

# Urticaria and pruritus: Uncommon manifestations of hyperthyroidism

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*The clinical course of 4 patients with hyperthyroidism and urticaria and 2 patients with hyperthyroidism and generalized pruritus alone strongly suggest an etiologic relationship. There was no specific difference in this group of patients when compared with the general hyperthyroid population with regard to age, race, menstrual status, allergic history, duration of hyperthyroidism, physical findings, or the laboratory indices of thyrotoxicosis. The urticaria or pruritus did not respond to antihistamines but cleared with control of the hyperthyroid state. The exact mechanism by which hyperthyroidism causes urticaria and pruritus is not known. Some theoretic relationships between the hyperthyroid state, kinin activation, and catecholamine activity are discussed.*

Urticaria or pruritus alone are uncommon dermatologic manifestations of hyperthyroidism and are seldom stressed in review articles on hyperthyroidism.<sup>1-4</sup>

The infrequency of these two clinical phenomena is suggested by Rothfield<sup>5</sup> in his review of 108 cases of hyperthyroidism. He found that pruritus appeared at the onset and disappeared with the control of the hyperthyroidism in 5 patients, while 2 others had urticaria which varied with the degree of hyperthyroidism. Pruritus as a chief manifestation of thyrotoxicosis has been described in 7 patients.<sup>6, 7</sup> There have been no detailed reports of urticaria as a prominent finding in this disease.

Although relatively benign symptoms of a major metabolic disease, it is the severe urticaria and pruritis that may first lead the patient to seek medical attention. A greater awareness of this relationship on the part of physicians would allow earlier diagnosis of the primary disorder.

The purpose of this study is to report 4 cases of hyperthyroidism with urticaria and 2 with generalized pruritus alone and to present speculations about the pathophysiologic mechanisms of these manifestations.

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## CASE REPORTS

### Case 1

D. O., a 12-year-old Puerto Rican premenstrual schoolgirl was followed over a 4 year period. She presented with a 6 month history of nervousness, insomnia, swelling of the neck, and increasing protrusion of the eyes.

Significant physical findings were: blood pressure 110/68 mm. Hg, pulse rate 112 beats per minute, slight exophthalmos, symmetrically enlarged thyroid, and a fine tremor of the hands.

Initial laboratory data were: hemoglobin 9.5 Gm. per 100 ml., hematocrit 33 per cent, white blood cell count 5,800 per cubic millimeter with 64 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes, 3 per cent monocytes, and 3 per cent eosinophils, serum protein-bound iodine 10.1  $\mu$ g per 100 ml., serum cholesterol 174 mg. per 100 ml., 24 hour radioactive iodine thyroidal uptake 100 per cent and a scan showing diffuse uptake, and a negative test for antithyroglobulin antibodies.

The patient was treated with 5 mg. of methimazole 3 times a day with resultant symptomatic relief. She was unreliable in taking medication and returned after 4 years with the complaints of sweating, tachycardia, and recurrent itching and hives for 1½ years during those periods when she had not taken medication. Diphenhydramine was ineffective in relieving the urticaria.

No previous history of urticaria was elicited nor were drugs, foods, infection, or emotional stress incriminated.

Significant physical findings included underweight, hyperactivity, mild exophthalmos, pulse rate 110 beats per minute, thyroid enlarged 2½ times normal with a bruit, and diffuse urticaria over the arms, chest, and abdomen.

The serum protein-bound iodine was 9.0  $\mu$ g per 100 ml., and 24 hour radioactive iodine thyroidal uptake was 78.2 per cent.

Methimazole was restarted, and 2 months later, the urticaria and other symptoms of hyperthyroidism were gone.

*Comments.* This patient first developed urticaria after a number of exacerbations of hyperthyroidism. The urticaria behaved as did the other manifestations of hyperthyroidism, being controlled through antithyroid medication.

### Case 2

D. T., a 23-year-old Caucasian housewife, was followed over a 6 month period. She presented with a 2 month history of hives, initially intermittent, involving the hands, forearms, and thighs. One month prior to her visit the hives gradually became more intense, constant, and generalized, involving the entire body including the palms and soles. Diphenhydramine, hydroxyzine, cyproheptadine, and a brompheniramine-phenylephrine compound were ineffective in relieving the urticaria. There was slight anxiety, anorexia, and a 7 pound weight loss but no other symptoms suggesting hyperthyroidism.

