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Occlusive Phlebitis, a Diagnostic Feature in Riedel's Thyroiditis

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Summary. Five cases of Riedel's invasive fibrous thyroiditis are presented.- Clinically and histopathologically all cases fulfilled the criteria for this lesion. In both small and large veins there were inflammatory changes and obliteration of the lumen, followed by sclerosis. These changes were found in each operative specimen, and seemed to be a diagnostic feature of invasive fibrous thyroiditis. We consider this change to be an occlusive phlebitis, and have noted that it occurs in association with multifocal fibrosclerosis. Three stages can be recognised: infiltrative, occlusive and sclerotic.

In other thyroid lesions such as Hashimoto's thyroiditis, granulomatous thyroiditis of the Quervain type and adenomatous goitre these peculiar changes in the veins were not found.

Key words: Riedel's thyroiditis – Occlusive phlebitis – Multifocal fibrosclerosis.

Introduction

In a previous communication (Meijer and Hausman, 1976) we described certain inflammatory changes of small and middle sized veins in two cases of retroperitoneal fibrosis, one of which was combined with a Riedel type thyroiditis. Numerous published reports have made it clear that both retroperitoneal fibrosis and Riedel's thyroiditis are part of a disseminated fibrosing process known in the literature as multifocal fibrosclerosis. We believe the vascular changes, which we have called occlusive phlebitis, are typical of this fibrosing process. Since our first paper we have had the opportunity to examine four more cases of Riedel's thyroiditis each of which demonstrated the vascular lesions. The present is an acccount of the clinical and histological signs of the five cases of Riedel's thyroiditis.

Observations

Case Reports

Case 1. A fortynine year old woman was admitted with complaints of difficulty in swallowing and stiffness of the neck due to a goiter of two months duration. On examination the thyroid

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was found to be markedly enlarged, tender and firm on palpation. Antibodies against colloid of the thyroid could be demonstrated whereas those against cytoplasm were lacking. A surgical exploration was performed. The right lobe especially was markedly enlarged and stony hard. A biopsy was taken for pathologic examination, which revealed a thyroiditis, probably Riedel's struma. Eleven years after the operation the patient is in good health.

Pathologic Examination. The biopsy measured about $2.5 \times 1.5 \times 1$ cm and was grey-white. Microscopically the tissue revealed large areas of collagenous fibrous tissue with scattered remnants of thyroid parenchyma. There was an infiltration, predominantly of lymphocytes with some plasma cells and a few eosinophilic granulocytes. The inflammatory fibrosing process extended into the surrounding striated muscle. In this small biopsy the distinctive vascular changes were present.

Case 2. A thirtyfour year old woman complained of a painfull mass on the right side of her neck. Examination revealed a very firm goiter on the right. In the serum tests for the presence of antibodies against thyroid colloid were weakly positive. At surgery an abnormality was located in the right lobe extending into the strap muscles. Right sided thyroidectomy was performed and rapid frozen section revealed no malignancy. The postoperative course was uneventful. Five years after operation the patient is without complaints.

Pathologic Examination. The surgical specimen measured about $7 \times 4.5 \times 3.5$ cm. The tissue was stony hard and had a grey-white cut surface with sparse thyroid parenchyma. On microscopic examination there was an abundance of fibrous tissue. At the junction of the thyroid tissue and the fibrosis there was marked infiltration of lymphocytes and plasma cells (Fig. 1). Elsewhere the inflammation was much less or altogether absent, especially in the partially hyalinized fibrotic areas.

At the outer margin the fibrosis invaded the fat and muscle.

Case 3. A fifty-four year old man was admitted because of a painless swelling of half a years duration in the right side of the neck. In addition he complained of a dull pain in the right flank. On palpation a hard goiter was found. Tests for antibodies against colloid were equivocal, but positive on repeat testing. An intravenous pyelogram showed a marked right-sided hydronephrosis and hydroureter which at lumbotomy were both found to have been caused by retroperitoneal fibrosis. Exploration of the neck revealed a nodular hard goiter firmly adherent to the strap muscles. A total thyroidectomy was performed. In the postoperative period the patient developed signs of myxoedema and hypoparathyroidism.

Pathologic Examination. The surgical specimen consisted of the right and left lobes and weighed 30 g. The cut sections were white and fibrous. The upper poles of the thyroid appeared normal. Microscopically there was extensive fibrosis, partially hyalinized. The thyroid parenchyma at the upper poles was normal but the acini were atrophic at the junction of the invading and encasing fibrosis. A parathyroid gland was found enclosed by the fibrous tissue (Fig. 2). The inflammatory fibrous process extended into the surrounding striated muscle.

