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Theories of the etiology of Riedel's struma : a review of the literature and a report of two cases

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THEORIES OF THE ETIOLOGY OF RIEDEL'S STRUMA
(A REVIEW OF THE LITERATURE AND A REPORT
OF TWO CASES)

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Submitted in Partial Fulfillment for the Degree of
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THEORIES OF THE ETIOLOGY OF RIEDEL'S STRUMA
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Theories concerning the etiology of Riedel's struma are as numerous as there are synonyms for this entity first described by Riedel in 1883. Unfortunately it is difficult to find any group of authors who will agree on the microscopical picture as such and I must agree with Levitt (1) when he suggests that - "the terms Hashimoto's and Riedel's diseases be dispensed with altogether as they are non-descript". To reach this conclusion we must work up to the present concepts just as it has developed throughout the years.

Confusion is noted early by the numerous types of terminology used by various authors discussing this entity.

Temple (2) discussed a case in 1868 which may well have been typical of Riedel's cases, but which he called "Fibroid enlargement of the thyroid". Again in

1885, Bowlby (3) describes a case of "Infiltrating fibroma (? sarcoma) of the thyroid". Riedel (4) did not report his cases until 1896 and he termed the condition "eisenharte (ironhard) strumitis". Cordua (5), at the same meeting told of a similar case in a twelve year old girl, in whom it was not possible to resect the gland completely. Since that time the following authors have discussed and labeled cases supposedly similar to those first recognized as a separate entity:

1. Tailhefer 1898 (6) Inflammation Chronique Primitive Canceriforme
2. Ricard 1901 (7) Degeneratione Fibreuse du corps Thyroide
3. Berry 1901 (8) Primary Chronic Inflammation
4. Silatschek 1910 (9) Eisenharten Strumitis. (Peri-strumitis Indurative)
5. Spannus 1910 (10) Riedel'sche Struma
6. Delore and Alamartine 1911 (11) Thyroidite Ligneuse Canceriforme
7. Murray and Southam 1912 (12) Ligneous Thyroiditis
8. Meyer 1913 (13) Thyroiditis Chronica Maligna
9. Heineke 1914 (14) Chronische Thyroiditis
10. Nicholason 1921 (15) Woody Thyroiditis
11. Ewing 1922(16) Benign Granuloma
12. Thomas and Webb 1923 (17) Chronic Thyroiditis (Primary)
13. Monod and Monod 1923 (18) Thyroidite Ligneuse Chronique

14. St. George 1924 (19) Chronic Productive Thyroiditis
15. Hahn 1925 (20) Non-suppurative Chronic Thyroiditis
16. Meeker 1925 (21) Riedel's Struma
17. Shaw and Smith 1925 (22) Riedel's Chronic Thyroiditis
18. Smith and Clute 1926 (23) Chronic Ligneous Thyroiditis
19. Heyd 1929 (24) Benign Granuloma of the Thyroid
20. Bruce 1931 (25) Thyroiditis Simplex (Riedel's Tumor)

Various theories have been proposed concerning the etiology and many have been disproved but the controversy still reigning over just what constitutes Riedel's struma has confused the issue immensely. The following list constitutes the avenues of thought by a multitude of authors in regards to etiology:

- I. Local Infection of Thyroid
- II. Systemic Infection Affecting Thyroid
- III. Cachectic Conditions
 - (a) Carcinoma
 - (b) Leukemia
- IV. Acute Thyroiditis
- V. Non-bacterial
- VI. Perithyroiditis
- VII. Biochemical Irritant

- VIII. Abnormal Response of Thyroid to Stimulus
 - (a) Decreased Vitality of the Thyroid
 - (b) Exhaustion
 - (c) Oxidation
 - (d) Circulatory
 - (e) Trauma
- IX. Exophthalmic Goitre
 - (a) Graves' Constitution
 - (b) BMR
 - (c) I¹³¹
 - (d) SPT
 - (e) Iodine Therapy
- X. Strumitis
- XI. Constitutional
 - (a) Dietary Deficiency
 - (b) Addison's Disease
 - (c) Simmond's Disease
- XII. Lymphoid Hyperplasia
- XIII. Lymphadenoid Goitre
- XIV. Chronic Primary Inflammation
- XV. Granuloma
- XVI. Associated with Adenomata
- XVII. Cirrhosis and Fibrosis
- XVIII. Fibroma and Fibroid

- XIX. Lymphosarcoma
- XX. Hodgkins' Disease
- XXI. Mickulicz' Disease
- XXII. Scirrhus Cancer
- XXIII. Cancer
- XXIV. Embryologic
- XXV. Psychogenic

It would be most difficult to discuss these theories in chronological order, therefore they will be discussed as they are previously categorized.

LOCAL INFECTION OF THE THYROID GLAND:

Some of the earlier pathologists were prone to call Riedel's chronic thyroiditis a local manifestation of potential systemic diseases. Poncet et al (26) in 1901 expressed the view that some cases were actinomycotic in origin although cultures at the time of operation, and animal inoculations, yielded no clues as to the cause of the inflammatory process. Crotti (27) also felt that Mycosis and especially Actinomycosis might be the factor in some cases. Leptothrix was incriminated by Meeker (21).

Bohan (28) reported a case of ligneous thyroiditis associated with a high-grade dental infection. Cultures showed colonies of green-producing strepto-

coccus and staphylococcus. Injection of rabbits with his culture resulted in only extensive hemorrhages of the thyroid and thymus glands. Searles and Bartlett (29) cultivated *Streptococcus viridans* from the isthmus of one of their cases. They also obtained an identical organism from the patient's throat. Graham (30) expressed the belief that Riedel's struma is a local inflammation in the thyroid, the general body state being affected only secondarily by reason of destruction of thyroid tissue, respiratory difficulty, or injuries to important blood vessels and nerves. Later Graham and McCullagh (31) state that Riedel's more nearly approaches a true inflammation (vs. Hashimoto's). Gerlak (32) found staphylococci and streptococci in both smears and cultures. Tearnan (33) merely called it a local infection, while McQuillan (34) states that *Staphylococcus aureus* and *albus*, various streptococci and colon bacilli have been reported. Schilling (35) believes it to be a bacterial inflammation. Richard (36) reported six cases in which a dental infection was an important etiological factor. Patterson and Starke (37) reported cases following osteomyelitis of the jaw, an upper respiratory infection, and one case following a tooth extraction.

deQuervain and Giordanengo (38) found that the introduction of bacterial toxins into the general and thyroid circulation produced a picture resembling Riedel's. A pure culture of bacteria into the artery of the thyroid could pass through without effects or might cause the disappearance of colloid, desquamation of the epithelium and leucocytic infiltration.

Brayton (39) believes that the etiology of Riedel's is a local manifestation, and Allen and Reeves (40) report that 70% of their cases had previous histories of an upper respiratory, dental, or other accompanying infection, and at times there was a cervical adenitis. Others have also attempted to associate the process with an oral or upper respiratory infection (41, 42, 43, 44, 45, 46). Graham (30) in an excellent review of the literature states that Riedel's struma "may be looked upon as having a local inflammatory process in the thyroid for which an etiological factor should be sought". He contends that the thyroid is situated so that complications can occur more readily than in other organs with the same condition. Berengo et al (47) state that hyperfunction of the thyroid lowers the natural resistance of the organ to infections - septicemia may give rise to mild connective tissue reactions.

Pratti (48) in 1931 discovered an unidentified bacillus, and an unidentified diptheroid was cultured in one of the cases to be reported in this paper (1953).

VIRUS:

Tucker and Gertz (41) remarked on the microscopic picture in Riedel's struma in regards to its resemblance to a viral involvement (such as Hodgkins' disease). Lea (49) believes that the condition may be viral and is therefore susceptible to X-radiation. Several cases responded to such treatment. It is Criles' (50) contention also that thyroiditis is viral and follows upper respiratory infections of virus etiology.

Other authors have merely classified Riedel's struma as a non-specific, or unspecific, thyroiditis. (13, 16, 21, 22, 37, 51, 52, 53, 54, 55). Some authors classify other chronic thyroid manifestations (lymphadenoid goiter) as an unspecific thyroiditis (56, 57, 58, 59, 60).

SYPHILIS AND TUBERCULOSIS:

Many authors have attempted to associate the condition with syphilis and tuberculosis because of the microscopic findings which in some instances resemble these lesions elsewhere in the body. Kuettner (61) in 1898 was the first of these proponents. Delore and

Alamartine (11) state - "Dan quelque cas il pent s'agir de lesions tuberculeuses (tuberculose inflammatoire de M. Poncet) ou syphilitiques mais le pluse souvent la cause semble bien etre une infection banale de nature inconnue." Monod and Monod (18) note that this condition is "probablement d'origine syphilitique". But the Wasserman tests were negative and they could not demonstrate spirochetes even with Levaditi preparations. They concluded that "La maladie de Riedel n'est pas un goitre fibreux, ni essentiellement une thyroidite, mais une affection a point de depart trochial, d'origine tres probablement syphilitique, une sorte de syphilome laryngo-trachial". Simmonds (62) reported several cases associated with syphilis. Poncet et al (26) endeavored to reproduce the disease experimentally in animals, using spirochetes, but was unsuccessful. Roger and Garnier (63), Plummer and Broders (64), Kuettner (61), Creite (65), Nicholson (15), and Weglin (56) were influenced to regard, as tuberculous, some thyroid glands because of the giant cells seen microscopically. Creite called them "interfollicular tubercules" in spite of the fact that the patient was free of tuberculosis elsewhere and did not develop tuberculosis within the five years following (66).