No previous history of urticaria was elicited, nor could a relationship be established to drugs, foods, infection, or emotional stress.

Significant physical findings were: blood pressure 130/70 mm. Hg, pulse rate 108 beats per minute, thyroid barely palpable, and the skin, including the palms, was warm and dry with multiple hives of varying size covering the entire body.

Initial laboratory data were: hemoglobin 14.4 Gm. per 100 ml., hematocrit 43 per cent, white blood cell count 10,200 per cubic millimeter with 66 per cent polymorphonuclear leukocytes, 32 per cent lymphocytes, and 2 per cent eosinophils, serum protein-bound iodine 14.5  $\mu$ g per 100 ml., serum cholesterol 178 mg. per 100 ml., thyroxine-by-column 11.2  $\mu$ g per 100 ml. (normal 2.9 to 6.4), 24 hour radioactive iodine thyroidal uptake 59.8 per cent (46.9 per cent after triiodothyronine suppression, 75  $\mu$ g per day for 7 days), and antithyroglobulin antibody titer less than 1:16 (normal under 1:32).

The patient was placed on 60 mg. of methimazole per day and within 10 days noticed a marked decrease in frequency, number, and severity of the hives. Subsequently a scattering

of hives has been noted infrequently. Thyroxine-by-column in the fourth month after initiation of therapy was 5.4  $\mu\text{g}$  per 100 ml.

*Comments.* Urticaria was the most prominent clinical manifestation of hyperthyroidism in this woman and cleared rapidly once antithyroid medication was started.

### Case 3

A. R., a 67-year-old Caucasian housewife, was followed over an 11 month period. Initial complaints were nervousness, palpitation, and increasing neck size for 12 months, an increased number of daily bowel movements and 8 pound weight loss for 4 months, and generalized persistent hives for one month. Diphenhydramine was ineffective in relieving the urticaria.

A 3 day episode of urticaria occurred 35 years before, the cause being unknown. A relationship could not be established to drugs, foods, infection, or emotional stress in the current presentation of urticaria.

Significant physical findings were: blood pressure 150/90 mm. Hg, pulse rate 100 beats per minute, thyroid diffusely enlarged, fine tremor of the hands, and multiple hives on the arms and chest.

Initial laboratory data were: hemoglobin 12.5 Gm. per 100 ml., hematocrit 39 per cent, white blood cell count 5,000 per cubic millimeter with 40 per cent polymorphonuclear leukocytes, 57 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophils, serum protein-bound iodine 11.0  $\mu\text{g}$  per 100 ml., serum cholesterol 183 mg. per 100 ml., and 24 hour radioactive iodine thyroidal uptake 66.2 per cent with prominent right lobe enlargement.

One month after the patient had been referred for radioactive iodine therapy, there was no change noted in either urticaria or hyperthyroid manifestations. It was found that she had mistakenly been given another diagnostic uptake (60.0 per cent) and serum protein-bound iodine (14.0  $\mu\text{g}$  per 100 ml.) instead of the therapeutic dose. She was then treated with 5 mc. of radioactive iodine. Within 3 weeks the urticaria had completely cleared, other symptoms gradually subsided, and a 17 pound weight gain was recorded in the 2 months after therapy.

Significant physical findings at this time were: blood pressure 160/90 mm. Hg, pulse rate 78 beats per minute, the thyroid appeared smaller, and tremors of the hands and urticaria were no longer present. The 24 hour radioactive thyroidal uptake was 11.7 per cent. Five months later there was no evidence of hyperthyroidism or urticaria.

*Comments.* The patient was a postmenopausal woman who developed urticaria 11 months after the onset of hyperthyroidism. Urticaria led the patient to seek medical attention. The mistaken second diagnostic radioactive iodine uptake served as a clinical experiment to demonstrate that relief of the urticaria was directly related only to the course of the hyperthyroid state.

### Case 4

M. D., a 70-year-old Caucasian female housekeeper, was followed over a 9 month period. Initial complaints were increasing anxiety for 13 months, a 10 pound weight loss, gradual increase in heart rate and hand tremors for 8 months, and generalized urticaria and progressive ophthalmoplegia for one month. Diphenhydramine, chlorpheniramine, and brompheniramine were ineffective in relieving the urticaria.

