

Asthma and hyperthyroidism

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Case histories of five patients with severe, intractable asthma, who were later found to have concomitant hyperthyroidism, are presented. Although the frequency of these two diseases in the same individual appears to be small, diagnosis and therapy of the hyperthyroid state provided dramatic amelioration of the asthma.

Intractable asthma, together with side effects of drugs used in its treatment, may mimic many symptoms associated with hyperthyroidism, such as extreme anxiety, tachycardia, palpitations, dyspnea, sweating, loss of weight, weakness, and tremors. The frequency of either asthma^{1, 2} or hyperthyroidism in the general population is such that it is not surprising that occasionally these two diseases occur concurrently in the same individual. When the presenting complaint is severe asthma, the diagnosis of concurrent hyperthyroidism may not be readily apparent.

A review of literature has revealed few pertinent references. In 1966, Schwartz³ studied 99 allergy patients and 35 control patients and concluded that there was no apparent association between the presence of an atopic state and functional thyroid abnormalities. In 1968, Kasperlik-Zaluska⁴ reported "two cases of bronchospastic states imitating bronchial asthma and associated with hyperthyroidism." In both cases, dyspnea was the most prominent symptom, and in both cases dyspnea disappeared upon effecting an euthyroid state with "thyreostatic drugs."

This report presents case histories of 5 patients with severe asthma considered intractable until the diagnosis and therapy of an associated hyperthyroid state resulted in prompt and striking improvement.

MATERIAL AND METHODS

In 1965 our initial patient, P. V., was hospitalized because of intractable asthma. During this admission an additional diagnosis of hyperthyroidism was made, and propylthiouracil (PTU) therapy was begun. With this antithyroid therapy, the patient's asthma responded promptly and dramatically. Because of this impressive response in severe status asthmaticus, an attempt has been made over the past six years to study prospectively our asthmatic patients, in both private allergy practice (G. S.) and the Rhode Island Hospital Allergy Clinic, by questioning them in detail about symptoms especially suggestive of abnormal thyroid function. Asthmatic patients with any question of abnormal thyroid symptoms were referred to an endocrinologist for further evaluation.

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A generally standardized protocol of laboratory tests included chest and sinus roentgenograms, urinalysis, complete blood count, blood urea nitrogen, lupus erythematosus cell preparation, electrolytes, serum protein electrophoresis, immunoglobulin levels (IgA, IgG, and IgM), arterial blood gas studies (pH, Pco_2 , Po_2 , O_2 saturation, and total CO_2), a complete battery of pulmonary function tests, allergy skin tests to common inhalant allergens* by the scratch technique and intracutaneous method when the latter was indicated, and a battery of thyroid function tests, including measurements of protein-bound iodine level (PBI), thyroxine level (T_4), radioactive triiodothyronine resin uptake (T_3), and 24 hour thyroid radioactive iodine (I^{131}) uptake. The pulmonary function tests, performed in the Division of Pulmonary Diseases,† included measurement of separate lung volumes, ventilation rates, and measurements before and after aerosolized bronchodilators of the maximum expiratory flow rate, maximum inspiratory flow rate, per cent vital capacity in one and 3 seconds, forced expiratory volume in one second, peak flow rate, and airway resistance. In addition, serum was drawn and stored at 0° C. under sterile conditions for special immunologic procedures for detection of possible antithyroid and antilung antibody with the use of TA-test‡ and double-diffusion Ouchterlony technique for evidence of any serum precipitins against both thyroglobulin (10 mg. per cubic centimeter.) and a crude aqueous extract of human lung tissue.