Proof against Lues and tuberculosis was supplied not only by Poncet as previously described, but also by Warthin (67) who stated that tuberculosis is never primary in the thyroid, while Pulford (68) states that neither syphilis nor tuberculosis are ever primary here. White (69) concludes that Riedel's bears no relation to these two diseases while German (70), after a careful analysis of material and the application of special methods to granulomata occurring in the thyroid, has shown that this gland is one of the areas where true tuberculosis is unlikely. Based on his own experimental evidence, Distefano (71) in 1952 concluded that Riedel's does not originate from a tuberculous process. On the other hand, Kocher (72) and Marine (73) state that thyroiditis is never primary.

SYSTEMIC INFECTIONS:

Chronic thyroiditis supposedly has been preceded by a multitude of other systemic infections:

Grip and Influenza - 19, 31, 53, 54, 56, 74,
75, 76, 77, 78

Tonsillitis - 19, 21, 74, 78, 79, 80, 81

Peritonsillar Abscess - 76

Alveolar Abscess - 76, 78, 79, 81

Erysipelas - 76

Parotitis - 76
Acute Articular Rheumatism - 76, 82, 83
Diphtheria - 76
Measles - 54, 76
Scarlet Fever - 76, 84
Typhoid Fever - 54, 76, 79
Bronchitis - 54, 76
Pharyngitis - 29, 72, 79, 85, 86
Pemphigus - 87
Angina - 54
Acute Appendix - 54
Rheumatic Fever - 88

Simpson (89) states that chronic thyroiditis is the result of an invasion of pathogenic micro-organisms such as streptococci, staphylococci, etc., from a definite focus of infection elsewhere in the body. Eberts and Fitzgerald (90) had previously stated however that "for lack of fuller knowledge ligneous thyroiditis (described by Riedel as "eisenharte strumitis, etc.") it is included in the group of specific infections". (i.e. tuberculosis, etc.)

Wallis (91) states that, in the material studied, considerable evidence was found which pointed toward a bacterial cause. He also stated, however, that some

infections preceded the thyroiditis by several years and that the cause of chronic thyroiditis was probably a bacterial-toxin reaction.

CACHECTIC CONDITIONS:

Sokoloff (92) in 1895, and Muller (93) in 1896, independently showed that in acute infectious diseases, fatty degeneration of the acinar epithelium occurred with desquamation. Rodger and Garnier (63) reached similar conclusions, as did deQuervain (94) and Sarbach (95). Loeper and Esmonet (96) found the same basic changes in cachectic conditions such as carcinomatosis, tuberculosis, and leukemia. Howard (91) reported a case with syphilis, tuberculosis, carcinomatosis, Addison's disease and Hashimoto's disease.

RESULTS OF ACUTE THYROIDITIS:

Many of the authors mentioned above believe that chronic thyroiditis may be the end-result of acute thyroiditis which is caused by an infectious process elsewhere (77, 78, 97, 98).

In-so-far as actual bacterial studies are concerned there are very few detailed reports. This is probably a result of the fact that very few cases of Riedel's struma are diagnosed preoperatively, and by the time that the diagnosis is made, the tissue is contaminated.

NON-BACTERIAL INFLAMMATION:

Womack (99) concludes that "chronic degenerative thyroiditis" is an inflammatory process with a non-bacterial origin. In his work done with Cole (100) cultures of glands were, for the most part, sterile and thyroid changes were not discernible when they injected bacteria directly in the superior thyroid arteries of dogs and rabbits. Previously Smith and Clute (23) had attempted a culture of one of their cases but were unsuccessful (neither bacteria nor spirochetes). They inoculated both filtrate and emulsified material directly into animal thyroids and noted no changes in the animals receiving filtrate alone, but necrosis and fibrosis in those receiving actual emulsified material. Perman and Wahlgren (101) reported an operation for Riedel's disease in a chronic, partly suppurating and necrosing thyroiditis, while others (32, 48, 102, 103, 104) found necrotic areas and small abscesses in cases similar in many respects to Riedel's. Maloney (103) says cases never go through the stage of acute infection, bacteria are not found in the gland, and that culture and animal inoculation are always negative. Young (105) has also stated that cultures of the specimens are almost always negative. Conklin and Hall (106)

and Lyons (107) are of the opinion that acute cases do not become the subacute or chronic, and subacute does not become chronic. On the other hand, Wegelin (56) had shown positive thyroid cultures for bacteria in the absence of any inflammatory change in the gland. Burhans (108) believes that there is doubt as to a true inflammatory nature of Riedel's struma.

PERITHYROIDITIS:

One of the newer theories which meets our eye is that proposed, and apparently well studied, by DeCourcy (109, 110, 111). It is this author's contention that Riedel's struma is not a primary disease of the thyroid gland at all, but begins as a perithyroiditis. He believes that the fibrous growth begins outside the thyroid gland proper, the adherent muscles causing a constriction of the thyroid vessels with resulting ischemia of the gland. Fibrous changes follow the ischemia in a manner similar to the Goldblatt Kidney. According to this author, Riedel's may develop within a matter of weeks after a perithyroiditis (which may be so mild as to escape diagnosis) "and its onset has probably been diagnosed by others as acute non-suppurative thyroiditis". Earlier King (79) stated that he wished to call some aspects of thyroiditis "progressive or migratory"

because he observed in one patient progression of a hard, inflammatory area gradually creep down one lobe, cross the isthmus and invade the opposite lobe, then regression. Two of his cases, however, did not regress and were described histologically as Riedel's.

BIOCHEMICAL IRRITANTS (COLLOID):

Wilke (112) was one of the few authors who concerned himself specifically with the origin and function of the giant cells associated with chronic, non-specific thyroiditis of the Riedel type. He said they were produced by irritation of the colloid acting as a foreign body and described the apparent erosion of the colloid in them. Reist (113) and Joll (114) expressed the same opinion. In experiments to determine the reaction on connective tissue of sterile dehydrated colloid from the human thyroid gland, Ferguson (115) in 1933 produced reactions which had striking resemblance to the lesion produced by the tubercule bacillus. Fibrosis without necrosis was prominent within 6-8 days. Earlier examination of the tissues revealed many new fibroblasts at peripheral fields of the area of injection while the center of the lesion consisted of giant cells, polymorphonuclear leukocytes, lymphocytes and thrombosis of the small veins. He concluded that his

experimental study "appears to show that such inflammatory structures occurring at times in human thyroid glands are caused by fatty acids. The fatty acids are formed in disintegrating follicles as a result of hydrolysis of the lipid content of the colloid and of the epithelium". Opler (116) reached a similar conclusion after alcohol injections, into the thyroid gland of dogs, produced epithelial giant cells "resembling those seen in Riedel's". He regarded them as resulting from foreign body irritation by the colloid, as did Hellwig (117). "There are times in which an inflammatory reaction to colloid is most marked, and whether the colloid undergoes a chemical change as suggested by Mallory (118), the reaction seems to be related definitely to its fatty acid content as has been demonstrated by Ferguson." (99)

INTERNAL THYROID SECRETION:

It was the conclusion of McKnight (119) that "Riedel's thyroiditis is an inflammatory reaction to some biochemical irritant, probably an abnormal type of thyroid internal secretion - differing from that produced in or causing exophthalmic goiter". Hellwig (120, 121) reaches a similar conclusion but thinks that the stimulus may be an excess of thyrotropic hormone.

Chesky et al (122) concludes that "an excess of thyrotropic hormone seems to be the most important etiological factor" causing lymphocytic infiltration after colloid macrophages disintegrate. "There are only quantitative differences between the severe grades of thyroiditis (Riedel's, Hashimoto's, and deQuervain's type) and the localized foci of thyroiditis in exophthalmic goitre and nodular goitre".

CHEMICAL POISONS:

Chemical poisons such as phosphorous and silver nitrate cause a toxic thyroiditis with a histological picture resembling Riedel's but with less fibrosis (35). German (31) has discussed sclerosis as being caused by intoxication and relates it to this condition. McKensie and McKensie (123), Astwood et al (124), and Shirer et al (125) found thyroid intoxication from thiouracil which gave a histologic picture similar to Riedel's. Richard (36) believes that there may be some relation between the toxic symptoms in various infections and the "much contested detoxicating effect of the thyroid gland".

ABNORMAL RESPONSE TO STIMULUS:

That Riedel's struma may be an abnormal response on the part of the thyroid gland to a stimulus is a

relatively new concept. Connor and Searles (126) in 1930 believed that there was some abnormality residing in the acinar epithelium (intrinsic) which could produce chronic thyroiditis. Parmley and Hellwig (127) stated that lymphadenoid goiter (a form of chronic thyroiditis) was due to a disturbance of the normal cycle of thyroid activity. Marshall et al (128, 129) expressed the opinion that one cause of thyroiditis was a reaction to injury or irritation.

DECREASED VITALITY:

Heyd (24) was probably the first of several authors to question the normal physiologic factors involved in the thyroid gland prior to disease. He wondered if the condition might not be related to a decreased vitality of the gland. Meeker (21) made similar comments but both authors had reference to embryologic remnants which will be discussed later. Pedigo and Abramson (130) state that the result is due to the gland burning itself out due to the demands of the body. Graham (31), and McClintock and Wright (42) had previously discussed the possibility in regards to burned out toxic goitres.

