., SUBY H.I., LE COMPTE P.R., SADOWSKI N.L. Fibrotic disorders associated with methysergide therapy for headache. *New Engl. J. Med.*, 1966, **274** : 359-368.
91. GRAHAM J.R. Cardiac and pulmonary fibrosis during methysergide therapy for headache. *Am. J. Med. Sciences*, 1967, **254** : 23-24.
92. UTZ D.C., ROOKE E.D., SPITTELL J.A., BARTHOLOMEW C.G. . Retroperitoneal fibrosis in patients taking methysergide. *JAMA*, 1965, **191** : 983-985.
93. RAPER F.P. Bilateral, symmetrical, periureteric fibrosis. *Proceed Roy. Soc. Med.*, 1955, **48** : 736-740.
94. HARBRECHT P.J. Variants of retroperitoneal fibrosis. *Ann. Surgery*, 1967, **165** : 388-401.
95. DEMKO T.M., DIAMOND J.R., GROFF J. Obstructive nephropathy as a result of retroperitoneal fibrosis :a review of its pathogenesis and associations. *J.Am.Soc.Nephrol.*, 1977, **8** : 684-688.
96. COSTE F., PIGUET B., BASSET F. Periurétérite primitive unilatérale à symptomatologie rhumatoïde ou de connectivite (collagénose). *J. Belge Med. Phys., Rhumat.*, 1960, **15** : 179-187.
97. ZABETAKIS P.M., NOVICH R.K., MATARESE R.A. Idiopathic retroperitoneal fibrosis : a systemic connective tissue disease *? J. Urol*., 1979, **122** : 100-102.
98 . HOLLINGWORTH P., DENMAN A.M., GUMPEL J.M. Retroperitoneal fibrosis and polyarteritis nodosa successfully treated by intensive immunosuppression. *J. Roy. Soc. Med.*, 1980, **73** : 61-64.
99. WALKER D.J., BLOOR K., WILLIAMS G., GILLIE I. Inflammatory aneurysms of the abdominal aorta. *Brit. J. Surgery*, 1972, **59** : 609-614.
100. MITCHINSON M.J. Aortic disease in idiopathic retroperitoneal and mediastinal fibrosis. *J. Clin. Pathol.*, 1972, **25** : 287-293.
101. MITCHINSON M.J. Chronic periaortitis and periarteritis. *Histopathol.*, **1984,** 8 : 589-600.
102. MITCHINSON M.J. Retroperitoneal fibrosis revisited. *Arch. Pathol.Lab. Med.*, 1986, **116** : 784-786.
103. PARUMS D.V. The spectrum of chronic periaortitis. *Histopathology*, 1990, **16** : 423-431.
104. PARUMS D.V., CHOUDHURY R.P., SHIELDS S.A., DAVIE A.H. Characterization of inflammatory cells associated with idiopathic retroperitoneal fibrosis. *Brit. J. Urol.*, 1991, **67** : 564-568.
105. RAMSHAW A.L., ROSKELL D.E., PARUMS D.V. Cytokine gene expressed in aortic adventitial inflammation associated with advanced arteriosclerosis (chronic periaortitis). *J. Clin. Pathol.*, 1994, **47** : 721-727.
106. MARTINA B. Chronic periaortitis : a new interpretation of Ormond's disease. *Urological Res.*, 1990, **18** : 165-167.
107. MORONI G., DEL PAPA N., MORONETTI L.M., VITALI C., MAGLIONE W., COMINA D.P., URGNANI F., SANTI S., PONTICELLI C., CORTELEZZI A. Increased levels of circulating endothelial cells in chronic periaortitis as marker of active disease. *Kidney Int*., 2005, **68** : 562-568.
108. SCHWAEGERLE S.M., BAUER Th .W., ESSELSTYN C.B. Single case reports. Riedel's thyroïditis. *Am. J. Clin. Pathol.*., 1988, **90** : 715-722.
109. KRUIT W.H.J., den OTTOLANDER G.J.H. Riedel's thyroïditis in a patient with retroperitoneal fibrosis. *Netherl. J. Med.*, 1991, **39** : 17-19.
110. DE BOER W.A., VAN COEVORDEN F., WIERSING W.M. A rare case of Riedel's thyroïditis 6 years after retroperitoneal fibrosis : two diseases with one pathogenesis. *Netherl. J. Med.*, 1992, **40** : 190-196.
111. COPPRIDGEW.M., ROBERTS L.C., HUGHES J. Sclerosing lipogranuloma. *Southern Med. J.*, 1955, **48** : 827-833.
112. CRANE J.T., AGUILAR M.J., GRIMES O.F. Isolated lipodystrophy, a form of mesenteric tumor. *Am. J. Surg.*, 1955, **90** : 169-179.