During the previous 25 years the patient had suffered infrequent 1 to 2 day episodes of urticaria of unknown etiology. A relationship could not be established to drugs, foods, infection, or emotional stress in the current presence of urticaria.

Significant physical findings were: blood pressure 170/90 mm. Hg, pulse rate 100 beats per minute, moderate ophthalmoplegia, diffusely enlarged thyroid, and a fine tremor of the hands. Multiple hives were present over her entire body.

Initial laboratory data included: white blood cell count 4,850 per cubic millimeter with 37 per cent polymorphonuclear leukocytes, 50 per cent lymphocytes, 4 per cent

monocytes, 1 per cent basophils, and 8 per cent eosinophils, serum protein-bound iodine 8.0  $\mu\text{g}$  per 100 ml., serum cholesterol 180 mg. per 100 ml., and 24 hour radioactive iodine thyroidal uptake 48 per cent.

Three weeks after radioactive iodine therapy, the patient noted improvement in tachycardia, tremors, and urticaria. Six weeks later the urticaria had completely cleared, and she had been symptom free for the next 4 months when last seen. At this time the serum protein-bound iodine was 4.5  $\mu\text{g}$  per 100 ml., and serum cholesterol was 300 mg. per 100 ml.

*Comments.* The patient developed urticaria 12 months after the onset of hyperthyroid symptoms. Despite these prominent symptoms, it was the urticaria that first led her to seek medical attention. The urticaria disappeared upon return to a euthyroid state.

### Case 5

A 26-year-old Negro housewife was followed over a 3 year period. She presented with persistent progressive generalized pruritus, 23 pound weight loss, multiple daily bowel movements, palpitation, tachycardia, neck enlargement, and increasing anxiety of 14 months duration. Hydroxyzine and brompheniramine did not relieve the pruritus.

No previous history of pruritus or urticaria could be elicited, nor could a relationship be established to drugs, foods, infection, or emotional stress.

Significant physical findings were: blood pressure 136/72 mm. Hg, pulse rate 108 beats per minute, a rapid and explosive speech pattern, slight exophthalmos and lid lag, thyroid diffusely enlarged, and a fine tremor of the hands. Multiple skin excoriations were present on the extremities, chest, and abdomen. Hydroxyzine, ephedrine, and brompheniramine were ineffective.

Initial laboratory data included: hemoglobin 12.3 Gm. per 100 ml., hematocrit 26 per cent, white blood cell count 6,100 per cubic millimeter with 42 per cent polymorphonuclear leukocytes, 48 per cent lymphocytes, 8 per cent basophils, and 2 per cent eosinophils, serum protein-bound iodine 11.0  $\mu\text{g}$  per 100 ml., and serum cholesterol 115 mg. per 100 ml.

The patient was placed on methimazole, 45 mg. a day. Because of a poor response, Lugol's solution was added 11 days later. Within 72 hours the pruritus and other symptoms of hyperthyroidism were brought under control.

The patient was maintained on methimazole and thyroid extract for one year when they were voluntarily discontinued. Gradually the initial signs and symptoms of hyperthyroidism, including generalized pruritus, recurred. Methimazole was reinstituted and the pruritus subsided as the antithyroid medication became effective.

*Comments.* Generalized pruritus was the major initial symptom of hyperthyroidism in this patient. Several physicians attempted symptomatic therapy of the intractable pruritus and overlooked the existing hyperthyroid state. Antithyroid therapy relieved the pruritus along with the other manifestations of hyperthyroidism initially and following the second exacerbation.

### Case 6

M. G., a 61-year-old Caucasian unmarried saleswoman, was followed over an 8 month period. Initial complaints were hand tremors and 25 pound weight loss of 24 months duration, mild intermittent pruritus, palpitation, shortness of breath, ankle swelling, and generalized weakness of 12 months duration, and severe, unremitting pruritus of the neck, arms, trunk, and legs of several days duration. She consulted a physician because of the intractable pruritus and was treated during the ensuing 3 weeks with chlorpheniramine and prednisone without effect. At this juncture hyperthyroidism was considered on the basis of persistent tachycardia, tremor, and warm, diaphoretic skin, and the patient was admitted to the hospital.