EXHAUSTION:

Along this same line are those writers who attribute the disease process to exhaustion of the gland.

Marine (73) described cases of thyroid pathology as "exhaustion atrophy" with advancing sclerosis which very closely resembles the microscopic picture of Riedel's struma. Graham and McCullagh (31) commenting on the sclerosis of Riedel's thyroiditis say that "the fibrosis may be looked on as the natural result of atrophy and degeneration of glandular tissue". An abnormal response of the thyroid to physiologic demands produces histologic changes which, to Zelle et al (131), represents exhaustion atrophy as well as regeneration of thyroid parenchyma - "the inflammation and fibrotic changes are secondary to this process".

Williamson and Pearse (132), in discussing the etiology of lymphadenoid goiter (Hashimoto's), believed that the cause was an abnormal involution of the thyroid - a failure of hyperplasia. German (70) states that the microscopic picture of Riedel's struma suggests a degenerative process at work over a period of years. "The usual explanations for the sclerosing process are (1) exhaustion from overwork with an adequate period of recovery, (2) interference with nutrition as a result of circulatory or trophic disturbances, and (3) intoxications. All of these have as a primary effect degenerative changes in the cells or tissue and fibrosis follows."

OXIDATION:

Jarvis (133) was able to show that the size of lymphoid tissue in the upper respiratory tract was related to oxidation. He therefore concluded that this may be related to Riedel's struma in the early stage.

CIRCULATORY:

deQuervain (94) and Kocher (72) were interested in the circulatory mechanism involved in this disease process. They expressed the opinion that the frequently existing condition of reflex hyperemia of the thyroid gland in the female sex (menses, gravidity, menopause) enters into consideration as a predisposing factor for chronic thyroiditis. St. George (19) was of the opinion that the condition was a result of organization following hemorrhage, i.e. hemorrhage into the thyroid as a result of disease or trauma to a vessel, with subsequent "replacement fibrosis in a manner analagous to the development of a fibroid". We have already mentioned German's (70) opinion in favor of trauma.

TRAUMA:

In two of the one hundred cases reported by Wallis (54), indirect trauma followed by slight bleeding preceded the involvement. In one the swelling occurred soon after strenuous and continuous vocal effort; in the oth-

er it followed an attempt at strangulation. Schoninger (134) reported the case of a girl who, after lifting a heavy weight, felt a sharp pain in the thyroid with subsequent development of strumitis. Kocher states that men who carried heavy loads on their heads, and Army officers who had to shout orders while their uniforms fitted too tightly were prone to strumitis. Marshall (129) reaffirmed that Riedel's struma was the end stage of infection, but he also stated that the reactions may be due to irritation or to trauma, neither of which was defined.

EXOPHTHALMIC GOITRE:

Proponents of the theory that chronic thyroiditis is an end-product of previous enlargement or hyperplasia have been many. All authors are in agreement that the normal functioning and healthy thyroid gland falls prey to inflammatory processes far less often than does the gland showing nodular generation. The theories advanced to substantiate this claim are, that in the latter, either the glandular secretion of the thyroid has become weakened, has lost its normal power of immunity and can no longer kill invading bacteria, or that the normal resistance of the organ to generalized infection has been lowered. deQuervain (135) expressed the opin-

ion that the nodular form of enlargement of the thyroid gland is especially amenable to the settlement of bacteria which produce inflammatory lesions, first because of the necrosis of the tissue which often takes place in these nodules and, secondly, because of the frequent occurrence of spontaneous bleeding. According to this author, even a lesser change in the thyroid gland, such as a slight diffuse hypertrophy, can cause a predisposition to inflammation of the gland.

When Riedel first described the entity which bears his name, he discussed the condition as "eisenharter tumoren" (1896) and his second case the following year as "chronischer Strumitis" (136). "Chronic strumitis implies chronic inflammation superimposed upon a goitrous condition" (86). Eberts and Fitzgerald (90) also state that an inflammatory lesion of the normal gland produces thyroiditis while if in a goitrous gland it produces strumitis. According to Kocher (72), goiter should be regarded as a prerequisite for strumitis or thyroiditis.

Apparently Brunger (137) and Gurken (138) were the only authors who found full-blown exophthalmic goiter and its symptoms associated with chronic thyroiditis but other authors (139), (140), and (141) were of the

opinion also that chronic thyroiditis was the result of previous exophthalmic goiter. In one case reported by Berry (142) the patient had a goitre and a family history of goitre. Warthin (67) believed that the etiology was a constitutional factor with a Grave's constitution underlying both toxic adenoma and exophthalmic goiter. Crane (81) reported that 25% of his cases had previous symptomless goiter (5-15 years with 9 year average). That a pre-existing constitutional abnormality was the cause of a secondary inflammatory reaction was proposed by Boyden (143). Wallis (54) reported 76% of his cases had a history of previous enlargement while of Goodman's cases (144), 30% had a history of pre-existing goitre. Nordlund's (145) case of Riedel's was associated with a history of "goitre" for more than 20 years. Vaux (146) believes that the cause is an excessive involution following mild thyretotoxicosis. She believes that this involution is comparable with the changes in other glandular organs such as breast, prostate, and ovary, and that some disturbance of the balance of secretions of the ductless glands may initiate the condition. The discrepancy, here however, is the fact that many patients are much too young to be considered in this category. She also states that in some instances it may

well be that a non-specific chronic inflammation is superimposed. One of the cases she presented had had a goitre for 19 years. Marshall (129) says that the "so-called exhaustion atrophy of the thyroid gland is a state that presumable follows overactivity". Beattie et al (147) believe that some examples of Riedel's struma may represent a final state of a primary hyperplastic (primary exophthalmic) goitre - "as a result of exhaustion (lymphadenoid goitre) there may be degeneration and general atrophy of the epithelium". Hertz (104) presented two cases with a history of goitre for 15 and 6 years. German (70) states that all of his cases were residents of Michigan, an endemic goiter area, and he believed that the etiology was prolonged ingestion of iodine in individuals of the Grave's constitution type.

As early as 1898 Tailhefer had made the same observation. Kisner et al (148) however state that thyroiditis is more common in the Gulf States than in other parts of the United States. "That thyroiditis appears to be more common in the Gulf area is more likely explained by the fact that thyroiditis occurs independently of goitre and since the Gulf area is not endemic goitre area, the number of goitres is reduced while thyroiditis is not." (Lyons 107). Lundbaek (149) quotes the case

of Braendstrup (150) and the opinion of Bastenie (151) that this disease may follow an "extinct" exophthalmic goitre. Rabson and Arata (152) state that "in the involutinal history of goiters of persons with the Grave's constitution, a sequence beginning with lymphoid hyperplasia may be identified as follows: lymphadenoid goiter, struma lymphomatosa (Hashimoto's) and struma fibrosa (Riedel's). The involution may stop with any level, either temporarily or permanently". Goetsch (55) reaches the same conclusion, i.e. "Riedel's is the terminal phase - nature's way of curing hyperthyroidism". Levitt (153) suggested that the toxic thyroid gland undergoes a gradual transition from the epithelial hyperplasia, focal and then diffuse lymphoid hyperplasia and fibro-lymphoid hyperplasia to the final stage of fibrosis. Rienhoff (154) points out that in their series, 23% had goitre from one to seven years, while 40% of all the cases described up to 1925 had goitre. DeCourcy (111) however, states that "In general, the history discloses no evidence of previous involvement or dysfunction of the thyroid gland, and it is therefore unlikely to be a degeneration of a previously enlarged gland, either hyper or hypothyroid."

The preceding author does say that the B.M.R. in Riedel's is normal or slightly elevated. Cases reported by Bohan (28), Schultz (52), Tucker and Gertz (41), Wingate (155), Bothe (156), Diez (157), Hori (158), and this author (1953) have shown mild toxic symptoms with a moderate elevation of B. M. R. Crane (81) and McQuillan (34) believe that a definite indication of hypothyroidism strongly favors thyroiditis. Whitesell and Black (159) have found that with greater degrees of fibrous replacement the B.M.R. was lower, while Cameron (160) presented two cases of definite Riedel's with hypothyroidism and two cases of Hashimoto's with hyperthyroidism.

McConahey and Keating (161) found that the thyroid accumulation of I^{131} was usually normal in patients with chronic thyroiditis, while Peters and Mann (162) report that a high S P I (serum precipitated iodine) is found in hypothyroidism.

IODINE THERAPY:

Many authors, over the years, have felt that iodine therapy was probably one of the primary causes of the fibrosis and giant cell formation seen in chronic thyroiditis. Von Werdt (163) in 1911 first posed this question and Reist (113) brought out the same idea. Warthin (164)

has been one of its greatest proponents. Iodine therapy in his opinion results in many cases of diffuse lymphoid infiltration and a proliferation of the stroma presenting the picture of Riedel's struma. He was referring to the microscopic picture seen in the case of adenomatous goitre treated by Lugol's with "unfortunate clinical results in the form of so-called iodine hyperthyroidism". He reiterated this fact again in 1930. (67). Payr (165), Roulet (166), and Krenzbauer (97) mentioned the ingestion of iodine in some cases as a possible factor in the production of the disease. Orywall (167) produced a histological picture in iodine-fed mice, which he believed was similar to a chronic thyroiditis. Boyden et al (145) discuss several cases of which three had previous iodine medication and which they believed was largely the cause of Riedel's, but not the sole etiological factor. However, they bring out the point that Lugol's solution was developed after Riedel's struma had been described (168). Wallis (54) reported 14 cases that could be traced back to toxic origin and all had been taking therapeutic doses of iodine over a period of years. Three of the cases reported by Brayton (39) had had Lugol's solution and each was diagnosed as a different

phase of chronic thyroiditis (i.e. Hashimoto's, Giant Cell, chronic).

