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PULMONARY SPOROTRICHOSIS*

Report of Two Cases with Cavitation

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SPOROTRICHOSIS is an uncommon mycotic infection and pulmonary lesions are exceedingly rare. These lesions appear as necrotic foci and cavitations. Twenty cases have previously been reported, but in only 2 has the fungus been cultured from lung tissue.[1,2] In the 2 cases presented below, both cavitary, the organism was obtained in pure culture from either cavity or necrotic lesion and was demonstrated histologically in the cavity lining of both. One of these is the only known case in which resection has been carried out.

Sporotrichum, first described by Link in 1809, is a protean saprophyte of plants, insects, animals and man. In 1898 Schenck[3] demonstrated pathogenicity of this organism. There have been many excellent reviews[4-8] of this disease, but the rarity of pulmonary involvement prompts us to report the following cases in detail.

CASE REPORTS

CASE 1. A 26-year-old x-ray technician was first admitted to the hospital on October 23, 1954. He had resided in North Carolina except while in the Service from 1944 to 1948, when he was stationed in the eastern half of the United States, and from 1951 to 1954, when he served in the Caribbean area. He was addicted to alcohol. In May, 1954, a routine x-ray examination of the chest revealed an infiltration in the right apex, with central cavitation. Studies at 2 Navy hospitals did not produce a definitive diagnosis. The patient refused pulmonary resection and was subsequently retired from the Service and transferred to Oteen Veterans Administration Hospital.

All sputum samples and gastric washings were negative for acid-fast bacilli by concentrate and culture, but were repeatedly positive for *Sporotrichum schenckii*. A serologic test for syphilis was negative. Skin and complement-fixation tests were negative for blastomycosis, histoplasmosis and coccidioidomycosis. First-strength P.P.D. was positive. Agglutination for sporotrichosis using autogenous yeast-phase antigen gave a titer of 1:640. Treatment with potassium iodide and pulmonary resection was recommended, but the patient failed to return from a leave of absence on December 22, 1954.

He was readmitted to the hospital in May, 1955, with a low-grade fever, a history of night sweats and a weight loss of 9.1 kg. (20 pounds). X-ray study of the chest revealed spread of the disease throughout the right lung (Fig. 1). Sputum was again positive by culture for *S. schenckii*. He was treated with saturated solution of potassium iodide. The infiltration cleared on subsequent roentgenograms. He left the hospital against advice after 7 weeks.

He discontinued therapy and resumed heavy drinking. He was admitted to the hospital for the 3d and last time on November 15, 1955. For 4 weeks he had had increasing edema of the lower half of the body, productive cough, with hemoptysis on 2 occasions, and severe hoarseness. Diarrhea had developed 3 weeks before admission, and he had been vomiting for several days. He was severely ill, dyspneic and orthopneic. Physical findings suggested either bilateral pneumonitis or edema. Fluid in the right base was confirmed radiographically. Hepatomegaly and jaundice were present, as was cardiac decompensation. He became comatose shortly after admission, failing to respond to supportive therapy, and died 12 hours later.

At post-mortem examination, performed 65 hours after death, the body was well developed and well nourished. Positive findings were almost wholly confined to the thorax. The right pleural cavity contained approximately 600 ml., and the left 300 ml. of serous fluid. The heart weighed 475 gm. The ventricles were dilated and filled with soft, red, clotted blood. The ventricular walls were of normal thickness. There was microscopic edema. The right lung weighed 1320 gm., and the left 1290 gm. Both were edematous, especially the left. At the right apex was a thin-walled cavity, 3 cm. in diameter, containing some grayish-white exudate. The right middle and lower lobes contained numerous grayish-white necrotic lesions from one of which *S. schenckii* was cultured. Microscopical examination of the cavity in the right apex demonstrated a lining in which a few ovoid and elongate organisms were visible on staining with the periodic acid-Schiff method. Microscopical study of the left lung revealed little aside from congestion and edema. The liver weighed 3390 gm. and extended 10 cm. below the left costal margin. Grossly, it had a typical "nutmeg" appearance, and microscopically there was not only extreme passive congestion but also severe fatty metamorphosis. The spleen weighed 240 gm., was firm and had a deep-red cut surface, with evidence of passive congestion on microscopical examination. Study of the other organs gave negative results except for congestion.