Case 4. A fifty-two year old woman was admitted because of dysphagia and dyspnoea of effort. On admission a stony hard, tender goiter was found. After a few weeks the antibodies against colloid that had been negative initially became strongly positive. Preoperatively Riedel's struma was suspected. At surgery a hard mass was found invading the strap muscles. Resection of the isthmus was performed with remission of symptoms. For hypothyroidism the patient received dessicated thyroid. Despite corticosteroid administration there was a recurrence of symtoms and sugiccal intervention became necessary because of marked dyspnoea. With difficulty a thyroidectomy was performed.

Pathologic Examination. The isthmus measured $4 \times 2.1 \times 1.5$ cm and was similar to the thyroidectomy specimen which consisted of two lobes, together weighing 115 g. In the left lobe were cystic spaces filled with clear fluid and with a diameter of up to 1.5 cm (Fig. 3). Thyroid parenchyma was recognizable at the upper poles. Microscopically the isthmus was found to be made up of

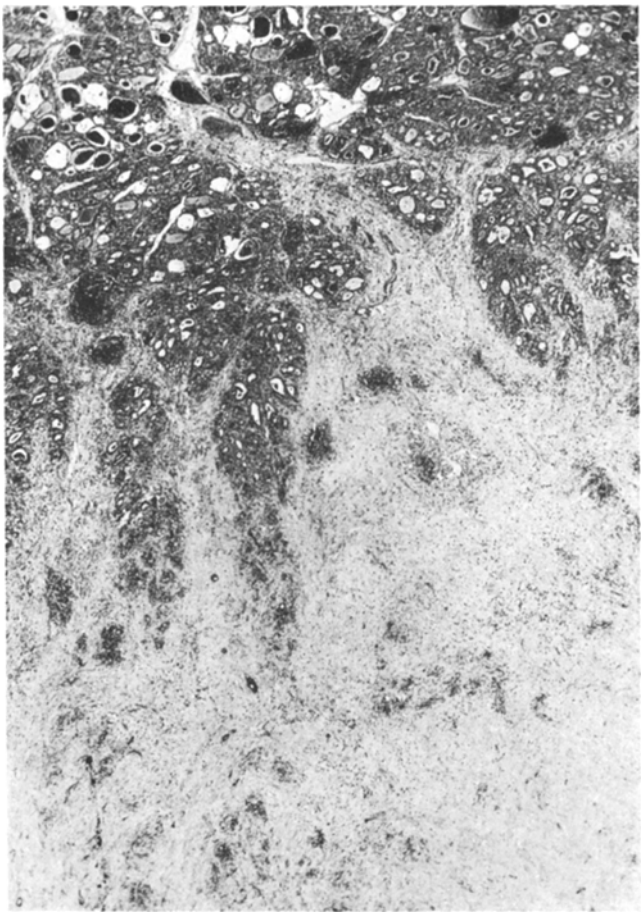

Fig. 1. The characteristic picture of Riedel's thyroiditis: invasive fibrosis. At the border aggregates of inflammatory cells and disapplaringa thyroid follicles. Right below extensive hyalinization. (Hematoxylin-eosin, × 13,2)

collagenous fibrous tissue enclosing areas of thyroid tissue of varying sizes. The fibrosis extended into the surrounding adipose tissue and striated musculature. The fibrous tissue contained scattered foci of lymphocytic and plasma-cellular infiltration with small numbers of eosinophilic granulocytes. The thyroidectomy specimen differed from the isthmus in that fibrosis and hyalinization were more marked and infiltrations were markedly decreased. A small parathyroid, enclosed by fibrous tissue was found.

Case 5. A fifty seven year old woman complained of a tender goiter of several weeks duration. She was found to be myxoedematous and to have a hard goiter. Scanning showed bilateral uptake of radio-active iodine. Antibodies against thyroid tissue were lacking. Surgical exploration was done and several biopsies were taken. Postoperatively the patient was treated with dessicated thyroid. Thirteen years after admission the patient is in good health. The hard goiter had disappeared.

Pathologic Examination. The largest of the tissue pieces measured about 1.5 × 1 × 1.5 cm. Microscopically there was marked fibrosis with aggregated of inflammatory cells invading the thyroid parenchyma and striated muscle. The findings fullfilled all criteria of Riedel's invasive fibrous thyroiditis. In some of the tissue pieces the distinctive changes in the veins were present.