That iodine could not be the instigating factor was expressed in 1938 when Jarvis (133) was able to cause complete regression of a "golf-ball sized" tumor diagnosed as Riedel's struma by the use of iodine and insulin as oxidizing catalyts. DeCourcy (110) stated that iodine was not the cause of Riedel's because some of his patients had never had iodine. Gurkan (138) felt that the histological changes observed by Orywall (167) in his experiments could not be compared with the structure of Riedel's "goiter".

CONSTITUTIONAL - DIET:

That a dietary deficiency was an important etiologic factor in the production of lymphadenoid goitre was well established by McCarrison (169) in 1929 by experimental work on young rats. His diet contained an abundance of iron, and was made up of white flour (American) primarily. Goitres occurred in 25% of the young rats and he believed that, in view of the almost universal use of white flour as the main staple of the dietary in Western countries, of the widespread use of vitamin-poor carbohydrate foods, of substitutes for butter which are relatively poor in Vitamin A, etc.,

the observations were significant. Lasser and Grazzell (170) were also of this opinion as far as lymphadenoid goitre was concerned. Hellwig (120) reported that a calcium rich diet would produce goitre in rats.

OTHER DISEASE PROCESSES:

Other constitutional factors considered in this controversial subject have been suggested. Shaw and Smith (22) reported one case of Riedel's struma with analagous changes in the adrenal glands of a patient with Addison's disease. They suggest that it may be an expression of some disease affecting the ductless gland system in general. In 1937 Jaffe (58) reported four autopsy cases - all women who had undergone long and debilitating diseases and who had other changes identical to those seen in adrenal cortex insufficiency. Lasser was also of the opinion that this was the etiology of Riedel's. Vines (171) reported that 20% of the cases of Addison's disease, due to primary atrophy of the adrenal cortex, are also associated with fibro-lymphoid changes in the thyroid.

Ollgaard (172) reported a patient who had died of Simmond's disease with atrophy of the pituitary gland. This patient also had a moderate goitre of the Riedel type but "it is impossible to decide whether thyroid-

itis was a consequence of the lesion in the hypophysis or a cryptogenetic disease of the thyroid gland".

Simmonds (83) in considering the etiologic relationship between Basedow's disease and chronic inflammation of the thyroid concluded that the lymphoid infiltration was a primary replacement of disintegrated thyroid parenchyma by lymphoid tissue. Cases in which autopsy revealed generalized lymphoid hyperplasia caused Crile (173) to suggest a morbid condition of the entire lymphoid system was involved in "early chronic thyroiditis". Pulford (68) states emphatically that the type of inflammatory reaction seen in hyperfunctioning thyroid glands is mostly a lymphoid tissue increase and never a fibrous tissue replacement as described by Riedel. This point has actually been the center of many studies in the pathological picture of Riedel's, for it is a well-founded contention that many authors are discussing Hashimoto's disease and referring to it as Riedel's struma. Watkins (174) has said that "what has been called thyroiditis by many pathologists is probably only an expression of lymphatism". Warthen (164, 67) emphasized the fact that the most constant and striking finding in the pathology of exophthalmic goiter is the hyperplasia of large germ centers showing

lymphoid exhaustion characteristic of the thymicolymphatic constitution.

LYMPHADENOID GOITRE:

Williamson and Pearse (132) in their classification of chronic thyroiditis, described, as an early phase of Riedel's struma, an entity which they term lymphadenomatous goitre. McCarrison's experiment previously described produced a microscopic picture which was very similar to this term as proposed by the above authors. Ewing (175) also uses this terminology while, in a previous edition, he had discussed the same case under the title of benign granuloma (16).

Most of the authors have looked upon the condition as a result of a chronic inflammatory process (11, 12, 18, 22, 43, 45, 68, 81, 139, 144, 148, 155, 156, 176) but the agent causing the reaction is still admittedly obscure. In an excellent article on the relationship between chronic thyroiditis and "the peculiar rare conditions designated as Riedel's struma, Hashimoto's struma, and Williamson and Pearse's lymphadenoid goiter", Lundbaek (149) states that presumably a chronic inflammatory process (chronic thyroiditis) is the underlying factor in most cases of Riedel's struma. Patterson and Starkey (37) are also of this opinion.

Crile (177) enlarges somewhat by calling it a chronic, proliferating, fibrosing, inflammatory process.

GRANULOMA:

Several authors have referred to this process as a nonspecific granuloma (13, 16, 21, 52). Shaw and Smith (32) observed plasma cells in a larger number than are found in lymphoid tissues and felt that this excess speaks for an inflammatory process as does the extension beyond the capsule, the spontaneous recession of the tumor and retrogression after complete or partial thyroidectomy. Smith and Clute (23) state that the giant cell formation is an inflammatory condition similar to the proliferative hyperplasia which we see in syphilis, tuberculosis, and other granulomatous lesions, while Wingate (155) refers to it as a non-tuberculous granuloma. Heyd (24) terms this condition "a granulomatous strumitis". Lester (178) reports this disease as a benign granuloma, as does Goodman (144) and Konzelman (179).

ADENOMATA:

Watkins (174) was the first to observe and report that "aside from that caused by definite infective processes such as tuberculosis, syphilis, etc., the only true chronic nonsuppurative thyroiditis is that seen in

the thyroid tissue in the neighborhood of adenomata and is combined with evidences of pressure atrophy of the acini". Bruce (25) reported a case which he termed "Thyroiditis simplex (Riedel's)" but states that the gland was filled with small adenomata. deQuervain and Giordanengo (38) have also expressed such an opinion. Fox (180) reports that frequently the objective signs of long-standing goitre are either those of a diffuse adenoma or as adenomatous nodules. Both cases reported by Case (181) had adenomas, while Crile (177, 182, 183) states that in many instances the inflammatory reaction appears to center about a degenerating adenoma (7 of 11 cases). Greene (184) states that a gradation may be traced histologically between the thyrotoxic gland with a single nodule and the characteristic picture of Hashimoto's disease.

FIBROSIS AND CIRRHOSIS:

The histological picture of Riedel's struma appears to the perfectionist type of pathologist to be one of fibrosis or cirrhosis. Riedel (4), Tomaselli (185), and Crotti (27) discuss the entity as a type of cirrhosis. Recurrences of thyroid cirrhosis have been reported by a number of authors (24, 35, 42, 101, 104, 166, 186, 187). Hertz (104) and Sheehan and Summers (188),

like Simmonds (62) and Rienhoff (189), lists the chronic forms of thyroiditis under the general heading of cirrhosis. Clute and Smith (23) compare the fibrotic processes in the thyroid to chronic progressive fibrosis seen in the liver and kidney.

FIBROID:

In 1868 Semple (2) described a pathologic picture which resembles what today we call Riedel's. He discussed the case as a "fibroid enlargement of the thyroid body". (Lee et al (190)). His patient developed tuberculosis and apparently died. The microscopic description was that of tissue made up of dense fibrous tissue, but the enlarged lymphatics "appear to be Lymphosarcoma as described by Virchow". Bowlby (3) in 1885 commented on a case of fibrosis of the thyroid which looked benign but because of the clinical picture he called it an infiltrating fibroma or sarcoma. Grossly it was stony hard and "was of such a nature as to suggest cartilage or bone".

LYMPHOSARCOMA:

Ricard (7) concluded "_____ mi d'une sclerose thyroidienne, sorte de cirrhose glandulaire _____ mais d'un fibrome adulte a evolution lente". Loewy and Loeper (191) in 1899 thought that the lesion was com-

parable with a "fibromyome uterin" although the clinical picture was that of lymphosarcoma.

The abundance of lymphocytic elements in this condition has led several authors (30, 192) to conjecture concerning its relationship and possible transition to lymphosarcoma of the thyroid. Lester (183) reports a case which was diagnosed as a malignant tumor, on frozen section as a lymphosarcoma, and a final diagnosis of a benign granuloma or Riedel's. Graham (30) and later Patterson and Starkey (37) reported cases (one each) which they believed had gone from Riedel's struma to lymphosarcoma.

Mention has already been made in regards to Tucker's (41) suggestion that the histological picture in Riedel's was similar to that seen in Hodgkins' disease. Goodman (144) in 1941 noted (in one case) a histological picture of plasma cells and eosinophiles similar to that seen in Hodgkins' disease, except for the absence of Sternberg cells.

MICKULICZ' DISEASE:

Tebutt et al (139) reminded us that the characteristic histological picture in chronic thyroiditis is not necessarily the prerogative of this gland, "for it appears that Von Mikulicz's disease of the lachrymal and salivary

glands present a similar lesion", which has been described by Von Mikulicz (193) in 1886 and Kuettner (61) in 1898. Tebutt had also seen a similar lesion in an atrophic calculous kidney. Riedel has described a fibrous, sclerotic process of the pancreas similar to the lesion of the thyroid. The same sclerotic process is known, too, in the digestive apparatus, especially in the stomach and gall-bladder. Willer (194) comments however that although "thyroid sclerosis" is reminiscent of Mikulicz's disease, the course of chronic thyroiditis resembles that of Laennec's cirrhosis.