CASE 2. A 42-year-old Negro florist was referred for admission by the County Health Department when a roentgenogram of the chest revealed a cavitary lesion in the left-upper-lung field. He was asymptomatic and denied any previous serious illness. He had had 1 episode of streaking hemoptysis with a respiratory infection in the winter of 1956. In 1930, and again in 1949, he had been treated for syphilis.

Physical examination revealed a well nourished man whose chest and lungs were within normal limits. There were no skin lesions or scars. X-ray study of the chest revealed a 4-cm. cavity in the left-upper-lung field (Fig. 2). Fibrotic infiltration extended from the cavity to the left hilus, and similar infiltration was present in the right-

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upper-lung field. Bronchograms showed that the cavity involved primarily the anterior segment, with cylindrical bronchiectasis in the apical and posterior segments.

Potassium iodide therapy was started and continued for 2 months. No significant change occurred on x-ray examination. On April 2, 1957, the left upper lobe was

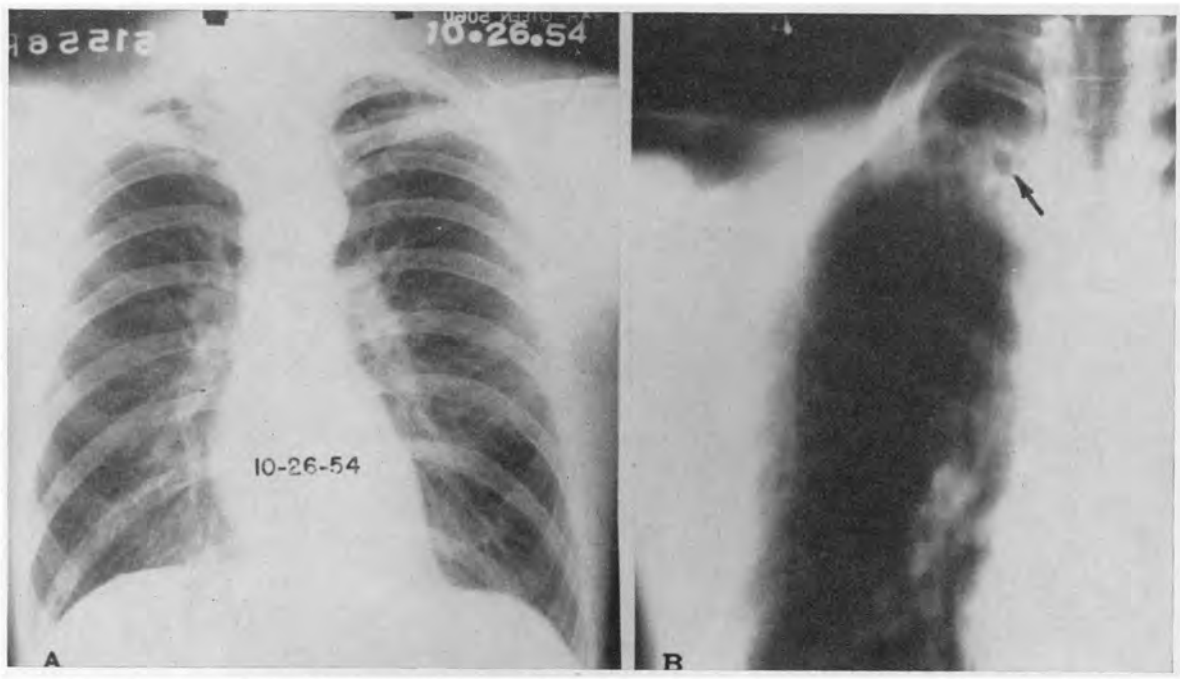

FIGURE 1. *Roentgenogram of the Chest on Admission* (A) *in Case 1, Showing Fibrocavitary Disease in the Right Apex, and Planigram* (B), *Showing the Cavity.*

All sputum specimens and gastric washings were negative for acid-fast bacilli, but were positive for *S. schenckii*. A serologic test for syphilis was positive. Skin tests for blastomycosis, histoplasmosis and coccidioidomycosis were

resected. The postoperative course was uneventful. Potassium iodide therapy was continued for 6 months after operation.