Fig. 2. Remnants of parathyroid tissue totally encased and invaded by collagenous fibrous tissue (Hematoxylin-eosin, ×33)

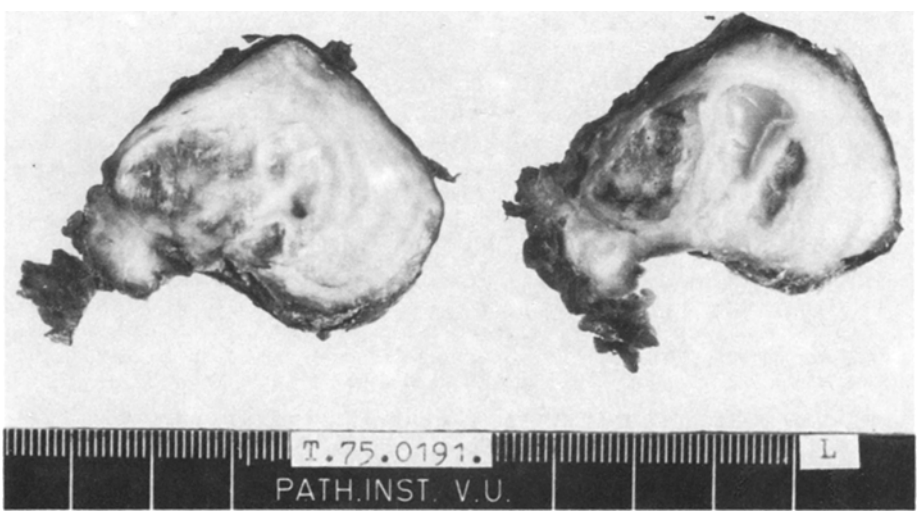

Fig. 3. Cut sections of the thyroidectomy specimen with a glistening white distinctly fibrous surface and a few cystic spaces

Occlusive Phlebitis in Riedel's Thyroiditis

In order to study the vascular changes in the resected specimens van Gieson-Elastica and Verhoeff-Elastica stains were employed in addition to the customary hematoxylin-eosin stain. An endophlebitis and periphlebitis with complete localized occlusion of the lumen was found in all five cases. It was possible to recognize several phases in this inflammatory process and this was particularly striking in the thyroidectomy specimens. It appeared that the phlebitis extended from the periphery towards the center.

From serial sections we concluded that the phlebitis had a progressive character with three stages that gradually merged into each other.

a) Infiltrative Stage. In the media and adventitia of medium sized and small veins ($\pm$ 150–1500 μ) there was an infiltration of lymphocytes and plasmacells with separation of smooth muscle fibers by the infiltrate. The changes might be very slight initially. The lumen was patent and there was little thickening of the intima. Stains for elastic fibers showed splitting of elastic lamellae, giving the impression of an increase in thickness of the elastic coat (Fig. 4).

It was striking that this initial phlebitis was present in or near normal thyroid parenchyma at the border of the advancing fibrosis.

The infiltrative stage extended into the occlusive stage.

b) Occlusive Stage. The changes of this stage were impressive and could be easily recognized in slides stained for elastic fibers. There was a increase of lymphocytes and plasma cells in the wall of the veins, while the lumen was gradually filled with granulation tissue. This tissue, at first loose textured and oedematous, covered the intima and ultimately obliterated the lumen completely