No previous history of urticaria was elicited nor were drugs, foods, infection, or emotional stress incriminated.

Significant physical findings were: blood pressure 140/60 mm. Hg, pulse rate 130 beats per minute, warm diaphoretic skin, fine tremor of the hands, and pedal edema.

Initial laboratory data were: hematocrit 39 per cent, white blood cell count 6,400 per cubic millimeter with 54 per cent polymorphonuclear leukocytes, 39 per cent lymphocytes, 4 per cent monocytes, and 3 per cent eosinophils, serum protein-bound iodine 14.0 and 24.0  $\mu\text{g}$  per 100 ml., serum cholesterol 130 mg. per 100 ml., and 24 hour radioactive iodine thyroidal uptake 80 per cent.

On the fourth hospital day the patient developed severe anxiety, agitation, rectal temperatures to 105.2° F., pulse rates to 148 beats per minute, diarrhea, and signs of congestive heart failure. She was treated for thyroid storm with intramuscular reserpine, intravenous sodium iodide, prednisone, antibiotics, hypothermia blanket, and methimazole. Digoxin, oxygen, and diuretics were administered for heart failure. The pruritus persisted during the week of thyroid storm and in a milder form for the following 2 weeks. Subsequently, pruritus has not been present. Radioactive iodine was administered, and 8 months later the patient has continued to be asymptomatic with a serum protein-bound iodine of 6.0  $\mu\text{g}$  per 100 ml.

*Comments.* Although hyperthyroid symptoms were present in this patient for more than 2 years, it was not until the pruritus became unbearable that medical attention was sought. The severity of the pruritus diverted the physician from suspecting the presence of hyperthyroidism for several weeks, and thyroid storm ensued. On intensive antithyroid therapy, the intractable pruritus slowly cleared along with the other manifestations of hyperthyroidism.

## DISCUSSION

All patients were women, ranging in age from 12 to 70 years. There was no relationship between the appearance of skin manifestations and age, race, menstrual status, duration of hyperthyroidism, physical findings, or the laboratory indices of hyperthyroidism (Table I).

The relationship between thyrotoxicosis and its dermatologic manifestations is obscure, since the latter may have multiple etiologies. Urticaria may be due to a variety of causes,<sup>8-10</sup> including hypersensitivity reactions, cholinergic reactions, infection, physical factors, such as stroking the skin, pressure, light, heat or cold, and emotional factors. The cause of chronic urticaria, however, is usually not found.<sup>8</sup>

Chemical mediators such as serotonin, acetylcholine, histamine, and the kinins have been suggested as possible causes of pruritus and the wheal and flare characteristic of urticaria.<sup>9, 10</sup> However, serotonin causes erythema, not whealing, in human subjects.<sup>11</sup> Acetylcholine produces a characteristic type of wheal and flare<sup>8</sup> not observed in our patients. Neither was the urticaria or pruritus induced by heat or effort, as would be expected if caused by acetylcholine.<sup>10</sup>

The possibility that the urticaria of hyperthyroidism might be related to an autoimmune phenomenon must be considered, since a variety of autoantibodies to components of the thyroid gland (thyroglobulin, microsomes, colloid antigen, nucleus) have been described in this disease.<sup>12</sup> However, levels of antithyroglobulin antibodies were normal in the 2 patients tested, and urticaria has not been described as a prominent symptom in patients with Hashimoto's disease, a condition in which the highest levels of these antibodies are found.<sup>13</sup> Another immunoglobulin found in the plasma of patients with Graves' disease, long-acting thyroid stimulator (LATS), has been measured with particular