CASE HISTORIES

Case No. 1

Patient P. V., a 29-year-old Caucasian woman, had been in good health until the past year when she experienced the acute onset of marked wheezing and dyspnea. Her episodes of asthma rapidly increased in frequency and severity to the point of causing the patient to become virtually bedridden, and she required frequent hospitalizations. She responded poorly to treatment with bronchodilators, iodides, and steroids (up to a maintenance dose of 30 mg. of prednisone daily). At times it was felt that epinephrine and intravenous aminophylline may have made her worse. During the preceding year, the patient had lost approximately 19 pounds, had intermittent diarrhea, and increased sweating. She was nervous and irritable, and she complained of prominent eyes, loss of hair, and change of menstrual pattern. On several occasions, aspirin caused severe bronchospasm.

Physical examination. Physical examination revealed the patient, who was alert, thin, and anxious, to be in acute respiratory distress. Blood pressure was 100/80, pulse was 130 and regular. Examination of the chest revealed an increased anteroposterior diameter with intercostal retraction on inspiration; there was generalized expiratory wheezing throughout both lung fields. Her eyes appeared slightly exophthalmic, and a mild lid lag was detected. There was a fine distal tremor, and the skin was warm and moist. The thyroid was palpable but was not thought to be significantly enlarged.

Laboratory tests. Sweat chloride, 5-hydroxyindoleacetic acid (5-HIAA) and urinary 17-ketosteroids were essentially normal. Total eosinophil count was 520. Arterial blood showed a pH of 7.45, Po_2 55 mm. Hg, O_2 saturation 89 per cent, total CO_2 26 mEq. per liter, and Pco_2 39 mm. Hg. PBI was 9.4 μg per cent (normal 3.5 to 7.5), total iodine 11.7 μg per cent, T_3 40.4 per cent (normal 25 to 35), and I^{131} uptake 11.7 per cent (normal 20 to 50). Scan revealed a normal-sized gland. The complete battery of pulmonary function studies were interpreted as being consistent with obstructive airway disease of moderate to marked severity, with significant reversibility of airway obstruction after an aerosol bronchodilator. Allergy skin tests done to 48 inhalants and selected foods were essentially negative.

Course in hospital. The patient continued to wheeze for most of her long hospital

* Hollister-Stier Laboratories, Spokane, Wash.

† We are indebted to the Pulmonary Division of Rhode Island Hospital for performance and interpretation of pulmonary function tests.

‡ Hyland Laboratories, Los Angeles, Calif.

stay despite intravenous aminophylline, steroids, and intermittent positive-pressure breathing (IPPB). Bronchoscopy was negative, and a bronchial mucosal biopsy showed chronic inflammation with eosinophilia. Because of the persistence and severity of the asthma, the patient's clinical evidence of hyperthyroidism, and the elevated T_3 uptake and PBI, a trial of propylthiouracil (PTU) was initiated despite the low I^{131} uptake (patient had used iodides intermittently). After a 5 day period on antithyroid medication, she improved dramatically on PTU and was discharged free from wheezing and subsequently had only an occasional, transient episode of mild asthma. At a later date, during hot weather, hypoadrenocorticism was suspected because the patient became very lethargic during the course of an acute pharyngitis. She improved markedly on steroids and was maintained on a minimal amount of cortisone acetate orally and PTU. PTU was discontinued on a trial basis after approximately one year, after which the patient experienced an episode of wheezing which required hospitalization. PTU was then again given for a period of months with improvement in asthma; and when again discontinued, the patient remained in a euthyroid state. She was relatively free from asthma for another year but was readmitted to the hospital because of cushingoid appearance and hypertension. An attempt to taper the steroid dosage resulted in a severe episode of asthma which progressed to acute respiratory insufficiency necessitating a tracheotomy. Subsequent work-up confirmed the diagnosis of hypoadrenocorticism. The patient has since been maintained on 10 to 15 mg. of prednisone daily, and she has remained euthyroid and free from wheezing for the last 3 years.

