

IODIDE HYPERSENSITIVITY IN THE ETIOLOGY OF PERIARTERITIS NODOSA

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INTRODUCTION

IN 1866 Kussmaul and Maier¹ first described the pathologic lesions of periarteritis nodosa, but the clinical recognition of the disease did not materialize until after the turn of the century. Gruber,² in 1925, was the first to suggest that hypersensitivity reactions to foreign substances might play an etiological role in this disease. The occurrence of periarteritis in patients given foreign sera^{3, 4, 13, 22} and the demonstration of similar lesions developing in animals as a result of a hypersensitive immune response to foreign sera³³⁻³⁸ support this concept. A similar vasculitis has been ascribed to hypersensitivity reactions from simple chemical substances,^{3-19, 21-32} including iodides.⁵ Table I lists these compounds.

Serious reactions have resulted from the administration of iodine, iodides, and iodine-containing compounds.^{20, 39-76} These are listed in Table II. The clinical picture of some of the severe reactions was consistent with an underlying vasculitis, but description of pathologic material was lacking or was

TABLE I. POSSIBLE ETIOLOGICAL AGENTS IN CASES OF PERIARTERITIS NODOSA

1. Serum ^{3, 4, 13, 22}
2. Sulfonamides ^{4, 6-12, 21}
3. Penicillin ²⁵⁻²⁸
4. Iodides ^{5, 14}
5. Arsenicals ¹⁹
6. Mercury ²³
7. Aspirin ²⁴
8. Dilantin ^{29, 30}
9. Phenylbutazone ³¹
10. D.D.T. ³²
11. Thiourea, thiouracil, propylthiouracil ¹⁵⁻¹⁸
12. Phenobarbital ⁶

inadequate for substantiation.^{20, 40-43, 45, 68, 70, 76} Two patients with thyrotoxicosis developed periarteritis nodosa during combined thiourea and iodide treatment. In both patients, the periarteritis was ascribed to thiourea hypersensitivity, but a hypersensitive response to iodides cannot be excluded.^{15, 17} In only two instances has iodide hypersensitivity been clearly implicated in the etiology of periarteritis nodosa.^{5, 12}

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TABLE II. SENSITIVITY REACTIONS TO IODIDES^{20, 33-70}

1. Asthma
2. Angioneurotic edema, urticaria
3. Pulmonary edema
4. Peripheral edema
5. Transitory pulmonary infiltrations
6. Thrombopenic and nonthrombopenic purpura
7. Fever
8. Eosinophilia
9. Arthritis
10. Hematuria
11. Albuminuria
12. Localized necrotizing vascular lesions
13. Various cutaneous lesions
14. Lymphadenopathy

The following cases are reported, as they may represent two further instances in which periarteritis nodosa developed as a result of iodide hypersensitivity.

CASE REPORTS

CASE 1.—The patient, R. R. (MGH #787816), was a 60-year-old woman. In August of 1932, when the patient was 40 years of age, asthma first appeared; it cleared in October. Asthma has recurred each year from early August to October. Symptoms usually responded promptly to conservative therapy which, on at least two occasions, included potassium iodide. In August, 1952, she was referred to the Massachusetts General Hospital because her asthma did not respond to the usual medications. On admission, she had severe asthma. Blood pressure was 162/92; pulse, 100; and the heart was enlarged 1 cm. beyond the midclavicular line in the fifth left intercostal space. White blood count was 10,000 per cubic millimeter, with 1 per cent eosinophils. A roentgenogram of the chest showed slight cardiac enlargement and pulmonary emphysema. Epinephrine, aminophylline, and sedatives relieved her completely in two days. She was discharged on potassium iodide, ephedrine, aminophylline, and intramuscular penicillin for five days. Ten days later, nausea followed the ingestion of potassium iodide. In spite of this, she continued taking 10 drops three times a day. Within three days, she developed abdominal bloating, a constricting sensation in the lower anterior chest, dyspnea on exertion, and ankle edema. Re-examination in the outpatient department demonstrated bilateral pleural effusions and cardiac enlargement due to a pericardial effusion. Signs and symptoms continued in spite of digitalis and Mercuhydrin. She was readmitted, therefore, on Oct. 3, 1952. Blood pressure was 170/100; temperature, 101 to 104° F.; pulse, 100. In addition, a large liver and a pulsus paradoxus of 15 mm. Hg was noted. Her white blood count was 9,000, with 29 per cent eosinophils. Electrocardiographic changes were late inversion of the T waves in Leads I, II, aV_L, V₄₋₆, notched P waves, and an upright T wave in aV_R. On October 8, an objective arthritis developed in the right hand and wrist, and four days later a generalized petechial rash appeared. Platelet count was normal. On October 16, a pericardial tap was performed because of signs of increasing cardiac tamponade; 400 c.c. of serosanguineous fluid was removed, the sediment of which contained 40 per cent eosinophils. A muscle biopsy performed on October 18 showed a perivascular inflammatory reaction in one area and monocytic and eosinophilic infiltration in several other areas. The pathologist interpreted these findings as being consistent with periarteritis nodosa. These lesions are illustrated in Figs. 1 and 2. An eight-day course of intravenous ACTH, 25 mg. a day, resulted in a marked increase in appetite and a feeling of well-being; disappearance of eosinophilia, petechial rash, fever, and arthritis; and decrease in edema and heart size. Improvement persisted for two weeks after cessation of ACTH. Fever recurred, as well as a slight eosinophilia (6 to 10 per cent). In addition, a right radial nerve neuritis and left-sided Jacksonian seizures appeared. Dilantin and cortisone (300 mg. daily) therapy was started