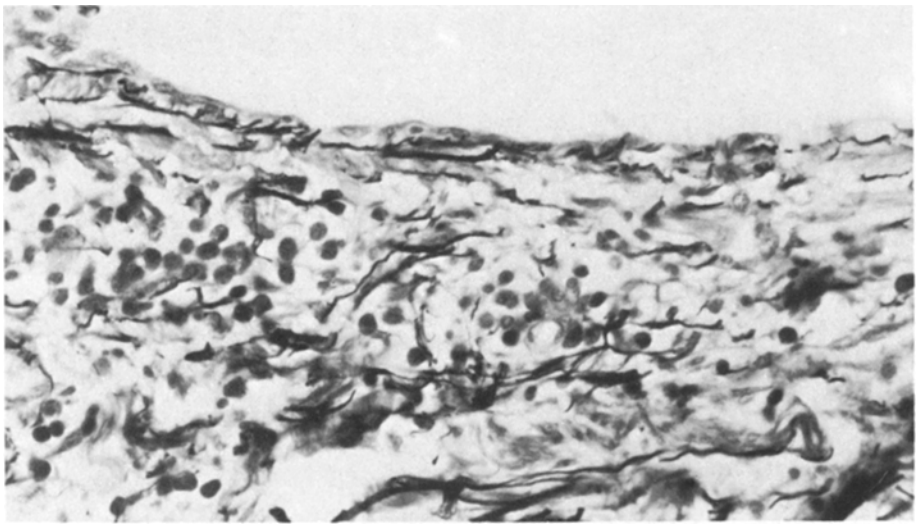

Fig. 4. Infiltrative stage: Detail of the wall of the vein with infiltration by inflammatory cells and splitting of the elastic fibers. (Verhoeff-Stain, × 330)

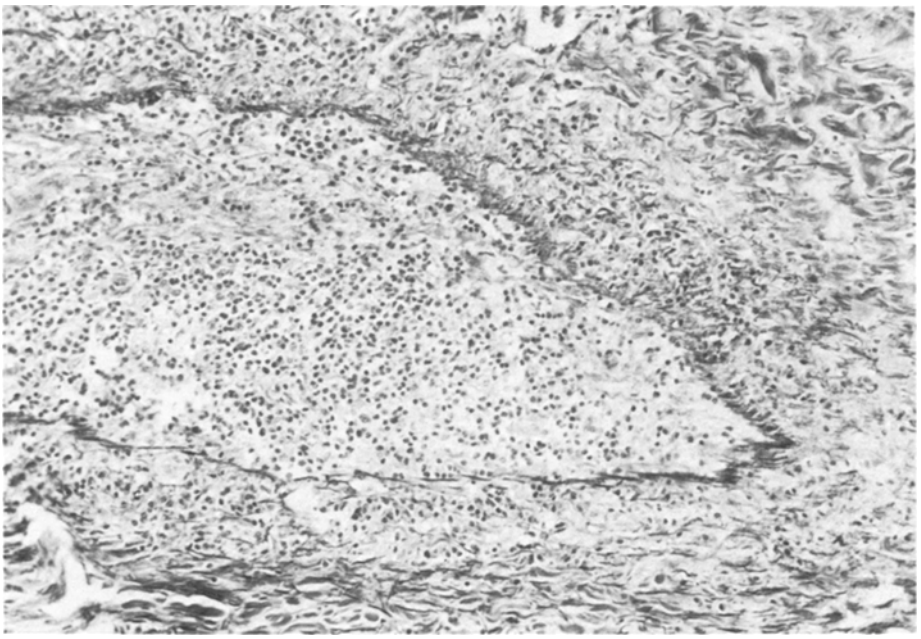

Fig. 5. Occlusive stage: Complete obliteration of the lumen by granulation tissue (Verhoeff-stain, ×66)

Fig. 6. Occlusive stage: Canalization is seen at the end of the occlusive fase. In the capillaries erythrocytes are sometimes present. (Verhoeff-Stain, ×66)