Case No. 2

Patient R. B., a 35-year-old Caucasian man, was admitted to the hospital for treatment of a severe episode of wheezing and dyspnea. He had a history of eczema and asthma since the age of five years and had also undergone resection of a benign thyroid adenoma at the age of 11 years. His asthma had been mild, and he had worked as a laborer until approximately one year prior to his present admission, when his episodes of asthma became progressively worse to the point at which he was unable to perform light work. Allergy skin tests done at an earlier date by the scratch technique had revealed large positive reactions to extracts of house dust, pollens, and animal danders; the patient had been started on hyposensitization and had also been treated with bronchodilators, steroids, iodides, and antibiotics without much relief. During the preceding year he had lost 20 to 30 pounds despite a clearly excessive caloric intake. He complained of palpitations and of frequent bowel movements, up to 8 or 9 per day. He had experienced a gross change in behavior pattern, consisting of markedly increased irritability and emotional lability manifested by frequent uncontrollable crying spells.

Physical examination. Upon examination the patient was found to be in marked respiratory distress. Pulse was 130 per minute and regular, blood pressure was 120/70. The anteroposterior diameter of the chest was increased, and intercostal retraction was noted on inspiration. Auscultation of the chest revealed generalized expiratory wheezing in both lung fields. The thyroid was palpably enlarged, but there were no elicitable eye signs or tremor.

Laboratory tests. Arterial blood showed a pH of 7.36, with PO_2 of 45 mm. Hg, O_2 saturation 80 per cent, total CO_2 23 mEq. per liter, PCO_2 42 mm. Hg. PBI was 10.1 μ g per cent, total iodine over 20 μ g per cent, T_3 42.6 per cent, T_4 2.3 μ g per cent (normal 2.6 to 7.1), I^{131} uptake 48.7 per cent, and basal metabolism rate (BMR) +16 per cent. Sinus roentgenograms revealed evidence of chronic sinusitis. Pulmonary function tests were consistent with a moderately severe degree of airway obstruction, with a significant reversible component after the administration of an aerosol bronchodilator.

Hospital course. The patient was treated with bronchodilators, steroids, and IPPB with slight improvement, but he continued to have moderate wheezing. He was given a therapeutic trial of propylthiouracil, 600 mg. daily, in divided doses, and on this regimen the patient showed dramatic improvement in asthma, a return to normal emotional stability, a decrease in the number of bowel movements to two daily, and a stabilization of weight. Although he continued to require bronchodilators and oral steroids (10 mg. of prednisone daily), asthma

was well controlled, and he was able to return to work. After several months PTU was discontinued, and the asthma became much worse. On reinstituting PTU medication, asthma again dramatically improved. At a later date he received treatment with radioactive iodine and has maintained this improvement in asthma for the past 3 years, despite the fact that he has required exogenous thyroid medication for a subsequent state of hypothyroidism.

Case No. 3

Patient E. H., a 66-year-old Caucasian woman, was admitted to the hospital because of wheezing and shortness of breath of acute onset. She was unresponsive to epinephrine, oral bronchodilators, and intravenous aminophylline. The patient's first episode of asthma had occurred 12 years prior to her present hospitalization; a work-up at that time revealed a hyperthyroid state, and she had been treated with radioactive iodine. She subsequently improved, and, though she continued to have intermittent episodes of wheezing, these were mild and controllable with oral bronchodilators. However, during the 8 months preceding her present hospitalization, episodes of wheezing and shortness of breath had increased in frequency and severity to the point at which she was bedridden, despite the use of bronchodilators and steroids.

Physical examination. Upon examination, the patient was found to be in moderate respiratory distress. Pulse was 120 per minute and regular, blood pressure was 130/90. The anteroposterior diameter of the chest was increased and the expiratory phase of respiration was prolonged. Upon auscultation, generalized expiratory wheezing was heard throughout both lungs. A fine distal tremor was noted, as well as mild lid lag. The upper pole of the thyroid was palpable upon deglutition. The trachea was displaced to the right, and there was increased sternal dullness to percussion.