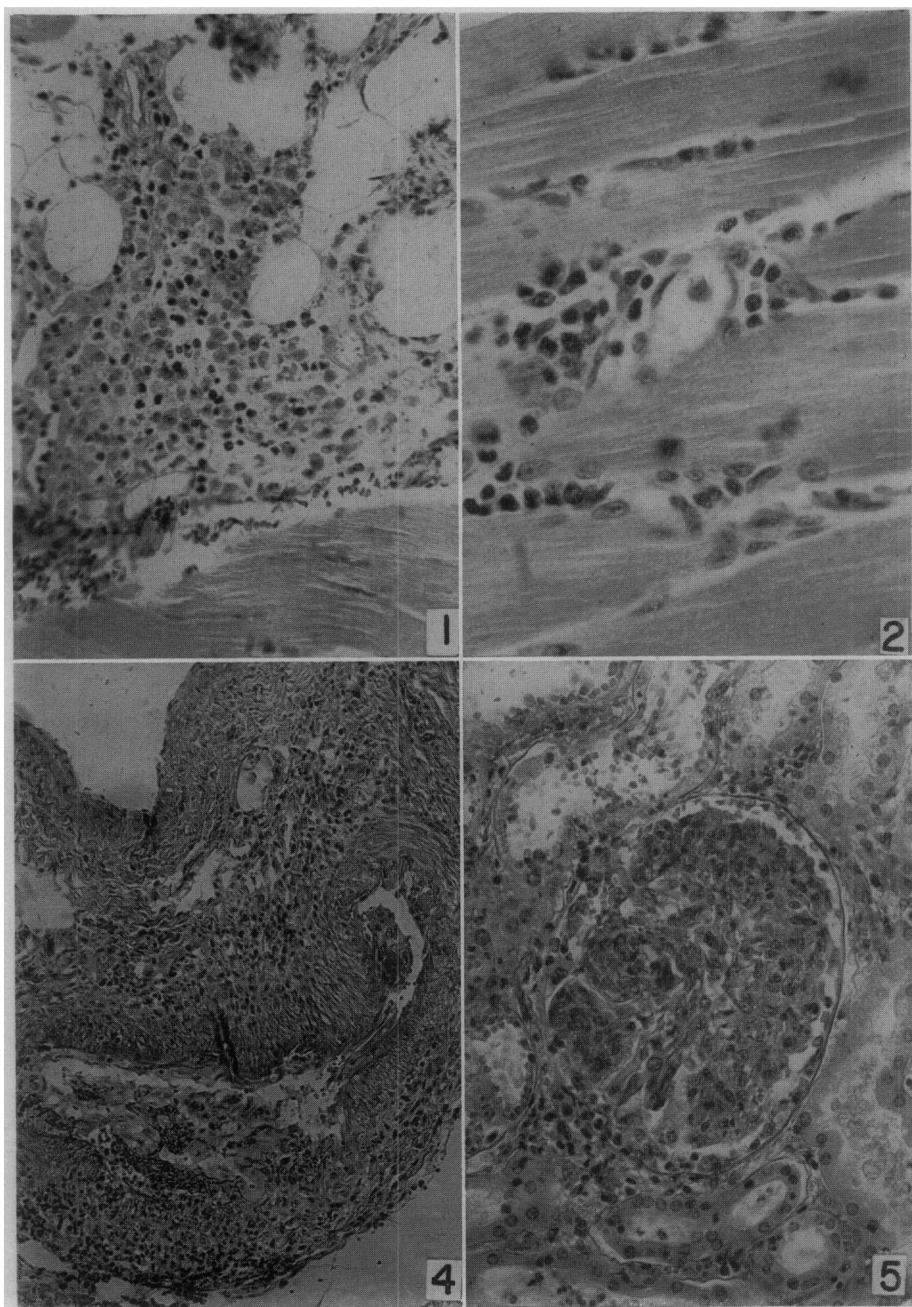


Fig. 1.—Patient R. R. An inflammatory infiltrate in skeletal muscle composed of monocytes, lymphocytes, and eosinophils. (Magnification, $\times 200$; reduced $\frac{1}{8}$.)

Fig. 2.—Patient R. R. A small blood vessel, in skeletal muscle, surrounded by lymphocytes and plasma cells. (Magnification, $\times 400$; reduced $\frac{1}{8}$.)

Fig. 4.—Patient N. D. A marked inflammatory reaction around and in the walls of a small arteriole in the mesentery of the colon. (Magnification, $\times 200$; reduced $\frac{1}{8}$.)

Fig. 5.—Patient N. D. A glomerulus, showing partial destruction of Bowman's capsule, proliferation of glomerular tufts, and thrombosis of some of the capillaries. (Magnification, $\times 200$; reduced $\frac{1}{8}$.)

at once. Within three days, signs and symptoms disappeared, but were followed by the development of a left hemiparesis, which gradually improved. Dilantin and cortisone were continued for three months. For the next two years, the patient was carefully followed and she has been well except for asthma during the months of August through October. A repeat muscle biopsy on Jan. 28, 1954, revealed no diagnostic abnormality.

Although the first muscle biopsy was not completely diagnostic of periarteritis, it was consistent with this diagnosis and similar to lesions ascribed to this disease.^{5, 77, 78} The diagnosis was established on the basis of these findings and the clinical course.