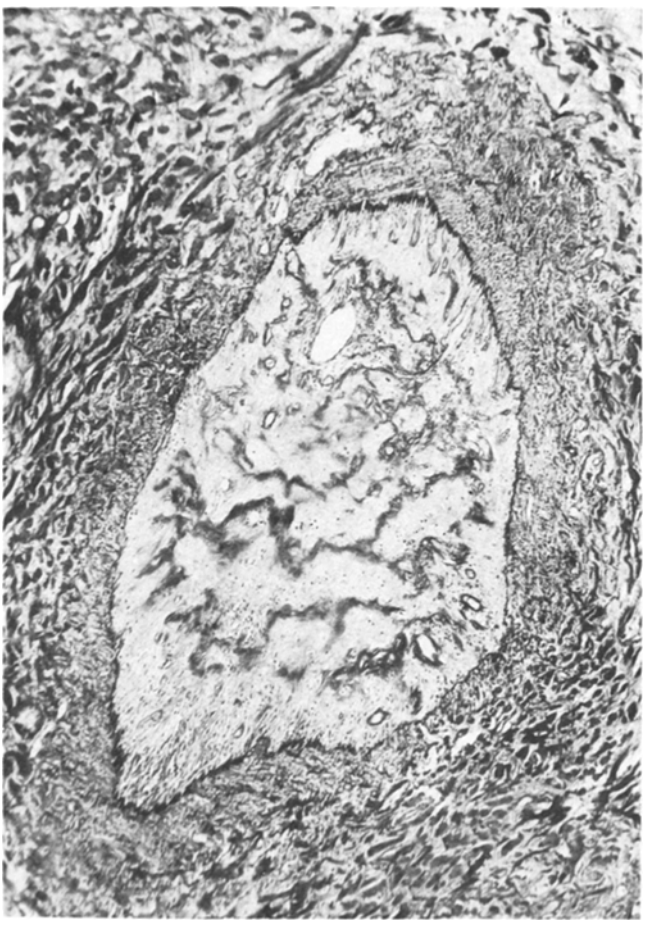

Fig. 7. Sclerosing stage: In the beginning there is a decrease of inflammatory cells in the wall as well as in the lumen. The collagenous fibrous tissue shows hyalinization. (Verhoeff-Stain, × 52,8)

(Fig. 5). There were quite a few granulocytes, including eosinophils. Collagenous fiber bundles and capillaries appeared fairly rapidly. This capillarization gave an impression of some form of recanalization (Fig. 6). There were no signs of hemorrhage and iron pigment was not noticed. This occlusive stage gradually changed into the sclerosing stage.

c) Sclerosing Stage. This end stage was characterized by an increase of collagen and decrease in the extent of the inflammatory reaction (Fig. 7). The lymphocytes and plasma cells in the wall of veins also decreased in numbers, and the smooth muscle cells of the media were replaced by connective tissue. In both lumen and wall there was hyalinization with diminution in numbers of cells and nuclei. There were still occasional capillaries which appeared to be empty.

The end stage was a complete sclerosis of the blood vessel, which was recognizable only by the pattern of elastic fibers remaining (Fig. 8). The

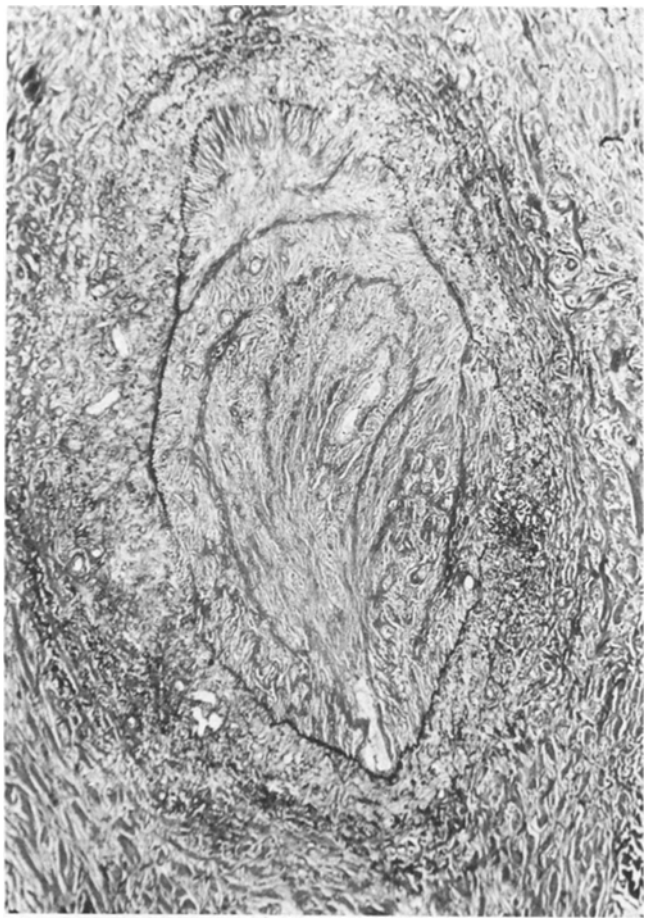

Fig. 8. Sclerosing stage: In the final phase the blood vessel is only recognizable by the framework of elastic fibers. There is sclerosis of the wall and an obliterated lumen. (Verhoeff-Stain, ×52,8)

completely sclerosed vein was only found in fibrosed areas of the thyroid at some distance from the remaining follicles.

The fibrosing process apparently extended into the surrounding tissue beyond the thyroid capsule along the veins, as determined by microscopic examination.

Vascular Changes in Other Thyroid Lesions

For comparison a total of twentythree cases of Hashimoto's thyroiditis, *subacute granulomatous thyroiditis (de Quervain)* and multinodular goiter with signs of thyroiditis were studied. A few of the cases of Hashimoto's autoimmune thyroiditis showed marked fibrosis and represented the so-called fibrous variety. In these there were no signs of fibrosis beyond the capsule or in the muscle.