Laboratory tests. T_3 was 43.6 μg per cent, PBI 6.3 μg per cent, total iodine 7.0 μg per cent, and I^{131} uptake 23.9 per cent. (This was later felt to be possibly an incomplete reading as it was performed in a conventional manner by the technician, who was unaware of the substernal extension of the thyroid in this patient). Pulmonary function tests were indicative of severe obstructive lung disease, with slight improvement after bronchodilator aerosol. Paranasal sinus roentgenograms revealed sinusitis. Roentgenograms of the chest and a barium swallow confirmed the presence of a substernal goiter. Allergy skin tests to common inhalants and selected foods were negative.

Hospital course. The patient responded well to treatment with intravenous steroids, aminophylline, and IPPB. An endocrine consultation was obtained, and the patient was considered to be clinically hyperthyroid. She was given 10 mc. of radioactive iodine with improvement after about 3 weeks. The patient's asthma stabilized and has been controlled on bronchodilators and an average of 10 mg. of prednisone daily for the past 3 years.

Case No. 4

Patient L. A., a 49-year-old Negro woman, was admitted to the hospital for the tenth time for treatment of status asthmaticus. There was a past history of pulmonary tuberculosis diagnosed at age 34, which required a left pneumonectomy and had remained inactive for the past 10 years. Her episodes of asthma dated to her teens and had become progressively worse, requiring frequent emergency treatment. Repeated chest roentgenograms prior to age 34 were negative for tuberculosis. Her other symptoms were preference for cold weather, stiffness of both hands, perspiration upon minimal effort, at least 2 bowel movements daily, and increased menstrual flow.

Physical examination. Examination showed the patient to be thin and dyspneic. Blood pressure was 130/90, pulse was 97 per minute and regular. The left hemithorax was deformed secondary to an old pneumonectomy. There were inspiratory and expiratory wheezes audible throughout the right lung field. The thyroid was not palpably enlarged.

Laboratory tests. Arterial blood revealed a pH of 7.49, with Po_2 of 60 mm. Hg, O_2 saturation of 92 per cent, total CO_2 29 mEq. per liter, Pco_2 of 39 mm. Hg. PBI was 8.4 μg per cent, total iodine 8.6 μg per cent, I^{131} uptake 35.5 μg per cent, and T_3 31.1 per cent.

Chest roentgenogram upon admission was reported as consistent with a left pneumonectomy. The right lung was clear and moderately hyperaerated. A few fibrotic streaks were present in the right apex. No signs of active tuberculosis were noted. Paranasal sinus roentgenograms revealed chronic sinusitis. ECG was consistent with cor pulmonale. Pulmonary function tests were reported as consistent with obstructive lung disease of marked severity with improvement in the airway resistance after the administration of an aerosol bronchodilator, she was treated with IPPB, sedatives, and antibiotics and improved somewhat, but she did not become free from wheezing. Because of the clinical evidence suggestive of hyperthyroidism, her elevated PBI and her relative refractoriness to conventional treatment, it was decided to give the patient a therapeutic trial of PTU. On the third day of PTU therapy her wheezing ceased completely, and she was discharged from the hospital. After several months PTU was discontinued, and her subjective symptoms of hyperthyroidism promptly returned together with worsening of her asthma. For this reason the patient was treated with radioactive iodine, after which the asthma has been controlled on an outpatient basis for the past year.

Case No. 5

Patient B. F., a 63-year-old Caucasian female, was first seen as an outpatient because of acute onset of wheezing and dyspnea. She had been well except for chronic sinusitis until 3 months prior to her current difficulties, when she began to notice increased nervousness, anxiety, tremors, and palpitations. She had also experienced an unexpected 15 pound weight loss despite maintenance of her usual food intake. Allergy skin tests were negative. Thyroid studies at this time revealed a PBI of 8 mg. per cent, total iodine 8.8 μ g per cent, T_3 36.2 μ g per cent, and BMR + 17 per cent. A few days prior to a scheduled hospitalization for a nasal polypectomy and antral window operation, she had another episode of asthma which required admission, and she was finally controlled with intravenous steroids. Nasal polypectomy and antral windows were performed, and the patient was tapered off steroids. She improved markedly after surgery and was completely asymptomatic. Repeat thyroid function studies were normal. Approximately 10 weeks later, she had another episode of severe wheezing and was admitted to the hospital in status asthmaticus and respiratory failure.