CASE 2.—The patient was N. D. (MGH #816443), a 37-year-old woman, who first noted asthma in May, 1953, when she was 36 years of age. Recurrent attacks persisted for the next month, and became progressively more severe, in spite of therapy. She came to the Massachusetts General Hospital on July 1, 1953, with intractable asthma. Treatment with sedatives, epinephrine, and aminophylline failed, and on the third hospital day an eleven-day course of cortisone was started. She obtained complete relief. Laboratory studies, including a roentgenogram of the chest, were normal. She remained well except for rare, mild, easily controlled attacks of asthma until June, 1954, when increasingly severe and persistent asthma



Fig. 3.—A photograph of the hands of patient N. D. On the dorsum of the left hand was a purpuric eruption which had an erythematous base and superimposed hemorrhagic vesicles. The last two fingers of the right hand could not be completely extended as a result of a radial nerve palsy.

reappeared. She returned to the hospital on July 4, 1954. On entry, she had severe asthma which responded promptly to epinephrine and aminophylline, but one week later she returned because of another attack which also responded rapidly. Routine laboratory studies and a chest roentgenogram were normal. Potassium iodide, 10 drops three times daily, was instituted on July 16, 1954. Within twenty-four hours, recurrent giant urticaria appeared and was followed by the appearance, during the next two weeks, of fever, malaise, arthritis, and muscle pains. All previous therapy was stopped on July 30 and she was given a two-week course of cortisone in decreasing daily doses after an initial dose of 300 mg. Two weeks later, while still taking 50 mg. of cortisone a day, these symptoms returned. In

addition, during the next two weeks she developed, in succession, nausea, bloody diarrhea, purpura, conjunctivitis, muscle pains, stabbing pains in the forearm, and weakness progressing to partial paralysis of the hands.

When readmitted on Aug. 30, 1954, it was determined that on two previous occasions (June, 1953, and June, 1954) she had developed periorbital edema, joint pains, and fever after the ingestion of an "asthma pill" found to be enteric-coated potassium iodide.

Two years prior to this admission, she had undergone a hysterectomy. Review of the pathologic material revealed no vascular disease.

The important physical findings were temperature 100.4° F.; pulse, 110; blood pressure, 108/70; petechiae on the conjunctival and buccal mucosae; moist râles at the right lung base; right upper quadrant tenderness; a bilateral radial nerve neuritis, including motor and sensory loss; an absent right ankle jerk; ankle edema; and a generalized dermatitis, maximal on the distal extremities, consisting of urticaria, petechiae, ecchymoses, and vesicles. A photograph of the skin lesions is shown in Fig. 3.

Laboratory studies revealed hemoglobin, 11.3 Gm. per cent; white blood count, 14,000 per cubic millimeter, with 14 per cent eosinophils; minimal microscopic hematuria; a positive stool guaiac; a normal platelet count; and an abnormal serum electrophoretic pattern, with low albumin and high gamma globulin. Sigmoidoscopy revealed extensive submucosal nonulcerating purpura. Electrocardiogram was abnormal, with S-T segment depression and low T waves in Leads II, III, aV_F, and V₆. A roentgenogram of the chest showed a localized infiltration in the right lower lobe. Using the technique of Prausnitz and Küstner, the patient's sera were tested with Benadryl, aspirin, and potassium iodide. One-tenth cubic centimeter of the patient's serum was injected intracutaneously and the sites were challenged twenty-four hours later. Benadryl gave a positive control, so the results were of no value. Aspirin gave a questionable reaction in one of two subjects. A 1:20 dilution of potassium iodide, applied as a scratch test, gave an immediate type reaction (flare and wheal within twenty minutes) in both recipients. Precipitating antibodies were not demonstrated in the patient's serum, using as antigen either potassium iodide or serum from a patient ingesting this compound.

Initially, the patient seemed to improve on 6.5 Gm. of aspirin a day, but by the sixth hospital day the hemoglobin had fallen to 8.5 Gm. per cent, and eosinophilia had risen to 54 per cent. She was transfused with two units of whole blood, and promptly developed pulmonary edema. At the same time, thymol iodide was applied inadvertently to a small decubitus ulcer. In spite of all measures (including gitalin, compound F, and positive-pressure oxygen), pulmonary edema continued, she became hypotensive, and developed azotemia, increasing cardiac enlargement, and progressive widespread electrocardiographic changes consistent with severe myocardial ischemia and infarction. She died on the eleventh hospital day.

There were widespread changes at postmortem examination. The dermatitis was as previously described. The heart weighed 325 grams. Nearly the entire left ventricle, the septum, and the inferior portion of the right ventricle were infarcted. There was an overlying fibrinous pericarditis. The coronary vessels were soft and uninvolved with atherosclerosis. A pericardial effusion of 125 c.c. and bilateral pleural effusions, 400 c.c. each, were present. The lower lobe of each lung contained a hemorrhagic consolidation. The upper lobes were markedly edematous. Multiple small cerebral infarcts were seen in the area of distribution of the right posterior cerebral artery. There was a widespread hemorrhagic ulcerating process involving the mucosa of the colon, terminal ileum, and gall bladder.