On pathological examination the left upper lobe weighed

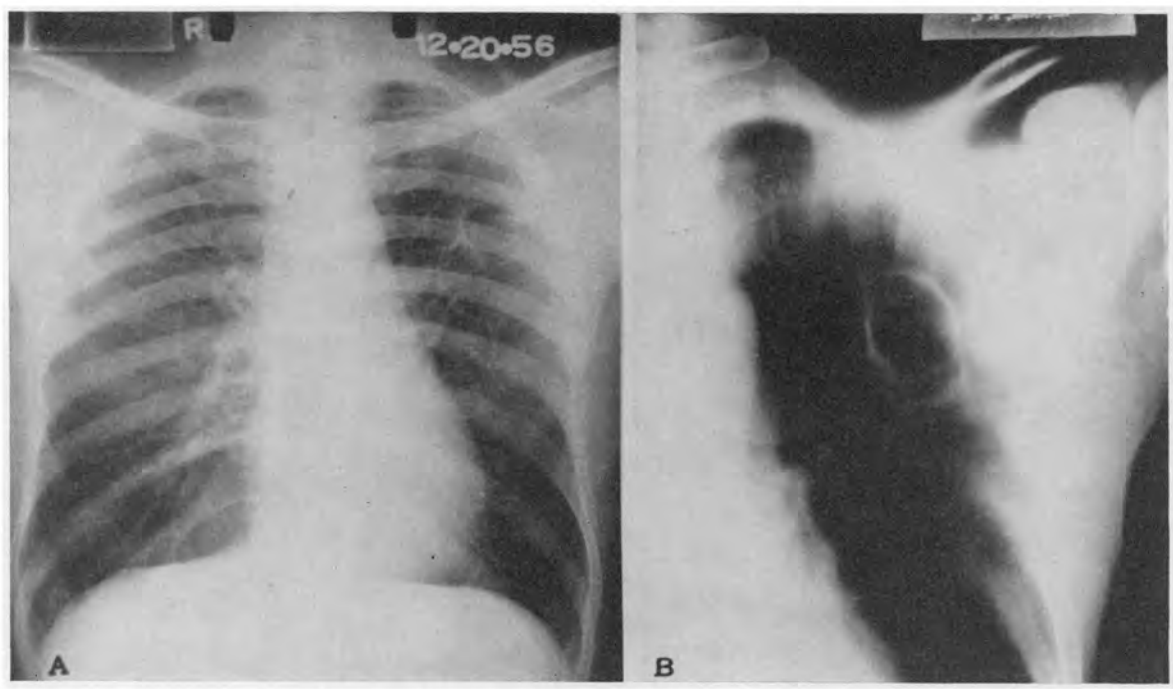

FIGURE 2. *Roentgenogram of the Chest on Admission* (A) *in Case 2, Showing a Cavity in the Left Upper Lobe, and Planigram* (B), *Showing the Thin-Walled Cavity.*

negative, as was an autogenous agglutination titer for sporotrichosis.

200 gm. The pleura was smooth except for an area over the anterior segment. When incised, this area revealed a

cavity, 3.5 cm. in diameter, 1 cm. below the pleural surface (Fig. 3). The wall was dense and white and measured 0.3 cm. in thickness. The lining consisted of an irregular, grayish-white exudate. Yellow fluid partially filled the cavity. No other lesions were found.

On microscopical examination the cavity wall was composed of dense fibrous tissue of irregular thickness. It had a lining of necrotic tissue with an irregular zone of exudate rich in polymorphonuclear leukocytes.