Physical examination. Upon examination, the patient was found to be in marked respiratory distress. Pulse was 130 per minute and regular, blood pressure was 140/60. Examination of the chest showed an increased anteroposterior diameter, mild intercostal retraction, and expiratory wheezing audible throughout both lung fields. There was slight exophthalmos, but the thyroid was not thought to be significantly enlarged.

Laboratory tests. Complete blood count revealed 12 per cent eosinophils. Arterial blood showed a pH of 7.27, PO_2 of 52 mm. Hg, O_2 saturation of 81 per cent, total CO_2 of 26 mEq. per liter and P_{CO_2} of 59 mm. Hg. PBI was 9.5 μ g per cent, butanol-extractable iodine (BEI) 7.8 μ g per cent, T_3 44.4 μ g per cent, T_4 8.4 μ g per cent, and I^{131} uptake 11 per cent. Sinus roentgenograms showed evidence of chronic sinusitis. A complete battery of pulmonary function studies was reported as being consistent with chronic obstructive lung disease with a bronchospastic component.

Hospital course. The patient was treated with bronchodilators, steroids, and IPPB and improved markedly in regard to wheezing. However, she continued to be extremely nervous and tremulous, and her tachycardia persisted even when her lungs were clear. Because of clinical evidence of hyperthyroidism, it was decided to give the patient a therapeutic trial of propylthiouracil. Over a period of 3 months she was completely free from wheezing, was no longer "nervous," and had regained approximately 12 pounds. Thus antithyroid medication was discontinued on a trial basis. She did well for about the following 5 months but then began to complain of feeling nervous and jittery, weight loss, and of having 4 to 5 bowel movements daily. Her next episode of wheezing was severe and required hospitalization. She improved with PTU, aminophylline, and steroids. At that time a repeat I^{131} uptake was 78.1 per cent, and a thyroid scan was reported as showing an enlarged thyroid gland with uniform and intense uptake. She was later treated with radioactive iodine, after which the patient regained a total of 27 pounds and has been clinically euthyroid for the past 4

TABLE I

Name	Sex	Age of onset asthma (yr.)	Age hyperthyroidism was diagnosed (yr.)	Family history asthma and/or hay fever	Allergy skin tests	Roentgenographic evidence of sinusitis	Abnormal thyroid tests
P. V.	F	28	29	H. F. (father)	Neg.	No	PBI, T ₁
R. B.	M	5	35	Neg.	Many positives (dust, pollens, danders, mold)	Yes	T ₃ , borderline I ¹³¹
E. H.	F	54	54	Neg.	Neg.	Yes	T ₃
L. A.	F	19	49	Asthma (father, brother sister)	Neg.	Yes	PBI
B. F.	F	63	63	Asthma (sister)	Neg.	Yes	PBI, T ₄ , T ₃ , I ¹³¹ , BEI

years. She has occasional episodes of mild wheezing which are readily controlled with oral bronchodilators.

Special immunologic procedures were negative in all these patients. Tests of the patients' sera for autoantibody of the antithyroglobulin type were negative with the TA-tests and Ouchterlony technique. No antilung antibody was detected when the patients' sera and a crude aqueous extract of human lung antigen were used with the Ouchterlony technique.

DISCUSSION

Each of these patients presented with severe, uncontrollable asthma, and all were initially undiagnosed as far as the hyperthyroidism was concerned. In most instances the severe asthma became manageable within a few days after the hyperthyroidism was treated and controlled with PTU. It generally was impossible to determine by history which of these two diseases occurred first because of the similarity of some of the symptoms. The onset of asthma in all of our patients occurred in adult life, except for the male patient, R. B., whose asthma began at age of 5 years (Table I).