The microscopic findings were striking. There was extensive necrosis of the walls of the heart, with areas of inflammatory infiltrate composed of neutrophils, lymphocytes, plasma cells, and eosinophils, the latter predominating. The inflammatory reaction was seen in the myocardium, endocardium, and epicardium. Mural thrombi were present over the endocardial surface of the left ventricle. There were several areas of focal necrosis

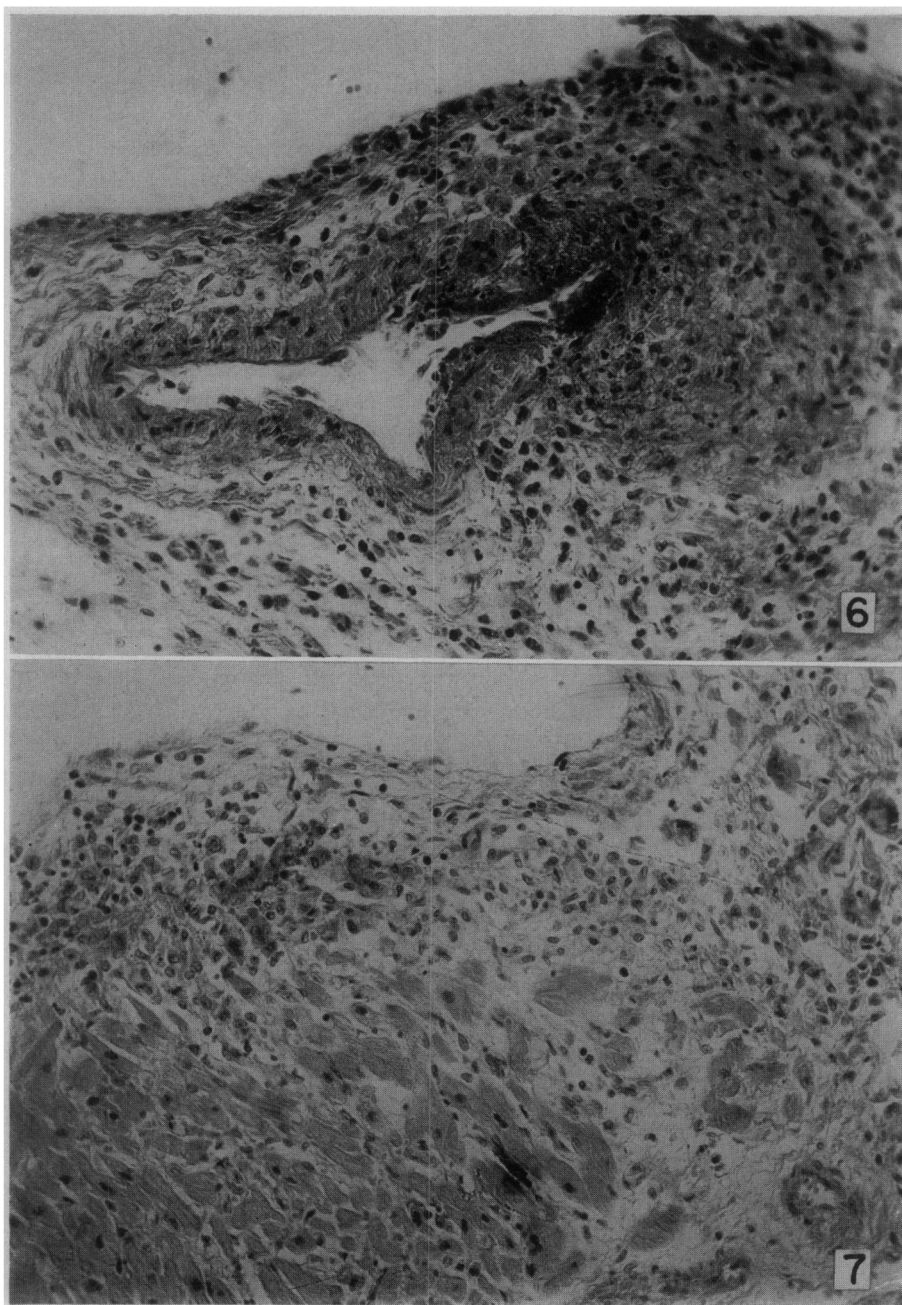


Fig. 6.—Patient N. D. A typical lesion in a coronary arteriole, showing fibrinoid necrosis of the vessel wall and perivascular inflammation. (Magnification, $\times 200$; reduced $\frac{1}{8}$.)

Fig. 7.—Patient N. D. A section of myocardium containing multinucleated giant cells on the right and an area of fibrinoid necrosis with surrounding inflammatory cells on the left. (This lesion had many of the characteristics of an Aschoff body.) (Magnification, $\times 200$; reduced $\frac{1}{8}$.)

with surrounding inflammatory reaction and multinucleated giant cells in the myocardium. These resembled Aschoff's nodules. Widespread involvement of the small arterioles (250 μ or less) was present in the pancreas, heart, peripheral nerves, colon, skeletal muscle, gall bladder, kidneys, and stomach, and less so in the lungs. The lesions were of several types:

1. Occlusion of arterioles with fibrin thrombi of various ages.
2. Focal collections of inflammatory cells perivascularly without inflammation of the vessel wall. (These collections of cells were of two types—in certain areas they were predominantly lymphocytes, while in others they were neutrophils, plasma cells, and eosinophils.)
3. Fibrinoid necrosis of vessel walls with perivascular inflammation, and destructive inflammation of all three layers of the vessel wall.

Similar lesions were seen in a few venules. The bone marrow showed eosinophilic hyperplasia and was otherwise normal. Both kidneys contained focal granulomatous lesions composed of monocytes, plasma cells, neutrophils, lymphocytes, and eosinophils. Focal necrosis and fibrin thrombi in capillaries with proliferation of endothelial cells were seen in some glomeruli. The lungs contained edema and a hemorrhagic organizing pneumonia, in which there were areas of necrosis and eosinophilic infiltration. Photomicrographs of some of these lesions are shown in Figs. 4, 5, 6, and 7.