TABLE I. Patient summary

| Patient data                                            | Urticaria            |             |             |                    | Pruritus    |             |
|---------------------------------------------------------|----------------------|-------------|-------------|--------------------|-------------|-------------|
| Case No.                                                | 1                    | 2           | 3           | 4                  | 5           | 6           |
| Age (yr.)                                               | 12                   | 23          | 67          | 70                 | 26          | 61          |
| Race                                                    | PR                   | C           | C           | C                  | N           | C           |
| Sex                                                     | F                    | F           | F           | F                  | F           | F           |
| Hyperthyroid symptoms prior to urticaria-pruritus (mo.) | 36                   | 0           | 11          | 12                 | 0           | 24          |
| Eye Signs (0-4+)                                        | 1+                   | 0           | 0           | 2+                 | 1+          | 0           |
| Pulse rate                                              | 112                  | 108         | 100         | 100                | 120         | 130         |
| Weight loss (pounds)                                    | —                    | 7           | 8           | 10                 | 23          | 25          |
| Location urticaria-pruritus                             | Arms, chest, abdomen | Generalized | Arms, chest | Trunk, extremities | Generalized | Generalized |
| Response to anti-histamines                             | None                 | None        | None        | Worse              | None        | None        |
| Serum PBI ( $\mu$ g/100 ml.) (normal 4-8)               | 10.1                 | 14.5        | 9.7         | 8.0                | 11.0        | 14.0, 24.0  |
| Serum cholesterol (mg./100 ml.) (normal 150-250)        | 174                  | 173         | 158         | 180                | 115         | 130         |
| 24 hr. RAI uptake (%) (normal 15-45%)                   | 100                  | 59.8        | 66.2        | 48                 |             | 80          |
| Antithyroglobulin titer (normal < 1:32)                 | 0                    | < 1:16      |             |                    |             |             |

PR = Puerto Rican, C = Caucasian, N = Negro, PBI = protein-bound iodine, RAI = radioactive iodine.

regularity in the plasma of patients with another dermatologic manifestation of hyperthyroidism—pretibial myxedema.<sup>14</sup> LATS levels, however, remain elevated for up to 2 years, even after complete radioablation of the thyroid gland,<sup>15</sup> while the urticaria and pruritus in our patients seemed related to the severity of the hypermetabolic state.

While histamine has long been considered the most important mediator in pruritus and urticaria,<sup>10, 11</sup> antihistamines were ineffective in relieving the urticaria and pruritus in our patients. Furthermore, histamine does not cause itching without objective skin manifestation,<sup>16, 17</sup> as was the case in 2 of our patients.

Patients with chronic urticaria exhibit varying responsiveness to antihistamines,<sup>8, 18</sup> strengthening the possibility of mediators other than histamine. Juhlin and Michaelsson<sup>19</sup> treated 6 such patients unrelieved by antihistamines and corticosteroids with intravenous infusion of a commercial kallikrein inhibitor, Trasylol. The daily urticarial eruptions cleared for periods of 5 to 90 days. Kallikreins are a group of peptidases which, when activated, convert kininogens to kinins, shown to cause both pruritus and the wheal and flare characteristic of urticaria.<sup>11, 20, 21</sup>

The relationship of the thyroid hormones to the kallikrein-kinin system has not been studied specifically. The increase in local tissue metabolism in hyperthyroidism results in increased heat production and an acidic environment.<sup>22, 23</sup> Furthermore, since evidence exists for increased catabolism of protein in thyrotoxicosis<sup>24</sup> or in animals given large quantities of thyroxine,<sup>25</sup> increased release of tissue proteolytic enzymes is possible. Any or all of these three factors—heat, tissue acidity, and increased proteolytic enzymes—are conducive to the activation of the kininogens to kinins by kallikreins<sup>26</sup> which could cause pruritus or urticaria. The development of a slightly acid tissue pH contributes to the accumulation of kinins (bradykinin, lysyl-bradykinin) by a reduction in kininase activity and the formation of a kininase-resistant kinin (methyl-lysyl-bradykinin), as well as by a reduction of kallikrein inhibitor.<sup>27</sup>

Cutaneous vasodilatation, which is a prominent feature of hyperthyroidism, is an important factor in lowering the threshold to itch.<sup>28</sup> The parenteral administration of a vasoconstrictor (ergotamine) has been demonstrated to transiently relieve the pruritus of hyperthyroidism.<sup>6</sup>