CANCER:

That the lesion could be truly cancerous has been mentioned in the literature. Riedel (4) assumed his first case to be a malignant goitre grossly because it was so extremely hard and immovable, but he concluded "we had plainly to deal with an inflammatory process .." Sitalschek (9) and Balfour (195) diagnosed their cases as cancer, while Sibilleau (196) in 1911 stated that he had presented his case to the students as an example of "cancer thyroïden". Rienhoff (154) reminds us that, even at Johns Hopkins in the past twenty years, 81.2% of the cases are diagnosed preoperatively as malignant. Poncet (26) and Von Eiselsberg (197) discussed the process as

scirrhous cancer of the slow growing type. Clute and Lahey (78) reported one case which was diagnosed as Riedel's and later turned out to be malignant. The second case reported in this paper was reported as both Riedel's and malignant.

On the other hand Bernard and Dunet (198) state that Riedel's struma is never associated with cancer (but infections may be a factor in other parts of the body to stimulate cancer). (Stout, 199).

EMBRYOLOGIC:

Embryologic considerations were first encountered by Heyd (24) when in one of his cases he noted post-bronchial bodies (solid cell nests). He proposed that they might be incriminated in the process of extracapsular extension. These had previously been found only in cretins with myxedema and for this reason he proposed that Riedel's struma might be related to decreased vitality of the gland. Meeker (21) reported a similar case and proposed that, since post-bronchial (ultimo-bronchial body) remnants are found in human embryos, in athyriosis, and in cretins, and have not been found in normal adult thyroid glands, thyroids containing such rudiments may be of low vitality. In this condition a stage of exhaustion could be rapidly

reached and the gland would be particularly susceptible to the extreme form of atrophy and fibrous replacement seen in Riedel's struma. An instance of Riedel's goitre in aberrant thyroid tissue has been described by Rienhoff and Hertz. Demme reported a congenital strumitis (200).

PSYCHOGENIC:

The ever present psychic element turned up in 1928 when Eason (141) noted that "the emotional element alone is the most frequent (cause of goitre); in the course of the disorder so begun, trival infections may assist in instituting inflammatory processes (or without infection go to hypertrophy and hyperplasia)". Davison et al (201) in 1949 commented - "it is interesting to note that all of our patients claim to have had some emotional upset prior to the onset of the goiter".

We have now discussed the theories of the etiology of Riedel's struma, and it is apparent that we cannot come to a definite conclusion as to the most important etiologic agent. This statement is not strictly true however, for first we must decide just what constitutes the entity that was first described and later named after Riedel. For in this conglomeration we have not only discussed the etiology of Riedel's struma, but also

in part the etiology of Hashimoto's lymphomatosa, Williamson and Pearse's lymphadenoid goitre, deQuervain's giant cell thyroiditis and several other divisions of chronic thyroiditis. In other words, I have endeavored to discuss the etiology of an entity which may actually not exist as such. Certainly Riedel had a definite characteristic process in mind when he first reported "eisenharte struma" in 1898, and Hashimoto (202) had a different concept of his cases which he reported in 1912, but since that time most authors have had trouble in deciding who described what. So let us review the literature again to see if our problem can be more clearly elucidated. Since Graham (30) alone, and later (31) with McCullagh, separated the diseases described by Riedel and Hashimoto, significant contributions by Clute et al (203), McClintock and Wright (42), Joll (114), Harry (43), McSwain, Barton, and Moore (204) and many others have supported the theory.

The following is a chronological listing of various authors and their stand as to whether Riedel's struma is an entity or whether Hashimoto's disease is merely a different phase of the same disease process (as was concluded by Eisen who set off this great disagreement):

Two Distinct Entities

deQuervain - 1904, '06 (135)
Delore & Allamartine - 1911
(11)
Hashimoto - 1912 (202)
Reist - 1922 (113)
Simmonds - 1923 (62)
Wegelin - 1926 (56)
Perman & Wahlgren - 1927
(101)
McCarrison - 1929 (169)
Roulet - 1931 (166)
Graham - 1931, '40 (30, 225)
Graham & McCullagh - 1931
(31)
Clute & Lahey - 1932 (78)
Polowe - 1934 (208)
Howard - 1934 (91)
Clute, Eckerson, & Warren -
1935 (203)
Lee - 1935 (209)
Gilchrist - 1935 (211)
Hellwig - 1935, '38, '39, '51
(120, 59, 121, 117)
McClintoch & Wright - 1937
(42)
McQuillan - 1938 (34)
Joll - 1939 (114)
Young - 1940 (105)
Ziskind & Schattenberg - 1940
(214)
Harry - 1940 (43)
Fox - 1941 (180)
Hertzler - 1941 (60)
Weyeneth - 1941, '43 (215, 216)
McSwain, Barton, & Moore - 1943 (204)
Schilling - 1945 (35)
Ficarra - 1946 (217)
*Bothe - 1948 (218)
*Means - 1948 (219)
Marshall, Meissner, & Smith - 1948 (128)
Crile - 1948, '50 (182, 177)
Willer - 1949 (194)
Frantz - 1950 (220)
Konzelman - 1950 (179)

Different Manifestations
Of The Same Disease Process

Ewing - 1922, '40 (16)
Shaw & Smith - 1925 (32)
Eberts & Fitzgerald - 1927
(90)
Tebutt et al - 1927 (139)
Kent - 1929 (86)
Heyd - 1929 (24)
Williamson & Pearse - 1929
(132)
Taylor - 1929 (205)
Maloney - 1930 (103)
Crane - 1931 (81)
*Bothe - 1931 (156)
Eisen - 1934, '36 (206, 207)
Boyden, Collier, and Burger -
1935 (143)
Benson - 1935 (53)
Wallis - 1936 (54)
Poer, Davidson, & Bishop -
1936 (210)
Cameron - 1937 (160)
*Means - 1937 (212)
Renton, Charteris, Heggie -
1938 (176)
Goodman - 1941 (144)
Hertz - 1943, '49 (187, 104)
Womach - 1944 (99)
Toker - 1947 (213)
Vaux - 1948 (146)
Fortuna - 1949 (88)
Rabson & Arata - 1949 (152)
Levitt - 1951, '52 (153, 1)

Crile & Hazzard - 1951 (221)
 Stalker & Walther - 1951 (222)
 Schliche - 1951 (223)
 Lyons - 1953 (107)
 Barr - 1953 (224)

"Riedel's struma is not necessarily preceded by struma lymphomatosa; that struma lymphomatosa does not necessarily progress to Riedel's struma; and that it is highly improbable that there is any necessary relationship between these two conditions" was Graham's conclusion as he compiled the following statistics:

<u>Riedel</u>	<u>Hashimoto</u>
41.5% ----- Male -----	4.2%
58.5% ----- Female -----	95.8%
43.5 years --- Mean Age -----	57 years
50% ----- Bilateral -----	100%
1 year ----- Duration of symptoms -----	1.3 years
0 ----- Hypertension -----	20%
90% ----- Diagnosed as malignancy -----	55%
19% ----- Hypothyroid postoperatively --	50%

Gilchrist (211) echoed Graham's views. He had also found Hashimoto's in older persons. Clute, Eckerson, and Warren (203) commented that in Hashimoto's, fibrosis is rarely a prominent feature, in contrast to Riedel's struma.

A long fuse was ignited in 1929 when Williamson and Pearse (132) introduced the term "lymphadenoid goitre". They stated that other goitres, which essentially belong to this group, had been called by earlier observ-

ers "chronic inflammatory thyroiditis", "granulomatous thyroiditis", "endothelioma", "sarcoma", and "Riedel's disease or woody thyroiditis". It was their contention that although these various designations fail to convey the true pathogenesis of this condition "they do indicate its most striking features; (1) the lymphocytic activity which is typical of the early or progressive stages of the process and (2) the fibrosis and atrophy which accompany its later stages". Since then a battle royal has been fiercely joined between pathologists, physicians, surgeons, and cynics of all kinds, each assessing the problem through his own specialized viewpoint. Tebutt et al (139) implied that lymphadenoid goitre was the same as struma lymphomatosa (Hashimoto). Howard (91), McClintoch and Wright (42), Hellwig (59), Lehman (226), Harry (43), McGavach (227) used the terms synonymously. Gurken (138) was of the opinion that lymphadenoid goitre is observed only in certain countries such as Japan, England, and North America. Cases of Weyeneth and Chavel came from Geneva. Levitt (153) is of the opinion that lymphadenoid goitre is a distinct clinical and pathological entity - the result of a functional disorder.

Contrary to the general opinion, Riedel did not describe the pathological picture as one of fibrous replacement and sclerosis in the thyroid, but as accumulations of round cells, sprinkled between normal thyroid tissue, by which the thyroid tissue is more or less destroyed. "Upon looking at the slides one does not realize how hard the tumor is. One would expect firm fibrous tissue as a constituent of the tumor, but one sees only infiltration by round cells."