A total of ten cases of *Hashimoto's thyroiditis* were studied; each of them with the typical clinical and pathological signs of struma lymphomatosa. In

none were there the changes in the veins described above. Even in the areas of fibrosis there were no sclerosed or obliterated veins, and arteries showed no evidence of inflammation. Occasionally a slight to moderate intimal thickening was noted.

The blood vessels in three cases of subacute granulomatous thyroiditis (de Quervain) were investigated. There were no significant changes in arteries or veins and no evidence whatsoever of occlusive phlebitis. Similar results were found in a study of ten cases of nodular goiter of which five had varying degrees of diffuse and localized lymphocytic infiltrations. Even where there was fibrosis in the goiter no vascular changes were noted.

Discussion

In 1896 and 1897 Riedel described three patients with "eisenharten" goiter due to a fibrous process in the thyroid extending into the soft tissues of the neck. Since these reports the thyroid lesion has been known as Riedel's struma or invasive fibrous thyroiditis.

The disease is very rare and is found in about 0.05% of all thyroidectomies (Woolner et al., 1962). Morphologically there is unilateral or bilateral fibrosis of the thyroid extending into the adjacent tissues with aggregates of inflammatory cells and without giant cells or granulomas. The process causes destruction of the thyroid parenchyma.

Riedel's thyroiditis is not the end result of either subacute thyroiditis (de Quervain) or struma lymphomatosa (Hashimoto) but is *a separate entity* of which the etiology and the pathogenesis are obscure. There is little literature on the morphology of Riedel's thyroiditis, probably due to the fact that nonspecific fibrosis and inflammation constitute the pathological basis of the disease. Only a few publications have been devoted to the vascular changes in Riedel's thyroiditis. In their study on arterial lesions Hardmeier and Hedinger (1964) pointed out the resemblance between the vascular process in Riedel's thyroiditis and that in Takayashu's arteritis. They also described inflammatory changes in the walls of small arteries and veins, and postulated that Riedel's thyroiditis might be a primary arteritis with generalized fibrosis of the soft tissues of the neck.

Bogomoletz (1966) also observed arterial lesions which he called a granulomatous giant cell arteritis. This arteritis, in his opinion initiated a Riedel's struma. Roulet may be credited with the first extensive description of the characteristic changes in the veins in Virchows Archiv (Roulet, 1931). As he related it, there was a diffuse infiltration of lymphocytes and plasma cells in the wall of small and middle sized veins. The elastic fibers were split up by the inflammatory process. Signs of thrombosis were lacking although granulation tissue filled the lumen and some kind of recanalization had occured. Roulet thought that the obliterative changes had their origin in the adventitia and extended through the wall into the lumen.

There is a striking similarity with the changes which we have called occlusive phlebitis (Meijer and Hausman, 1976) even though we have not been able

to confirm Roulet's notion that the inflammation originated in the adventitia. Arterial changes, specifically those in middle sized arteries, consisted only of intimal thickening on an arteriosclerotic basis. The constant finding of this type of phlebitis in the five patients and its absence in other thyroid lesions of twenty-three patients makes us reasonably certain that the vascular lesion is an important diagnostic feature of Riedel's thyroiditis.

In the introduction we briefly referred to the association of Riedel's thyroiditis with multifocal fibrosclerosis. This disseminated fibrosing process may be manifest as mediastinal or retroperitoneal fibrosis, pseudotumor of the orbit, sclerosing cholangitis or any combination of these disease conditions (Comings et al., 1967; Gleeson et al.,1970; Meijer et al., 1976). An active chronic phlebitis with cellular infiltration of the wall of the veins has been described by Jones et al. (1970) in retroperitoneal fibrosis. They found no arterial changes. We noticed the changes of occlusive phlebitis, as described above, in two cases of retroperitoneal fibrosis.[1]

We have not been able to ascertain the role of the occlusive phlebitis in the pathogenesis of Riedel's thyroiditis, and one can only speculate on the cause of the inflammatory process in the vessel wall. Because of the elevated globulin fractions that have been reported (Jones etal., 1970; Rao et al., 1973) and the sometimes favorable response to corticosteroids (Thomson et al., 1968; Gleeson et al., 1970) immunological factors have been considered. However, the significance of antibodies against thyroid tissue that are sometimes found (especially against colloid) is unclear. Their presence may be due to secondary destruction of the parenchyma and not be causative.

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[1] We have seen in consultation another case of retroperitoneal fibrosis in the pelvic region with the same changes in small veins

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