Numerous ovoid and elongate organisms were seen with

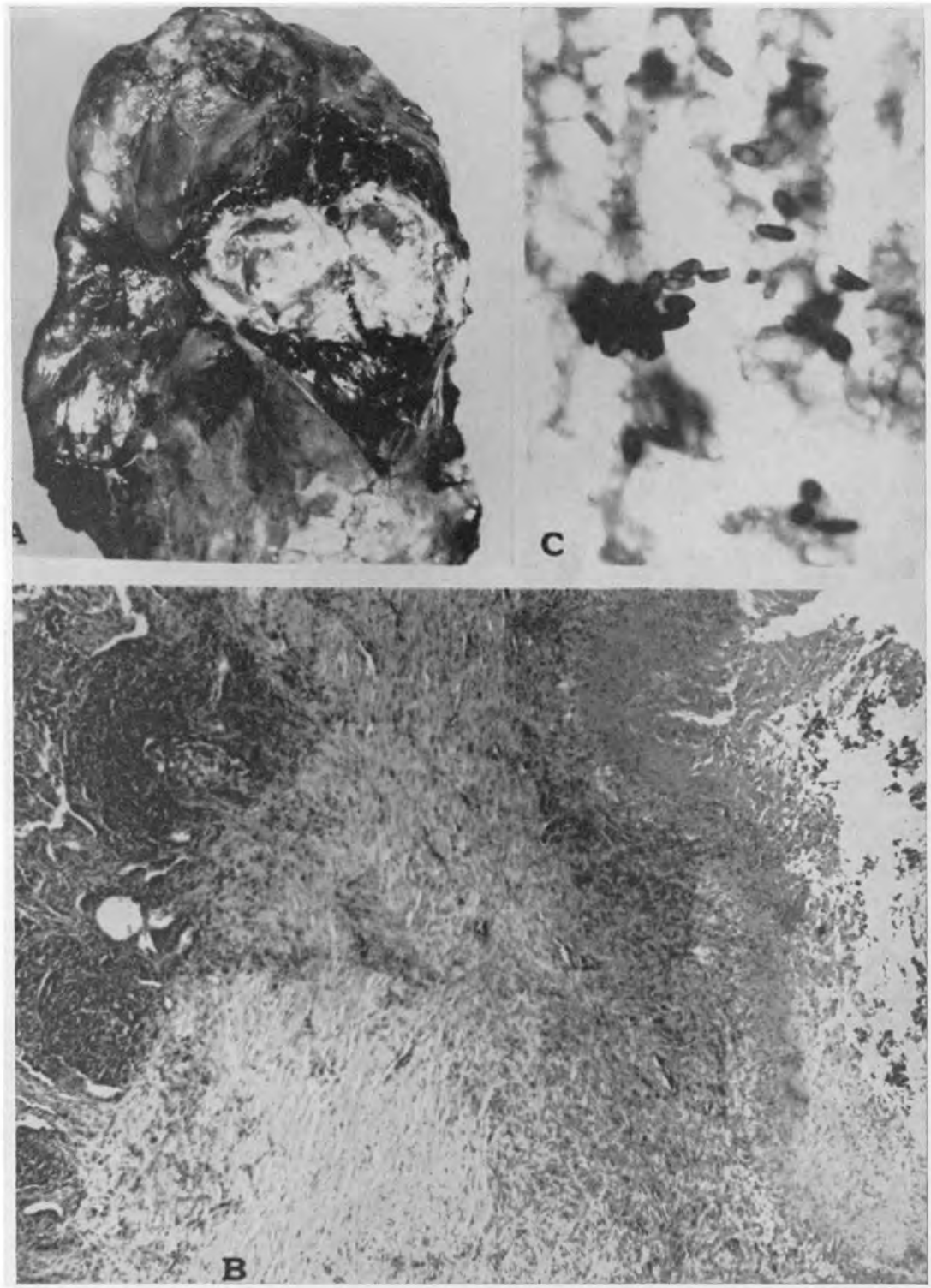

FIGURE 3. *Cavity in the Anterior Segment of the Resected Left Upper Lobe in Case 2* (A), *Microscopical Structure of the Cavity Wall* (B), *with No Specific Histologic Pattern (X25), and* (C) S. schenckii *in the Cavity Lining (PAS Stain X750).*

the periodic acid-Schiff method. A pure culture of *S. schenckii* was grown from the cavity.