DISCUSSION

The serum sickness type of hypersensitivity can be induced by the injection of foreign sera.^{3, 22, 24, 35} A similar state can occur following the use of some simple chemical substances. Pathologically, damage to small blood vessels has been described. This ranges from reversible, visually undetectable changes resulting in local edema formation to irreversible, necrotizing vasculitis with resultant organ dysfunction.^{22, 35-38, 77}

The occurrence of periarteritis nodosa in some patients is thought to represent such a severe, irreversible vasculitis.^{4, 79-81} The exact pathogenesis of this vasculitis remains undetermined. A clinical and pathologic differentiation of these cases of so-called hypersensitivity angiitis from other cases of periarteritis nodosa has been proposed,⁷⁹⁻⁸² but not generally accepted.⁸³⁻⁸⁵ The present cases may represent instances of a vasculitis of this type.

Since asthma may be a manifestation of periarteritis nodosa,^{73, 86} it is possible that both patients had periarteritis prior to iodide therapy, the asthma being an initial symptom of the disease. In each patient, however, the course of the disease altered dramatically shortly after the institution of iodides. In neither patient was asthma present during the course of the vasculitis, suggesting that the asthma and the vasculitis resulted from hypersensitivity reactions to different agents. The presence of asthma in the first patient, at a time when all signs of the vasculitis had disappeared, is consistent with the preceding interpretation, as is the clinical course. In the second patient, the past history of iodide sensitivity, the presence of skin-sensitizing antibodies to iodide, and the seasonal nature of the asthma support the theory of separate etiologies. A recrudescence of the vasculitis occurred in each after the cessation of a short course of steroid therapy, even though no iodides had been administered in the meantime. This is compatible with iodide hypersensitivity

being an etiological factor, since patients ingesting potassium iodide have elevated, nonthyroxine, blood, protein-bound iodine, which may remain three to four weeks after cessation of iodide administration.^{87, 88}

Accepting iodide hypersensitivity as an etiological factor, it is reasonable to think that periarteritis may develop in other patients with bronchial asthma as a result of therapy with iodides or possibly other agents and, further, that the etiological agent may be overlooked if asthma is accepted as a symptom of the vasculitis. This is of some practical importance, as recognition and elimination of the sensitizing agent are therapeutically desirable. Iodides are used extensively in asthma therapy; yet the occurrence of vasculitis following their use is rare. This would indicate that either (1) such an occurrence is truly a rare phenomenon; (2) it occurs more frequently than suspected, but goes unrecognized; or (3) the severe, clinically serious form is rare, but less severe manifestations occur frequently and go unnoticed. The recognition of such early signs of sensitivity in the second patient might have been lifesaving. Abandonment of iodide therapy cannot be recommended on the basis of this evidence, but withdrawal of such treatment in patients developing any minor manifestations of sensitivity is clearly indicated.

If vasculitis of this nature can develop from iodide hypersensitivity, the mechanism of its production is of interest. Administration of simple chemical compounds can result in the development of hypersensitivity reactions.⁸⁹ Basically, the sequence of this development is thought to be: (1) the union of agent with plasma protein, forming an antigen; (2) stimulation of specific antibody production by this antigen; (3) union of antigen with antibody, resulting in vascular damage.⁸⁹

All substances, including iodides, proposed as etiological agents in cases of periarteritis (Table I) have been shown to form a complex with plasma proteins, when such studies have been carried out.⁹⁰ There has been intensive study of iodoproteins, including their immunologic properties. It is important, in discussing these, to distinguish iodine (I^0) from iodide (I^-), since their interactions with proteins differ. These are illustrated in Fig. 8 and are discussed. Iodide is the reduced form of iodine. Except in the thyroid gland, this substance exists in vivo in the reduced state (I^-), regardless of the route of administration,⁹¹⁻⁹⁵ with the one exception that subcutaneously administered iodine may exist, as such, for some time.⁹¹ These facts have an important bearing on the interpretation of the results of the immunologic studies and their relation to human iodide sensitivity.

Most of the immunologic studies have employed, as antigens, protein treated in vitro with iodine (I^0) solutions. Under these conditions, the combination of iodine (I^0) with protein involves either substitution on the phenolic group of tyrosine, or on the imidazole group of histidine, or addition on the thio-ether linkage of methionine.⁹⁶ Iodination may cause the disappearance of the (OH) group of diiodotyrosine.⁹⁷ The only one of these reactions which seems to have an important bearing on the problem of altered antigenicity is the substitution of iodine on tyrosine. Proteins iodinated in this way alter

their serologic specificity to a greater or lesser degree, depending on the percentage of iodine added.^{79, 89, 98-101} With "complete" substitution of the tyrosine groups, nearly complete loss of the original specificity occurs and a common specificity with other iodinated proteins appears.⁹⁸ From the nature of the changes in the protein molecule, iodide inhibition of the antigen-antibody reactions of these iodoproteins would not be expected. The precipitation of antibodies from the sera of rabbits sensitized by iodoproteins can be blocked by diiodotyrosine but not by potassium iodide.⁹⁹ Similarly, anaphylaxis in sensitized guinea pigs can be blocked by diiodotyrosine but not by potassium iodide.¹⁰⁰