113. OGDEN W.W., BRADBURN D.M., RIVES J.D. Panniculitis of the mesentery. *Ann. Surg.*, 1960, **151** : 659-667.
114. ROGERS Ch.E., DEMETRAKOOULOS N.J., HYMANS V. Isolated lipodystrophy affecting the mesentery, the retroperitoneal area and the small intestine. *Ann. Surg.*, 1961, **153** : 277-282.
115. SHAFIROFF B.G.P., KAU Q.Y. Lipodistrophy of adipose areolar tissue in the retroperitoneal space. *Surgery*, 1966, **59** : 696-702.
116. DURST A.L., FREUND H., ROSENMANN E., BIRNBAUM D. Mesenteric panniculitis : review of the literature and presentation of cases. *Surgery*, 1977, **81** : 203-211.
117. MASS. GEN. HOSPITAL. Weekly clinicopathological exercises. *New Engl. J. Med.*, 1984, **(21) 310** : 1374-1381.
118. PALLETTE E.M., PALLETTE E.C., HARRINGTON R.W. Sclerosing lipogranulomatosis : its several abdominal syndromes. *Arch. Surg*.,1987, **94** : 803-810.
119 . CROHN B.B.GINZBURG G.L., OPPENHEIMER G.D. Regional ileitis : a clinical and pathological entity. *JAMA*, 1932, **99** : 1323-1329.
120. JACOBS E., D'UDEKEM F., ENGELHOLM L., GREGOIR W., LEWINSON B., VAN REGEMORTER G. Sténose urétérale par maladie de Crohn. A propos de deux cas. *Acta Gastroenterol. Belg.*, 1981, **44** : 483-493.
121. WEAKLEY F.L., TURNBULL R.B. Recognition of regional ileitis in the operating room. *Dis. Colon Rectum*, 1971, **14** : 17-23.
122. SHEEHAN A.L., WARREN B.F., GEAR M.W.L., SHEPHERD N.A. Fat-wrapping in Crohn's disease : pathological basis and relevance to surgical practice. *Brit. J.Surg.*, 1992, **79** : 955-958.
123. DESREUMAUX P., ERNST O., GEBOES K., GAMBIEZ L., BERREBI D., MÜLLER-ALOUF H., HAFRAOUI S., EMILIE D., ECTORS N., PEUCHMAUR M., CORTOT A., CAPRON M., AUWERX J., COLOMBEL J.F. Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. *Gastroenterology*, 1999, **117** : 73-81.
124. YAMAMOTO K., KIYOHARA T., MURAYAMA Y., KIHARA S., OKAMOTO Y., FUNAHASHI T., ITO T., NEZU R., SUTSUI S., MIYAGAWA J.I., TAMURA S., MATSUZAWA Y., SHIMOMURA I., SHINOMURA Y. Production of adiponectin an anti inflammatory protein, in mesenteric adipose tissue in Crohn's disease. *GUT*, 2005, **54** : 789-796.
125. PEYRIN-BIROULET L., CHAMAILLARD M., GONZALEZ F., BECLIN E., DECOURCELLE C., ANTUNES L., GAY J., NEUT Ch., COLOMBEL J.F., DESREUMAUX P. Mesenteric fat in Crohn's disease : pathogenetic hallmark or an innocent bystander ? *GUT*, 2007, **56** : 577-583.
126. GAY J., TACHON M., NEUT Ch., BECLIN E., CHANG Y., BERREBI D., ENGLISH N., PHILIPPE D., GAMBIEZ L., COLOMBEL J. PH., DESREUMAUX P. Mesenteric adipose tissue is colonized by bacterial flora and and expresses pathogen recognition receptors in Crohn's disease. *Gastroenterology*, 2005, **128** suppl. 2 : A 503.
127. POND C.M. Long term changes in adipose tissue in human disease. *Proceed Nutrit. Soc.*, 2001, **60** : 365-374.
128. BEHRENS M.M., HOLLAND J.M. Periureteritis plastica : a report of a case following staphylococcal infection. *J. Urol.* 1967, **97** : 829-832.
129. HANDELSMAN J.C., SHELLEY W.M. Mesenteric panniculitis. *Arch. Surg.*, 1965, **91** : 842-850.
130. MULVANEY J.P. Periureteritis obliterans : a retroperitoneal inflammatory disease. *J. Urol.*, 1958, **79** : 410-417.
131. HOUSTON W. Periureteritis plastica : a report of a case, with indication of the probable pathology. *Brit. J. Urol.* 1957, **29** : 38-41.
132. SCHÄFFLER A., SCHÖLMERICH J. The role of adiponectin in inflammatory gastrointestinal diseases. *Gut*, 2009, **58** : 317-322.