Discussion

By 1912 enough cases of sporotrichosis had been recognized to warrant an exhaustive study by de Beurmann and Gougerot,[8] who recorded 6 cases of pulmonary sporotrichosis, but considered only 2 of them proved to their satisfaction. In 1927 Forbus[1] reviewed these 6 cases and 3 subsequently reported. He believed that the evidence was insufficient to support the diagnosis in all but 1 case, reported by Warfield[2] in 1922. Forbus then described in detail the autopsy of a thirty-four-year-old woman in whom *S. schenckii* had been cultured from lung tissue. Eight cases have been reported since 1927, but in none was the diagnosis supported by culture of the tissue.[4,9-15] In 3 of these the diagnosis was substantiated by sputum culture and elevated agglutination titers,[4,13,15] although 1 patient[15] failed to respond to potassium iodide therapy. The addition of the 2 cases reported above makes a total of 8 cases of pulmonary sporotrichosis presented to date that have been adequately documented (Table 1).

Once the organism has been cultured, pathogenicity must be established by animal inoculation. A host serum agglutination titer of 1:50 or greater will usually denote activity of the fungus. However, there was no agglutination in 1 of the cases reported above. Skin and complement-fixation tests and other immunologic responses are helpful, if interpreted with the knowledge that crossreactions to other fungi and bacteria do occur.[14] A therapeutic response to potassium iodide is also helpful.

There are no specific clinical or x-ray findings. Age distribution has varied from ten to fifty-four years. There is no sex or race predilection. Pleural effusion, hilar adenopathy, fibrosis, caseous nodularity and cavitation have all been described, chiefly on x-ray examination. Symptoms are frequently absent or masked by concomitant disease. Coexisting disease, such as syphilis, alcoholism, cirrhosis or pulmonary tuberculosis, is often noted, and may be a factor predisposing to the mycotic infection. It seems that visceral sporotrichosis predicates a loss of host resistance, as in Case 1, an alcoholic patient with a fatty liver, who died of congestive heart failure despite an initial response to potassium iodide therapy. The

Table 1. *Culturally Proved Cases of Pulmonary Sporotrichosis.*

Source of Data	Date	Culture of Sporotrichum			Agglutination Titer	Animal Pathogenicity	Treatment for Sporotrichosis	Response to Treatment
		Sputum	Lung	Extrapulmonary				
Dominguez[16]	1914	Positive	—*	Mastoid osteitis	—*	—*	Potassium iodide	Recovery
Warfield[2]	1922	Negative	Positive	—*	1:150	Positive	Potassium iodide	Death — autopsy performed
Forbus[1]	1927	Negative	Positive	—*	—*	Negative	None	Death — autopsy performed
Smith[4]	1945	Positive	—*	—*	1:1000	Positive	Potassium iodide	Recovery
Liu[13]	1955	Positive	—*	Subcutaneous nodule	1:320	Positive	Potassium iodide	Improvement
Post et al.[15]	1958	Positive	—*	—*	1:320	Positive	Potassium iodide	Improvement — sputum remained positive
Present report:								
Case 1	1961	Positive	Positive	—*	1:640	Positive	Potassium iodide	Death — autopsy performed
Case 2	1961	Positive	Positive	—*	Negative	Positive	Potassium iodide & surgery	Recovery

*Test not done.

The diagnosis of sporotrichosis obviously depends upon bacteriologic studies. The organisms cannot be positively identified morphologically in tissue or exudate. They sometimes appear as basophilic short rods, or as ovoid bodies with pale capsules. They can occur singly or in clusters, free or phagocytized. Rarely, there may be an asteroid form similar to actinomyces. However, identification is easily established by culture on Sabouraud's glucose agar. A typical black colony is formed, composed of hyaline-appearing mycelia, 1 or 2 microns in diameter, that branch frequently and bear ovoid conidiospores.