Many of the signs and symptoms of hyperthyroidism (tachycardia, increased cardiac output and systolic blood pressure, palpitation, tremor, sweating and heat intolerance, increased metabolic rate, and weight loss) are similar to those produced by excess exogenous or endogenous catecholamines.<sup>29, 30</sup> Most evidence indicates normal serum,<sup>29</sup> urinary,<sup>31</sup> and myocardial<sup>32</sup> catecholamine levels. The alternate explanation—that there is increased sensitivity to normal catecholamine levels<sup>29, 30</sup> mediated, perhaps, by the effects of both thyroxine and the catecholamines on adenylyl cyclase activation—has been challenged in a recent review.<sup>33</sup> Nevertheless, sympathetic blockade has been shown to reduce many metabolic<sup>34</sup> and clinical<sup>35</sup> manifestations of hyperthyroidism, including pruritus,<sup>6</sup> while all chemical indices of increased thyroid activity remain unchanged. Since many of the previously mentioned features of the hyperthyroid state which could play a role in the activation of kinins (increased tissue metabolism, heat reduction, tissue pH, vascular tone, and permeability) could be mediated through a catecholamine effect, the effect of sympathetic blockade on the urticaria of hyperthyroidism would be of great interest. To our knowledge, this has not been reported.

Clearly, further studies are necessary to clarify the role of these interrelated systems in pruritus and urticaria, and in hyperthyroidism in general. Such studies are under way in these laboratories.<sup>34, 36</sup>

Despite the complexity of the possible mechanisms by which the hyperthyroid state may contribute to these cutaneous symptoms, the 6 patients presented in this report illustrate some important clinical facts:

1. Pruritus and urticaria may be the symptoms of hyperthyroidism that first bring the patient to the attention of a physician.
2. These symptoms tend to be chronic and intractable and do not respond to conventional symptomatic therapy but clear with control of the hyperthyroid state.
3. Awareness of the relationship by the general physician may lead to earlier diagnosis of the primary disorder.

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## REFERENCES

- 1 Chapman, E. W., and Maloof, F.: Bizarre clinical manifestations of hyperthyroidism, *New Eng. J. Med.* **254**: 1, 1956.
- 2 Steinbeck, A. W.: Some aspects of the clinical diagnosis of thyroid disease, *Med. J. Aust.* **2**: 50, 1963.
- 3 Caravati, C. M., Jr., Richardson, D. R., Wood, B. T., and Cawley, E. P.: Cutaneous manifestations of hyperthyroidism, *Southern Med. J.* **62**: 1127, 1969.
- 4 Locke, W.: Unusual manifestations of Graves' disease, *Med. Clin. N. Amer.* **51**: 915, 1967.
- 5 Rothfield, B.: Pruritus as a symptom in hyperthyroidism, *J. A. M. A.* **205**: 122, 1968.
- 6 Eliakim, M., and Rachmilewitz, M.: Pruritus: A neglected symptom in thyrotoxicosis, *Israel Med. J.* **18**: 262, 1959.
- 7 Barrow, M. V., and Bird, E. D.: Pruritus in hyperthyroidism, *Arch. Derm.* **93**: 237, 1966.
- 8 Winklemann, R. K.: Chronic urticaria, *Mayo Clin. Proc.* **32**: 329, 1957.
- 9 Beall, G. N.: Urticaria: A review of laboratory and clinical observations, *Medicine* **43**: 131, 1964.
- 10 Thompson, J. S.: Urticaria and angioedema, *Ann. Intern. Med.* **69**: 361, 1968.
- 11 Herxheimer, A., and Schachter, M.: Wheal and flare in human skin produced by histamine and other substances, *Nature (Lond.)* **183**: 1510, 1959.
- 12 Hall, R.: Immunologic aspects of thyroid function, *New Eng. J. Med.* **266**: 1204, 1962.
- 13 Rose, N. R., and Witebsky, E.: Thyroid autoantibodies in thyroid disease, *Advances Metab. Dis.* **3**: 231, 1968.
- 14 Kriss, J. P., Pleshakov, V., and Chien, J. R.: Isolation and identification of the long-acting thyroid stimulator and its relation to hyperthyroidism and circumscribed pretibial myxedema, *J. Clin. Endocr.* **24**: 1005, 1964.
- 15 Volpe, R., Desbarats-Schonbaum, M., Schonbaum, E., Row, V. V., and Ezrin, C.: The effect of radioablation of the thyroid gland in Graves' disease with high levels of long-acting thyroid stimulator (LATS), *Amer. J. Med.* **46**: 217, 1969.
- 16 Arthur, R. P., and Shelley, W. B.: The nature of itching in dermatitic skin, *Ann. Intern. Med.* **49**: 900, 1958.
- 17 Cormia, F. E., Dougherty, J. W., and Unrau, S. A.: Proteolytic activity in dermatoses: Preliminary observations on inflammation and pruritus, *J. Invest. Derm.* **28**: 425, 1957.
- 18 Michaelsson, G.: Chronic urticaria—a clinical study with special reference to vascular reactions induced by the kallikrein-kinin system, *Acta Dermatoven. (Stockholm)* **49**: 404, 1969.
- 19 Juhlin, L., and Michaelsson, G.: Use of a kallikrein inhibitor in the treatment of urticaria and hereditary angioneurotic edema, *Acta Dermatoven. (Stockholm)* **49**: 37, 1969.
- 20 Michel, B., Russell, T., Winkelmann, R. K., and Gleich, G. J.: Release of kinins during wheal and flare allergic skin reactions, *J. Clin. Invest.* **47**: 68a, 1968.
- 21 Juhlin, L., and Michaelsson, G.: Cutaneous reactions to kallikrein, bradykinin and histamine in healthy subjects and in patients with urticaria, *Acta Dermatoven. (Stockholm)* **49**: 26, 1969.
- 22 Goldberg, M.: Comparative study of the adrenergic potentiating properties of various thyroid analogs in man, *J. Clin. Endocr.* **22**: 892, 1962.
- 23 Lundholm, L., Mohme-Lundholm, E., and Svedmyr, N.: Introductory remarks, *Pharmacol. Rev.* **18**: 255, 1966.
- 24 Havard, C. W. H., Campbell, E. D. R., Toss, H. B., and Spence, A. W.: Electromyographic and histological findings in the muscles of patients with thyrotoxicosis, *Quart. J. Med.* **32**: 145, 1963.
- 25 Ingbar, S. H., and Woerber, K. A.: In Williams, R. H., editor: *Textbook of endocrinology*, ed. 4, Philadelphia, 1968, W. B. Saunders Company, p. 182.
- 26 Rocha e Silva, M.: The physiological significance of bradykinin, *Ann. N. Y. Acad. Sci.* **104**: 190, 1963.
- 27 Zachariae, H., Malmquist, J., Oates, J. A., and Pettinger, W.: Studies on the mechanism of kinin formation in inflammation, *J. Physiol. (Lond.)* **190**: 81, 1967.