Lahey (44) tried to differentiate between these two types of thyroiditis (Riedel's and Hashimoto's) by pointing out that the invading cells were of different types, i.e. "round cell infiltration varying in grade up to Riedel's struma in which the gland is completely replaced by round cell infiltration. Struma lymphomatosa is caused by infiltration by a particular type of lymphomatous cell". Willer (194) expressed a somewhat similar view in that "thyroid sclerosis should be differentiated from chronic thyroiditis, as the increasing atrophy of the glandular tissue in the former is primary, and lymphocytic infiltration secondary. Hashimoto's belongs to the class of thyroid sclerosis". In-so-far as microscopic material is concerned, Levitt (1) in his analysis of Riedel's and Hashimoto's disease points

out that Riedel actually described two conditions - type 1 or fibrosis and type 2, chronic thyroiditis, an inflammatory phenomenon. Type 2 occurred in younger patients and, as Riedel pointed out, recovered spontaneously. Hashimoto described one case which is more typical of Riedel's (fibrosis) in his original four cases.

Other clinical manifestations have been shown to be more favorable for one type of thyroiditis as compared to the degree of fibrosis. Emerson (228) thought that it would be helpful to this end, of all cases in which the histologic picture is one of extreme lymphocytic infiltration, to compare the data concerning "age, sex, the previous existence of goiter; duration of symptoms, duration of the goiter, the extent as well as the character of the involvement of the thyroid; limitation of the process to the thyroid or extension beyond it (including more than the mere statement that the gland was adherent); adhesions to the trachea as opposed to adhesions to the surrounding structures; the presence in the thyroid of adenomata, cysts, areas of calcification, frank inflammation, including small or large abscesses, the presence or absence of hyperthyroidism, and hypothyroidism before or after operation; the amount of tissue removed; the character of the tissue remaining;

the gross characteristics of the lesion, and finally the microscopical findings", with the clinical and pathological pictures that have been described under the term of Hashimoto's struma.

Eisen (207) presented the following figures as typical of Riedel's struma:

1. Swelling in neck
 2. Dyspnea
 3. Dysphonia
 4. Mild hyperthyroidism
 5. Pain and dysphagia
 6. Choking feeling
 7. Duration of symptoms - 10 months
- } 25%
- } 20%

McClintoch and Wright's (42) cases had an average age of 40 with Riedel's, and 49 with Hashimoto's, while 95% of the latter were female and sex played no appreciable role in the former. The symptoms of Hashimoto's were present for a longer period of time. Wright's (46) cases had shorter clinical histories. Whitesell and Black (159) found that patients with mixed fibrolymphocytic type infiltration were somewhat older than patients with the lymphocytic type. Rabson and Arata (152) concluded that Riedel's struma and Hashimoto's disease do not differ in frequency in the sexes from that of thy-

roid disease generally. A chart prepared by Levitt shows patients of 47 years of age with Hashimoto's, 42 years of age with Riedel's fibrosis, and 26 years of age with Riedel's chronic thyroiditis but in writing he states that the ages are: Lymphadenoid goitre at 43, Hashimoto's at 48 and Riedel's fibrosis at 56, and concludes that Riedel's is, therefore, an advanced stage of Hashimoto's.

Lyons (107) believes that the processes are two distinct entities because his cases were recorded as follows:

<u>Riedel's</u>		<u>Hashimoto's</u>
2/3 female -----	Sex -----	Almost all female
1/2 -----	Bilateral ---	Almost all
Almost always -----	Adenoma -----	Practically never
43 years -----	Age -----	47 years

Graham (30), Joll (114), and McCullagh (31) believe that no relation exists between Riedel's and Hashimoto's disease for the following reasons:

1. Hashimoto's is confined to women over 45.
2. Riedel's may occur at any age, any sex.
3. Regardless of operation, Hashimoto's tends to develop myxedema, frequently preoperatively.
4. Riedel's, even after surgery, rarely leads to a defective function.

5. Hashimoto's is diffuse from the onset, no part of the gland escapes.
6. Riedel - localizations are not uncommon.
7. Widespread formation of deluate connective tissue is found resembling that in lymphadenoid goitre. In Riedel's disease, dense fibrosis resembling scar or keloid formation is found even in early stages.

Proven recurrent episodes have been of some help. Heyd (24) reported three cases of which one was a recurrence of Riedel's. Perman and Wahlgren (101) were able to show that the pathological tissue removed at two operations separated by a year's interval was of almost identical histologic structure as the original which had been diagnosed as Riedel's. Roulet (166) had a similar case, as did Graham and McCullagh (31), and McKnight (119). Clute, Erickson and Warren (203) reported two cases which recurred.

McClintoch and Wright did surgery on a case of Hashimoto's which at a later date was also diagnosed as such, as did Joll and Schilling. V. R. Erantz (220) revealed that two cases reoperated after 19 and 20 years revealed Hashimoto's originally and at the later date, while Crile and Hazzard (221) had a case which revealed

the same histologic features 23 years after the first biopsy. Heyd in 1929 reported a case of Hashimoto's (first operation) which 13 months later was diagnosed as Riedel's (second operation) because of a diminution of the number of lymphocytes and an increase in fibrosis.

Merrington (229) reported a case of thyroiditis with features of both Riedel's and Hashimoto's thyroiditis.

It seems that if these two were simply stages of one disease the reverse of the age groups and a similar distribution between sexes would be expected. McSwain, Barton, and Moore (204) state that there is no relationship between Riedel's and Hashimoto's diseases and that they are different both clinically and pathologically. Hertzler (60) goes so far as to state that "to confuse the two (Hashimoto's and Riedel's) clinically seems to me preposterous, and I believe it is possible to distinguish between them from the slide alone". Cameron (160), and German (70) state that Riedel's and Hashimoto's cannot be differentiated, either clinically or pathologically.

To fill the field with more confusion, other terms and different classifications of thyroid disease have been published from time to time. And, as Hellwig (121)

so aptly put it - "the lack of uniformity in the classification of thyroid changes is without doubt, one of the reasons why there is such a disagreement among surgical pathologists .."

Heyd (24) reported the process as a granulomatous strumitis which had been observed in his laboratory in three stages, (a) the earlier form representing only a moderate lymphoid increase with compressed epithelial elements, (b) the intermediary form characterized by a marked increase in lymphatic tissue with destruction of epithelial elements, and (c) the late stage characterized by an almost complete fibrosis of the gland.

Hertzler classifies inflammatory conditions of the thyroid gland as:

- (a) Acute diffuse thyroiditis (Riedel's struma)
- (b) Intracapsular thyroiditis (Hashimoto's)
- (c) Acute limited non-suppurative thyroiditis
- (d) Acute suppurative thyroiditis

Clute and Lahey:

- (a) Simple
- (b) Suppurative
- (c) Chronic
 - (1) Primary
 - (2) Secondary.

Brayton:

- (a) Riedel's struma
- (b) Struma lymphomatosa
- (c) Subacute "Giant cell" thyroiditis
- (d) Chronic thyroiditis not clearly included in other categories.

Patterson and Stark:

- (a) Hashimoto's
- (b) Riedel's
- (c) deQuervain's - giant cell - pseudo-tuberculous

Wright:

- (a) Riedel's
- (b) Chronic non-specific (sub-acute thyroiditis of Crile, also acute non-suppurative)
- (c) Hashimoto's

Rabson and Arata:

- (a) Hashimoto's
- (b) Riedel's
- (c) Chronic non-specific

They suggest that these lesions are not only related but appear to run a characteristic involutional and sequential course namely, "lymphadenoid goitre to struma lymphomatosa to Riedel's struma".

Lesser:

- (a) Pseudo-tuberculous subacute thyroiditis
- (b) Struma fibrosa
- (c) Struma lymphomatosa

Stalker:

- (a) Hashimoto's
- (b) Subacute thyroiditis (deQuervain type)
- (c) Riedel's

This author states that (a) and (c) are two divergent extremes of chronic thyroiditis with different clinical and pathological features.

From the preceding classification we find that other new terms have crept into the discussion of chronic thyroiditis. The most frequent are deQuervain's type, Pseudo-tuberculous, and Crile's subacute or Giant cell thyroiditis. At one time or another each of these have been described and labeled Riedel's thyroiditis or a variant of that process.

Schilling (35) pointed out that "at present many cases, reported as struma fibrosa are confused with the more acute and granulomatous form of chronic thyroiditis so beautifully described by deQuervain and Giordanengo (38)". Stalker and Walther (222) report that subacute thyroiditis of the deQuervain's type is an intermediate

group (between Hashimoto's and Riedel's) which is becoming an acceptable entity. Barr (224) lists three types of chronic thyroiditis - Hashimoto's, Riedel's, and deQuervain's giant cell type, the latter showing loss of acinar cells of the thyroid follicles leaving colloid residue.

Bardos (230) reported one case of Pseudo-tuberculus thyroiditis (according to Crile's classification). Crile and Hazzard (221) reported that biopsies of the thyroid glands from 14 patients in the clinically acute phase of subacute thyroiditis had shown that this disease was identical histologically with the pathologic entity of pseudo-tuberculous or giant cell thyroiditis. They followed 100 patients with this disease (clinically diagnosed), and found no instance of any evidence of the irreversible changes characteristic of Riedel's and concluded that this was a new entity. This condition is most probably the condition described by deQuervain as struma granulomatosa.