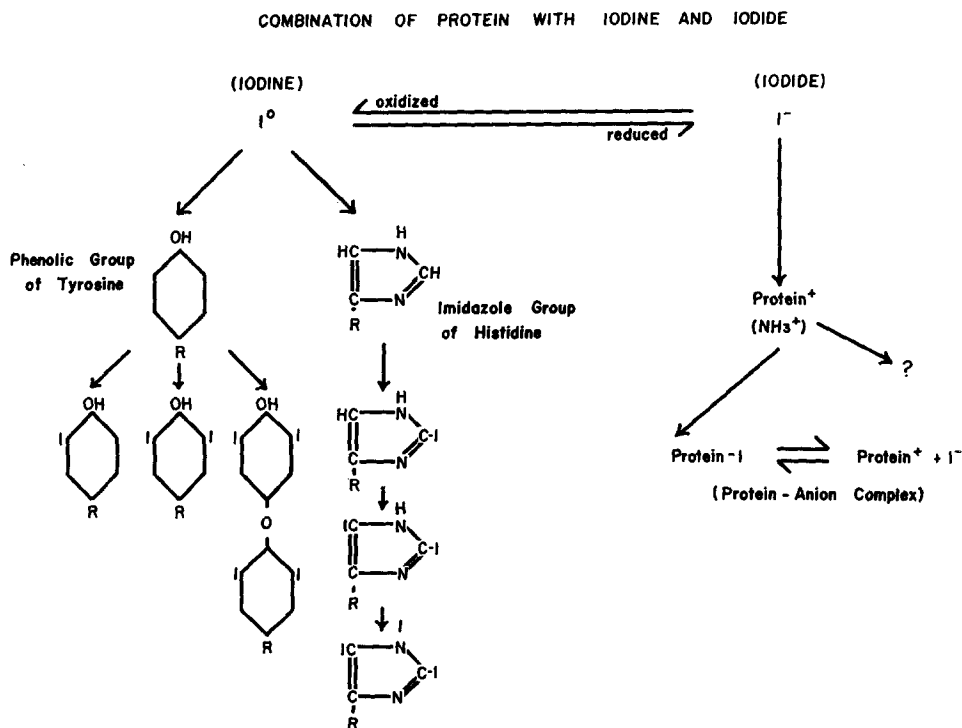


Fig. 8.—The interaction of protein with iodine (I_2) and iodide (I^-). Iodine combines with tyrosine to form mono- and di-iodotyrosine, and thyroxine. Its addition to histidine takes place in three successive steps, as illustrated. Iodide is ionically bound to protein, and may combine in other, undefined ways.

The interaction of iodide (I^-) with proteins has not been thoroughly studied. Small anions, such as chloride and thiocyanate are bound in vitro by certain unidentified groups of human serum albumin.^{102, 103} No data are available for iodide, but similar binding might be expected, from theoretical considerations. Iodide does form a complex with serum in vitro and 8 to 31 per cent of this bound iodide is protein precipitable.¹⁰⁴ The in vivo binding of iodide to serum albumin does occur in patients ingesting potassium iodide,^{87, 88} but the nature of this binding has not been investigated. This albumin-iodide complex is also, in part at least, protein precipitable. It is

conceivable that the iodides have been oxidized to iodine, and the latter substituted onto tyrosine radicals. This is not likely, however, since the *in vitro* iodination of serum produces a calorigenic substance (tyrosine-substituted protein),¹⁰⁵ and the *in vivo* production of a similar substance might be expected if iodide were converted to iodine. Such a substance has not been found. On the basis of the available data, it is reasonable to propose that the antigen responsible for the development of iodide sensitivity in man is a protein-iodide complex.

The demonstration of the skin-sensitizing antibodies to iodides, in the serum of the one patient, would be consistent with this proposal. The relationship of these antibodies to the development of the vasculitis cannot be defined. However, there is some experimental evidence equating such antibodies with the anaphylactoid state. Guinea pigs, sensitized to simple chemical substances, produce circulating, nonprecipitable antibodies which, when appropriately challenged, can induce either the immediate type of skin sensitization or passive anaphylaxis.¹⁰⁶

Assuming that sensitivity to iodides can produce a spectrum of anaphylactoid manifestations ranging from angioedema to severe vasculitis, and that the production of these is contingent upon a protein-iodide complex becoming antigenic, several problems remain unsolved. Does every person ingesting iodide form the same protein-iodide complex? If so, what factors determine when and in whom it becomes antigenic? What defines the severity and location of the ensuing sensitivity reaction? Further fruitful study of these problems might be undertaken using the readily available radioactive iodine I^{131} .

A discussion of sensitivity to iodine compounds would not be complete without mention of two other aspects. Sialorrhea, bronchorrhea, tearing, and salivary gland enlargement are described as common reactions to iodide administration.¹⁰⁷ From our present knowledge, it would seem that these symptoms may represent a heightened physiologic or pharmacologic effect of the drug, and not true sensitization. Many reactions occur with the use of iodine containing contrast substances in radiographic procedures.⁶⁶ The iodized oil, such as that used in bronchography is probably unreactive until swallowed and absorbed through the gastrointestinal tract or absorbed directly through the lung. In either case, the mechanism of sensitization is probably a combination of liberated iodide with plasma protein. Organic compounds, as used in pyelography, for example, probably become antigenic by combining with plasma proteins directly, rather than releasing iodide.

SUMMARY

Two patients with periarteritis nodosa are described. In both, iodide hypersensitivity was implicated as an etiological factor. Skin-sensitizing antibodies to potassium iodide were found in the serum of one patient. The significance of this finding is discussed. Possible mechanisms of iodide sensitivity are presented.