The recognition and culture of the pathogenic organism from a pulmonary lesion is ideal. However, since surgery is infrequently performed, the criteria used to establish a diagnosis are necessarily less specific. The organism should be repeatedly cultured from sputum or bronchial aspirations.

cardiac condition was probably beriberi. The low virulence of sporotrichum was demonstrated during a South African epidemic at the Witwatersrand Mines.[5] No visceral sporotrichosis was observed in 2825 cases of cutaneous and lymphatic sporotrichosis.

Potassium iodide is specific for lymphatic and cutaneous sporotrichosis and is the drug of choice for pulmonary infections. A number of patients suspected of having pulmonary sporotrichosis have been treated with potassium iodide, with a response before bacteriologic confirmation could be obtained. In 1 reported case with persistent positive sputum despite adequate iodide therapy, stilbamidine was also given but discontinued because of drug toxicity.[15] There have been no other attempts to treat this disease with stilbamidine, and there have been no reports concerning the value of amphotericin B. Pulmonary resection is indicated for persistent cavitation. Since the re-

sponse to treatment is usually so gratifying it is well to keep in mind this rare but very real entity.

Summary and Conclusions

Two cases of pulmonary sporotrichosis with cavitation are described.

Since 1912, 20 cases of pulmonary sporotrichosis have been reported. Of these, only 6 have been adequately documented.

The diagnosis of this rare mycotic infection must be established by bacteriologic methods. This fungus, ordinarily a saprophyte, should be shown to be pathogenic for animals. Potassium iodide is a specific drug frequently resulting in dramatic regression of the disease. Pulmonary resection is recommended for residual cavitation.

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TREATMENT OF HYPERTENSION WITH BENZYDROFLUMETHIAZIDE AS THE SOLE ANTIHYPERTENSIVE AGENT*

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BENZOTHIADIAZINE diuretics have become increasingly important in the treatment of arterial hypertension since the introduction of chlorothiazide in 1957.[1,2] Although chlorothiazide is effective and possesses relatively few toxic effects, much effort has been made to improve on this parent compound. Such endeavor has led to the synthesis of the dihydro derivative of chlorothiazide (hydrochlorothiazide), which is at least ten times as potent as chlorothiazide on a milligram basis.[3,4] In addition, fluorine-containing homologues of both drugs that appear to be similar in effectiveness and potency have been developed.[3,5]

A major difficulty in the use of these benzothiadiazine diuretics has been their tendency to cause depletion of potassium.[6] Consequently, further attempts have been made to develop a drug that would retain the potent natriuretic effect without excessive loss of potassium. Early reports suggest that some progress toward this objective may have been achieved by the development of a still more potent derivative of the benzothiadiazine compounds — that is, benzydroflumethiazide.¶ This new agent is thought to be approximately one hundred times more active, milligram for milligram, than chlorothiazide or flumethiazide and ten times more active than hydrochlorothiazide or hydroflumethiazide.[7-9] The structural relation of these various diuretic drugs is shown in Figure 1. It is the purpose of this report to present our findings on the use of benzydroflumethiazide‖ as the sole treat-

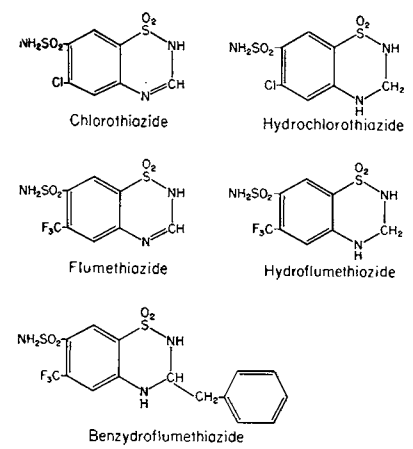

FIGURE 1. *Structural Formulas of Five Benzothiadiazine Diuretics.*

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¶Chemical name: 3-benzyl-3, 4-dihydro-6-(trifluoromethyl)-2H-1, 2, 4-benzothiadiazine-7-sulfonamide-1, 1-dioxide.

‖Kindly supplied as Naturetin by E. R. Squibb and Sons, Division of Olin Mathieson Chemical Corporation, New Brunswick, New Jersey.