"The work of the past is difficult to unravel since the condition when encountered clinically and allowed to subside spontaneously has been called acute or subacute non-suppurative thyroiditis. Yet the same syndrome when operated upon has been called Riedel's. Thus

DeCourcy in discussing the role of perithyroiditis in the etiology of what he supposed to be Riedel's struma was actually studying two cases of non-suppurative thyroiditis." (Lesser - 140). Crile (182), on the other hand, demonstrated by biopsy his view that the two conditions were identical.

Goetsch (66) admits that in Riedel's original report he did not mention giant cells while other authors have. However, he goes on to explain that they are supposedly foreign body giant cells possessing phagocytic properties. Furthermore, the presence and supposed phagocytic function of the giant cells described in many previous reports have lead to mistaken diagnoses of tuberculosis, syphilis, and cancer and to consequent misdirected therapy. He shows that the giant cells are derived from coalesced masses of degenerating, desquamated follicular cells which are in the process of destruction for probable nutritional reasons and states that it seems unwarranted to assume that they have phagocytic power. They are merely the first stage in the disintegration of thyroid parenchyma as multinucleated syncytial masses are thrown into the lumen of the follicle. German (70) believes that these are not true giant cells but represent thyroid epithelium embedded in or surrounding

masses of colloid. As late as 1950 Konzelman (179), in the discussion of the giant cell variant of Riedel's struma states that the cells are probably "foreign body giant cells which have responded to a degenerative process in the glandular epithelium".

One important phase of this process which we have not covered is the surgical aspect in-so-far as diagnosis is concerned. Riedel reported that, in an attempt to treat his case, surgery was done. At the table it was evident that "in places there was a strong growth of fibrous tissue and it was adherent to the carotids and jugulars". This was one of the reasons he first believed the condition to be malignant, and should be given consideration in the diagnosis if we are to call it Riedel's struma.

Dr. Claude J. Hunt (231) noted that Hashimoto's disease is distinctly confined to the gland, "it does not invade the surrounding tissues; the gland is easily removable and is not fixed (compared to Riedel's)". Crile (177) reports that Riedel's thyroiditis involves "usually one but sometimes both lobes of the thyroid as well as the trachea, and the muscles, fascia, nerves, and vessels in the vicinity of the thyroid". In 1951 (221) he again states - "It is fair to assume that any surgeon who speaks of having removed a Riedel's struma

is in reality speaking of a subacute thyroiditis. The involvement of the muscles, the carotid sheath, the trachea, the recurrent nerve and the parathyroids in the inflammatory process which embraces all the structures around the thyroid renders the conventional thyroidectomy impossible to accomplish. All that one can do is excise a portion of the lobe or isthmus in hope of relieving the symptoms of pressure, or to enucleate the adenoma which usually is found at the center of the mass." Stalker and Walther (222) state that a "complete thyroidectomy is impossible" in Riedel's.

When various authors discuss Hashimoto's disease as being confined within the capsule or gland and that Riedel's extends beyond, it is interesting to note that Thorek (232) has pointed out that there is no thyroid capsule. "There are cleavage planes, and pre and post thyroid spaces."

No author denies that Riedel's struma is not rare so for the sake of completeness we must add the incidence of this process even though we have not established of what the condition or process consists. Most authors report approximately 1%.

Riedel - 1910 (233)	-----	.002%
Mayo - 1926 (234)	-----	.1%

Means - 1937 (212) -----	1%
Renton - 1938 (176) -----	.20%
DeCourcy - 1948 (111) -----	2%
Marshall - 1948 (128) -----	.75%
Touro and Southern Baptist Hospitals (107) - 8%	

Marshall, Meissner, and Smith (128) report that their figures are compiled from 25,000 patients requiring thyroidectomy (in 18 years) and of these 0.75% (187) were chronic thyroiditis excluding all other conditions diagnosed preoperatively as Riedel's struma.

As early as 1928 John R. Wathen (235) made the comment that "I would be inclined to discard the term chronic thyroiditis or confine its meaning within very narrow limits." Boyden et al (143) not only agree with the unitarian concept but state that they do not believe the process is a distinct entity, while Lehman (226) admonishes that the pathologist alone cannot make the diagnosis. Lundbaek (149) believes that Riedel's struma is an entirely microscopic-clinical concept.

It is the opinion of Graham (30), Eisen (207), and this author that many case reports and reviews have given not only inaccurate but misleading information in the controversy in regards to the true picture of Riedel's struma. Eisen had reviewed the 187 reported cases of

Riedel's struma up to 1932 and accepted 82 of them as typical, while Graham reviewed 104 cases and accepted 41. Even these two competent authors could not agree 100% as to which cases were truly typical. Graham concluded "I believe that too great reliance upon the microscopical findings and too little attention to the clinical and pathological picture as a whole has resulted in more confusion than clarity. The microscopic findings alone are not sufficient to distinguish between Hashimoto's and Riedel's, or between these and certain cases of exophthalmic goitre, myxedema, syphilis, tuberculosis, chronic inflammation, degeneration and fibrous replacement in and around adenomata, and involutonal changes in senility."

"For a long time there has been a tendency on the part of many pathologists to group these cases (chronic non-specific thyroiditis) with those of Riedel's struma and, indeed, if gross and microscopic features alone are the basis of classification, such a grouping can often be made. However, in association with the clinical manifestations of the disease, differentiation is practically always possible." (Wright 46).

Levitt (1) suggests that the terms Hashimoto's and Riedel's diseases be dispensed with altogether as they

are "nondescript". He likewise believes that lymphadenoid goitre is ambiguous. In their places he would suggest fibrosis, fibrolymphoid hyperplasia, and diffuse lymphoid hyperplasia, i.e., the three terminal phases of the six stages of the degenerating toxic thyroid gland.

- (1) Epithelial hyperplasia
- (2) Lympho-epithelial hyperplasia
- (3) Focal lymphoid hyperplasia
- (4) Diffuse lymphoid hyperplasia
- (5) Fibro-lymphoid hyperplasia
- (6) Fibrosis

CASE REPORT

I. Mrs. E. D., Age 35. Chief complaint of pain in her neck for three months, a lump and tenderness over the left side of the thyroid cartilage. Lump did not enlarge but pain became bilateral, especially marked on the left side. Patient had been taking thyroid pills (Tapizol-propylthiouracil) for approximately three months and had noticed no improvement. She had noted a slow weight loss. Past history revealed a "goitre" at age of 13 years, scarlet fever and small pox at the same age. Examination revealed bilateral swelling of the mid anterior neck with a 1 X 2 cm. firm. tender nodule on the left side.

Significant laboratory findings: W.B.C. 10,100 with normal distribution of cells. R.B.C. 4.79 million. Hgb 12.5 gm. or 81%. Sedimentation rate (Wintrobe) 56 mm. per hour. Urine - slightly cloudy, 1.039 specific gravity. B.M.R. on day following admission \nearrow 45%, three days later \nearrow 19%.

Lugol's solution given for three days prior to surgery, surgery five days after admission. "Mid-collar incision made and the thyroid lobes seemed to be unusually firm. They were almost stony hard with the left lobe being about twice as large as the normal sized

right lobe. The tissue was so firm that the grasping forceps could not be held within its lumen". Two thirds of the left lobe was removed. The Prethyroid muscles were rather intimately adherent to the gland.

Pathology: Frozen section diagnosed as probably Riedel's struma. Tissue cultured.

Histology: Biopsy of the thyroid gland, seven sections are present. The pathology varies from section to section and consists mainly of varying stages of fibrosis with obliteration of thyroid acini, condensation of colloid and inflammatory cell infiltration. The gland is surrounded partially by a thick, fibrous capsule to which in areas are attached small masses of skeletal muscle. Throughout the muscular masses and in some areas of the fibrous capsule, small extra vascular hemorrhages of minor intensity are present. There is a diffuse inflammatory cell infiltration consisting mainly of lymphocytes which are perivascular in distribution, but which occur in very small focal aggregations. These cells are diffusely scattered throughout the fibrous capsule. Small vascular and lymph channels are abundantly placed within this fibrous stroma. Various portions of the gland appear to be selectively affected; the pathologic changes varying from minor

peri-acinar fibrosis to complete obliteration of acini and the contained colloid. The fibrosis is laid down in sheets and strands which in some areas are condensed; assuming a peri-acinar distribution. The acini vary in size from approximately 1/6 of a low-power field to very tiny remnants scarcely larger than 35 micra. The epithelium lining the intact and degenerating acini is for the most part flattened, though in some areas cuboidal cells are still present.

The colloid shows an uneven acidophilic staining reaction varying from faint pink to almost carmine. In many areas large vacuoles appear in the colloid masses. In some of the acini complete absorption of the colloid has occurred, the spaces being filled by a loose meshwork of fibrous tissue. At the periphery of the degenerated acinar structures there has been a condensation of the fibrous tissue and entrapped within it are small aggregates of lymphoid cells. The general impression of a granulomatous lesion is obtained in those portions of the gland more seriously affected. Scattered throughout the tissue in the acinar degenerating colloid are large multi-nucleated giant cells having both centrally and peripherally placed nuclei. These giant cells appear to have fib-

rillar attachments to the wall of the acinus. Small vascular channels are present within the fibrous stroma in the central portion of the gland but these are distorted by compression and devoid of blood elements. Some of the larger arterioles appear to be moderately sclerotic.