REFERENCES

1. Kussmaul, A., and Maier, R.: Über Eine Bisher Nicht Beschreibene Eigenthümliche Arterienkrankung (Periarteriitis Nodosa), die mit Morbus Brightii und Rapid Fortschreitender Allgemeiner Muskellähmung Einhergeht, *Deutsches Arch. klin. Med.* **1**: 484, 1866.
2. Gruber, G. B.: Zur Frage der Periarteriitis Nodosa, mit Besonderer Berücksichtigung der Gallenblasen und Nieren-Beterligung, *Arch. path. Anat.* **258**: 441, 1925.
3. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa, as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, *Bull. Johns Hopkins Hosp.* **71**: 123, 1942.
4. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, *Bull. Johns Hopkins Hosp.* **72**: 65, 1943.
5. Rich, A. R.: Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, *Bull. Johns Hopkins Hosp.* **77**: 43, 1945.
6. Lichtenstein, L., and Fox, L. J.: Necrotizing Arterial Lesions, Resembling Those of Periarteritis Nodosa, and Focal Visceral Necrosis Following Administration of Sulfathiazole, *Am. J. Path.* **22**: 665, 1946.
7. More, R. H., McMillan, G. C., and Duff, G. L.: The Pathology of Sulfonamide Allergy in Man, *Am. J. Path.* **22**: 703, 1946.
8. French, A. J.: Hypersensitivity in the Pathogenesis of the Histopathologic Changes Associated With Sulfonamide Chemotherapy, *Am. J. Path.* **22**: 679, 1946.
9. Black-Schaffer, B.: Pathology of Anaphylaxis Due to Sulfonamide Drugs, *Arch. Path.* **39**: 301, 1945.
10. Goodman, M. J.: Periarteritis Nodosa With Recovery, Report of an Unusual Case Apparently Due to Sensitivity to Sulfadiazine, *Ann. Int. Med.* **28**: 181, 1948.
11. Gelfand, M. L., and Arnonoff, S.: Periarteritis Nodosa, Possible Relation to Increased Usage of Sulfonamides, *Ann. Int. Med.* **30**: 919, 1949.
12. Thompson, R. T., and Zeek, P.: Acute Necrotizing Angiitis Due to Hypersensitivity Following Sulfonamide Therapy, *Ohio M. J.* **41**: 824, 1945.
13. Eason, J., and Carpenter, G.: Treatment of Acute Rheumatic Polyarthrititis With Concentrated Anti-Scarlatinal Serum, *Quart. J. Med.* **6**: 93, 1937.
14. Muller, C.: Periarteritis Nodosa—Asthma Bronchiale—Iododerma Tuberosum, *Acta med. scandinav.* **136**: 378, 1949-50.
15. Gibson, P. C., and Quinlan, J. T.: Periarteritis Nodosa in Thiourea Therapy, *Lancet* **2**: 108, 1945.
16. Dalgleish, P. G.: Polyarteritis Nodosa After Thiouracil, *Lancet* **2**: 319, 1952.
17. Barnum, D. R., de Takatas, G., and Dolkart, R. E.: Periarteritis Nodosa Following Thiouracil Therapy of Hyperthyroidism: Resultant Hypertension Benefited by Sympathectomy, *Angiology* **2**: 256, 1951.
18. McCormick, R. V.: Periarteritis Occurring During Prophyl-thiouracil Therapy, *J. A. M. A.* **144**: 1453, 1953.
19. Miller, H. G., and Nelson, M. G.: Polyarteritis Nodosa Developing During Anti-Syphilitic Treatment, *Lancet* **2**: 200, 1945.
20. Barker, W. B., and Wood, W. B., Jr.: Severe Fatal Iodism During Treatment of Hyperthyroidism, *J. A. M. A.* **114**: 1029, 1940.
21. Rich, A. R.: Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarteritis Nodosa: Another Case Associated With Sulfonamide Reaction, *Bull. Johns Hopkins Hosp.* **71**: 375, 1942.
22. Clark, E., and Kaplan, B. I.: Endocardial, Arterial, and Other Mesenchymal Alterations Associated With Serum Disease in Man, *Arch. Path.* **24**: 458, 1937.
23. Friedenthal, M., and Cagan, R. N.: Periarteritis Nodosa Associated With the Use of Proprietary Mercurial Preparation, *Am. Pract. & Digest Treat.* **3**: 218, 1952.
24. Rich, A. R.: Hypersensitivity in Disease, *Harvey Lect.* **42**: 106, 1946-47.
25. Waugh, D.: Myocarditis, Arteritis, and Focal Hepatic, Splenic, and Renal Granulomas Apparently Due to Penicillin Sensitivity, *Am. J. Path.* **28**: 437, 1952.
26. Berne, R. M.: An Unusual Sensitivity Reaction to Penicillin, *New England J. Med.* **242**: 814, 1950.
27. McCombs, R. P.: Drug Allergies: Case Reports of Unusual Sequelae in Three Patients, *Bull. New England M. Center* **13**: 39, 1951.
28. Surdakowski, A. Z.: Periarteritis Nodosa Due to Penicillin, *New York J. Med.* **54**: 388, 1954.
29. Rothermuch, N. O.: Polyarteritis Nodosa: A Review Together With Report of a Case Due to Hydantoin Sensitization Treated With Cortisone, *Ohio M. J.* **47**: 1013, 1951.