Patient R. B. was also the exception in that he was the only one who demonstrated significantly positive skin test reactions to pollens, molds, feathers, and house dust extracts. The other patients all had essentially negative reactions to a battery of 48 common allergens, which included such inhalants as pollens, molds, animal danders, and house dust.

The diagnosis of asthma was established by a history of long-standing symptoms of wheezing, cough, and shortness of breath, together with the fact that some degree of reversibility was noted in pulmonary function tests after aerosolized isoproterenol. In all our patients, the pulmonary symptoms were severe, and all required hospitalization for status asthmaticus. Dyspnea on ex-

TABLE II

Patient	Treatment of hyperthyroidism	Remissions on propylthiouracil	Present status
P. V.	PTU	Yes, (two occasions)	No asthma for 3 years
R. B.	PTU, I ¹³¹	Yes, (two occasions)	Mild daily wheezing
E. H.	I ¹³¹		Mild daily wheezing
L. A.	PTU, I ¹³¹	Yes, (two occasions)	Mild daily wheezing
B. F.	PTU, I ¹³¹	Yes, (two occasions)	Only occasional slight asthma with respiratory infections

bronchospasm but is most probably related to weakness in respiratory muscles and an increase in dead space ventilation.^{5, 6}

The diagnosis of hyperthyroidism was established by evaluation of clinical symptoms, at least one abnormal laboratory test for thyroid function, confirmation by an endocrinologist (M. H.), and a significant response to anti-thyroid treatment. All of these patients may have received iodide medication in some form and at some time for treatment of asthma prior to the diagnosis of concurrent hyperthyroidism. This exogenous iodine presented some problems in evaluating their laboratory results pertaining to thyroid status. However, the T₃ and T₄ thyroid tests were helpful in these cases. A possible important clue as an aid in diagnosing hyperthyroidism in asthmatic patients is the observation that routine dosages of epinephrine or intravenous aminophylline produced in some of our cases a severe hyperexcitability and at times a distinct worsening of the asthma.

Most of our cases responded well to PTU. However, when PTU was discontinued on a trial basis, symptoms of hyperthyroidism usually returned and the asthma worsened. These patients later received I¹³¹ therapy with good long-term response of asthma. Only one of our patients, P. V., could be maintained in a prolonged euthyroid state after PTU therapy alone (Table II).

The frequency of asthma and hyperthyroidism occurring in the same patient appears to be small. Since this investigation began in 1965, these 5 patients represent the total number of patients with both these diseases discovered by prospective screening of all our many asthmatic patients. However, we consider noteworthy the clinical severity and the apparent significant therapeutic benefit from treatment of the concurrent hyperthyroid state.

Asthma and hyperthyroidism have probably occurred together in our patients strictly by chance without any interrelating causes, especially since the frequency of these diseases occurring concurrently appears to be small. However, the administration of exogenous iodide and the emotional stress associated with acute asthma are two possible precipitating factors of hyperthyroidism.⁷ The first, the Jod-Basedow phenomenon, is rare but has been reported as occurring occasionally in endemic goiter areas after administration of several milligrams of iodide. The second possible precipitating factor, emo-

tional stress, has not been proved to be significant by controlled studies, but many endocrinologists have this impression.

A speculative pathogenetic interrelation is afforded by Szentivanyi's beta adrenergic theory of bronchial asthma. In hyperthyroidism there is an impaired production of intracellular adenosine triphosphate (ATP).⁹ In addition, thyroxine increases the synthesis of adenylyl cyclase, which in turn may increase cyclic 3', 5'-adenosine monophosphate (CAMP) synthesis¹⁰ from its source, ATP.¹¹ This further reduction of an already deficient ATP level may produce a situation in which the end result is an over-all decrease in cyclic 3' 5'-AMP. This decrease may further aggravate the already malfunctioning adenylyl cyclase system which may be found in asthmatic patients.

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