In some areas of the biopsy, condensations of fibrous tissue appear to separate the gland into pseudolobules encompassing areas of looser, more fibrillar connective tissue. In other areas, small remnants of acini devoid of colloid but maintaining their basic anatomic structure, lined by low cuboidal epithelium are seen. Inflammatory cell infiltration in the fibrous portion of the material is less prominent than at the peripheral portions of the glandular structure though small foci of lymphocytes are present in aggregates as well as in diffuse distribution. Hemorrhage within the gland is absent. In those areas in which complete destruction of the acinar architecture has been established, hyalinization of the connective tissue is apparent. In these areas so affected, only ghost remnants of previous acinar structures are occasionally seen.

Bacteriology: See bacteriologist's report on next page.

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February 2, 1954

Dr. J. R. Schenken, Pathologist
Methodist Hospital
3612 Cuming
Omaha, Nebraska

Dear Dr. Schenken:

Re culture from thyroid of patient Deal. The smear and culture materials submitted for study have been repeatedly reviewed. We were unable to determine, on the basis of the submitted smears, whether this organism represented a streptococcal type or a diptheroid.

We were able to grow this organism repeatedly under strict anaerobiasis and occasionally under microaerophilic conditions; however, we were not ever able to grow the organisms under normal aerobic conditions. Ultimately, we were convinced on the basis of reaction on potassium tellurite medium and by morphology that this organism was a microaerophilic Corynebacterium species. Sugar fermentation and gelatin reactions were technically very difficult and consistent results were not obtained. On the basis of the biochemical reactions present, this organism could not be placed into a species category conforming to the plan in the 6th edition of Bergey's Manual of Determinative Bacteriology. In some ways, this organism resembled C. pseudodiphtheriticum and in other ways Corynebacterium acne. However, the pattern did not resemble either species greatly.

We regret we have not been of much assistance in this interesting problem. We can assure you, however, that examination of this culture provided a considerable review of the diptheroids.

Yours very truly,

H. W. McFadden, Jr., M. D.
Asst. Professor of
Pathology & Bacteriology

HWM:AB

P. S. - A virulence test was performed on the skin of a guinea pig with a saline suspension of a 48 hour plate culture of this organism; we had hoped to grow the organism in broth and perform the test with a filtrate; however, we were not able to obtain sufficient growth in several different broths as to make a valid test. The virulence test was interpreted as negative. The test animal was examined up to 2 weeks.

II. Mr. Y. H., Age 37. Chief complaint on admission was referable to low abdominal pain referred to rectal area, 6-8 months duration. Past history of "hyperacidity" at the age of 16.

About seven months ago the patient had a feeling as though he had a lump in his throat. This persisted for two days and "felt like a toothache". Just before seeing his doctor, the pain went away. Received thyroid extract for approximately one year. Felt tired and listless part of the time.

Physical examination revealed a 2 X 3 cm. smooth, firm, movable lump above the sternal notch which moves with swallowing.

Significant laboratory findings: W B C 8,000.
R B C 4.46 million. Hgb. 13.5 grams. Urine - negative.

Surgery three days after admission consisted of biopsy and total bilateral thyroidectomy.

Pathology: Frozen section revealed Papillary Adenocarcinoma and chronic thyroiditis, Riedel's struma type.

Histology: The specimen consists of multiple sections taken from the right lobe of the thyroid gland. Surrounding the gland is a fibrous capsule varying in thickness from only a few condensed fibers to a rather broad band of fibrillar connective tissue. In the cap-

sule are small aggregates of round cells most of which are lymphocytes. These are seen diffusely distributed in the capsular area but to a more pronounced degree appear as small focal accumulations. In some areas the capsule contains condensed hyalinized connective tissue encompassing small masses of normal appearing areolar tissue. Extra vascular hemorrhages are not present, though numerous small blood vessels are present. The fibrosis seen in the capsule extends into the substance of the gland in broad meshes encompassing small islands of glandular tissue, the acini of which vary considerable in size, shape, and staining reaction. Numerous acini devoid of colloid material are present in the fibrous masses and have been compressed with complete loss of architecture and degeneration of the lining epithelium. Those acini still retaining colloid are lined by a low cuboidal or flattened epithelium the nuclear structures of which stain normally. Throughout the gland condensations of fibrous tissue appear around degenerating follicular masses giving the pattern of isolated islands of thyroid tissue. Very little inflammatory cell infiltration is seen in the central portion of the affected gland though occasional small aggregates of lymphocytes are present. In some areas

fibrosis is almost complete but even in these areas remnants of the thyroid acini are demonstrable. These have been compressed into various sizes and shapes by the encroaching fibrosis, and their epithelial cells have become vacuolated. In those areas where fibrosis has completely obliterated the thyroid architecture the connective tissue has become hyalinized.

A similar architectural pattern is seen in the sections of the left lobe but in this the inflammatory cell infiltration of the thyroid substance is more marked, and even small follicles of lymphoid tissue are scattered throughout the substance of the gland. The fibrous tissue reaction is, however, similar to that observed in the opposite lobe.

Bacteriology: Hemolytic Staphylococcus albus isolated.

Discussion: In the first case we can find five factors which have previously been discussed as possible etiologic agents in Riedel's struma, i.e. (1) a lump, (2) past history of a goitre, (3) treatment with thyroid medication, (4) Lugol's solution, and (5) isolation of a bacterial agent from the tissue.

Although excellent and extensive bacterial studies were done, the bacteria isolated did not conform to any of those listed in Bergey's Manual.

With these various factors it is impossible to evaluate the part each had to play in the etiology of the disease.

In case two we again find (1) a history of previous enlargement, (2) a lump in the gland, (3) thyroid medication, and (4) a bacterial agent cultured from the tissue. In this instance however, the bacteria may well have been a contaminant as the biopsy was done three days prior to surgery.

SUMMARY:

Riedel in 1896 presented three cases of what he thought to be a new pathological entity involving the thyroid gland. He termed this condition "eisenharte strumitis" or iron-hard strumitis because of its clinical aspects, i.e. a mass in the thyroid gland which was extremely hard and immovable. His clinical diagnosis was cancer but, after microscopic examination, he stated that "we had plainly to deal with an inflammatory process". "Upon looking at the slides one does not realize how hard the tumor is. One would expect firm fibrous tissue as a constituent of the tumor, but one sees only infiltration by round cells."

From time to time other cases were presented in the literature, until in 1912 Hashimoto described four cases of a process which he believed were entirely different from the cases discussed by Riedel. In 1926 Eisen, who carried much influence in the field of pathology, stated that Riedel and Hashimoto had described two different phases of the same basic disease. In 1931, Graham reviewed the literature and concluded that Riedel's eisenharte strumitis and Hashimoto's struma lymphomatosa were two distinct entities.

Since that time many authors have discussed this controversial subject and interjected different names, described different histological features, and all but called their cohorts incompetent in their ability to correctly identify a typical histologic pattern of Riedel's struma.

This paper has attempted to discuss the various theories proposed for the etiology of Riedel's strumitis. These theories range from a primary inflammatory process in the thyroid gland itself to psychogenic factors and all the processes which fit in between these extremes.

In order to discuss the etiology it was necessary to attempt to define the process about which we are

speaking. As was already pointed out no large group of authors could agree on this. As a consequence the paper consists of many theories of several processes involving the thyroid gland.

CONCLUSION:

The well known fact that any controversial subject is not completely understood certainly applies in this instance. As Lundbaek so aptly put it - "This problem might seem to have been discussed sufficiently (on the relationship between the various forms of chronic thyroiditis) - from Denmark no less than three papers are published on this subject - but on going through the accessible literature there appears to be good reason for trying to elucidate this rather intricate question."

Excellent discussions and reviews of the pathology of chronic thyroiditis can be found in detail in the papers of Womack, McClintock and Wright, Joll and others, therefore it was felt that a lengthy description was unnecessary here.

For the purposes of clinical comparison, it was found that cases of chronic thyroiditis could easily be segregated into three main groups, which are reasonably distinct both pathologically and clinically. Whether

they may progress from one to the other is highly questionable and for this reason the etiologic factors are not clearly seen.

It is the opinion of this author, based on very weak evidence from the literature, that Riedel's struma and Hashimoto's lymphomatosa are two distinct entities. It would seem most probable that if Riedel's is an end stage of Hashimoto's, as many authors contend, then there should be an equal distribution between the sexes. Actually, Hashimoto's disease is rare in the male population. It also seems logical to assume that patients with Riedel's struma would be of an older age group than those with Hashimoto's disease, but this is not borne out in the literature.

Most evidence appears to correlate Riedel's struma with either a phase of thyrotoxicosis or in relation to adenomata but these are by no means conclusive.

Until a definite histologic pattern can be agreed upon, or until a clear-cut clinical pathological correlation can be established, it will be useless to attempt to find an etiologic agent for Riedel's struma when we cannot agree upon the process involved.

I wish to express my appreciation for the wonderful interest, advice, and cooperation given to me by Dr. J. R. Schenken at Omaha Methodist Hospital, and his laboratory workers. Especial thanks and appreciation to Dr. H. W. McFadden and his laboratory assistants at the University of Nebraska College of Medicine for their extensive bacterial studies in these cases. Also to Dr. J. M. Brown for his pathological descriptions of the cases presented here and to Dr. C. W. McLaughlin and Dr. Dan Miller for allowing me to present their cases.

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