- 28 Graham, D. T., Goodell, H., and Wolff, H. G.: Studies on pain: The relation between cutaneous vasodilatation, pain threshold and spontaneous itching and pain, *Amer. J. Med. Sci.* **230**: 420, 1957.
- 29 Harrison, T. S.: Adrenal medullary and thyroid relationships, *Physiol. Rev.* **44**: 161, 1964.
- 30 Waldstein, S. S.: Thyroid-catecholamine interrelations, *Ann. Rev. Med.* **17**: 123, 1966.
- 31 Wiswell, J. G., Hurwitz, G. E., Coronho, V., Bing, O. H. L., and Child, D. L.: Urinary catecholamines and their metabolites in hyperthyroidism and hypothyroidism, *J. Clin. Endocr.* **23**: 1102, 1963.
- 32 Buccino, R. A., Spann, J. F., Jr., Pool, P. E., Sonnenblick, E. B., and Braunwald, E.: Influence of thyroid state on the intrinsic contractile properties and energy stores of the myocardium, *J. Clin. Invest.* **46**: 1669, 1967.
- 33 Levey, G. S.: Catecholamine sensitivity, thyroid hormone and the heart, *Amer. J. Med.* **50**: 413, 1971.
- 34 Husain, M. K., Ertel, N. H., Spergel, G., Bleicher, S. J., Levy, L., and Rodman, H. M.: Sympathetic regulation of blood pressure and insulin release in thyrotoxicosis: comparison of phentolamine and glucagon effects, *in* Program of The Endocrine Society, 1971.
- 35 Riddle, M. C., and Schwartz, T. B.: New tactics for hyperthyroidism: Sympathetic blockade, *Ann. Intern. Med.* **72**: 749, 1970.
- 36 Husain, M. K., Spergel, G., and Ertel, N. H.: A hypertensive response to glucagon in hyperthyroidism, *Clin. Res.* **19**: 374, 1971.