30. VanWyk, J. J., and Hoffman, C. R.: Periarthritis Nodosa: A Case of Fatal Exfoliative Dermatitis Resulting From "Dilantin Sodium" Sensitization, *Arch. Int. Med.* **81**: 605, 1948.
31. O'Brien, D. J., and Storey, G.: Death From Hypersensitivity, *Brit. M. J.* **1**: 792, 1954.
32. Hill, W. R., and Damiani, C. R.: Death Following Exposure to D.D.T.: Report of a Case, *New England J. Med.* **235**: 897, 1946.
33. Germuth, F. G., Jr.: A Comparative Histologic and Immunologic Study in Rabbits of Induced Hypersensitivity of the Serum Sickness Type, *J. Exper. Med.* **97**: 257, 1953.
34. Rich, A. R.: The Occurrence of Focal Tuberculoid Lesions in Experimental Serum Sickness, *Bull. Johns Hopkins Hosp.* **91**: 109, 1952.
35. Fox, R. A., and Jones, L. R.: Vascular Pathology in Rabbits Following Administration of a Foreign Protein, *Proc. Soc. Exper. Biol. & Med.* **55**: 294, 1944.
36. Hawn, C. V., and Janeway, C. A.: Histological and Serological Sequences in Experimental Hypersensitivity, *J. Exper. Med.* **85**: 571, 1947.
37. Hopps, H. C., and Wessler, R. W.: The Experimental Production of Generalized Arteritis and Periarthritis (Periarthritis Nodosa), *J. Lab. & Clin. Med.* **31**: 939, 1946.
38. Ehrlich, W. E., Seifter, J., and Forman, C.: Experimental Serum Disease, *J. Exper. Med.* **89**: 23, 1949.
39. Snodgrass, W. R.: Observations on the Therapeutic Use of Iodides, *Quart. J. Med.* **4**: 247, 1935.
40. Newman, E. A., and Ross, P. H.: Thyrotoxicosis Complicated by Severe Iodism; Preparation for Surgery With Propylthiouracil, *J. Clin. Endocrinol.* **7**: 212, 1947.
41. Hollander, L., and Fetterman, G. H.: Fatal Iododerma: The Eleventh Case Reported in the Literature, *Arch. Dermat. & Syph.* **34**: 228, 1936.
42. Eller, J. J., and Fox, E. C.: Fatal Iododerma, *Arch. Dermat. & Syph.* **24**: 745, 1931.
43. Mi, C. H., and Yang, C. T.: Iodide Fever, *Chinese M. J.* **52**: 887, 1937.
44. Davis, W. C., and Saunders, T. S.: Purpura Due to Iodides, *Arch. Dermat. & Syph.* **53**: 644, 1946.
45. Hed, A. R.: Jodallergi, *Nord. med.* **46**: 1371, 1951.
46. Ehrlich, W. E., and Seifter, J.: Thrombotic Thrombopenic Purpura Caused by Iodine, *Arch. Path.* **47**: 446, 1949.
47. Cleveland, D. E. H.: Iododerma From Asthma Remedy, *Canad. M. A. J.* **30**: 181, 1934.
48. Seymour, W. B., Jr.: Poisoning From Cutaneous Application of Iodine, *Arch. Int. Med.* **59**: 952, 1937.
49. Denning, H.: Thrombopenische Purpura Nach Jodeinnahme, *München. med. Wchnschr.* **80**: 562, 1933.
50. Katzenstein, L.: Fever Due to Iodides, *Am. J. Syph., Gonorr. & Ven. Dis.* **22**: 346, 1938.
51. Usher, B.: Iododerma Associated With Loeffler's Syndrome, *Canad. M. A. J.* **64**: 67, 1951.
52. Hyde, J. N.: A Contribution to the Study of the Bullous Eruption Induced by the Ingestion of the Iodide of Potassium, *Arch. Dermat.* **5**: 333, 1897.
53. Guptill, P.: Acute Iodism During Treatment of Toxic Goiter, *Surgery* **11**: 962, 1942.
54. Jacobs, J. L., and Colmes, A.: Cutaneous Hypersensitivity to Iodine, *J. Lab. & Clin. Med.* **26**: 302, 1940.
55. Snell, N. W., and Savin, L. H.: Iodism in Which Edema of Glottis Necessitated Tracheotomy, *Lancet* **1**: 759, 1927.
56. Rutherford, W. J.: Excessive Reaction Following the Use of Tincture of Iodine, *Brit. M. J.* **1**: 846, 1915.
57. Clifford, S. H.: Iodine Hypersensitivity, *Boston M. & S. J.* **195**: 931, 1926.
58. Alstead, S.: Iodism, *Glasgow M. J.* **123**: 196, 1935.
59. Wartski, I. M.: Acute Iodide Eruption Following the Ingestion of a Small Amount of Potassium Iodide, *M. J. Australia* **2**: 739, 1938.
60. Spencer, H. A.: Anaphylaxis Resulting From the Use of an Iodide, *J. Trop. Med.* **33**: 339, 1930.
61. Felsner, Z.: The Nature of Halogen Sensitivity in Dermatitis Herpetiformis and Pemphigus, *J. Invest. Dermat.* **8**: 55, 1947.
62. Perner, L.: Iodine Allergy, *J. Lab. & Clin. Med.* **27**: 1150, 1942.
63. Hand, E. A.: Temporary Unilateral Loss of Vision Associated With Iododerma, *Arch. Dermat. & Syph.* **54**: 29, 1946.
64. Sheldon, J. M., and Lovell, R. G.: Asthma Due to Halogens, *Am. Pract.* **4**: 43, 1949.
65. Sulzberger, M. B., and Wilten, V. H.: Allergic Dermatoses Due to Drugs, *Postgrad. Med.* **11**: 549, 1952.
66. Irwin, F. M.: Iodism, *Ann. Otol., Rhin. & Laryng.* **61**: 408, 1952.
67. Mackenzie, S.: Fatal Purpura From Iodide of Potassium, *Illust. Med. News* **1**: 169, 1888-89.

68. Wilson, J. H.: Purpura Haemorrhagica From Iodide of Potassium, *Brit. M. J.* 1: 470, 1889.
69. Robinson, T.: Rapid Production of Purpura After Small Doses of Iodide of Potassium, *Lancet* 1: 471, 1893.
70. Cape, R. D. T.: Iododerma of the Face and Marked Eosinophilia, *Brit. M. J.* 1: 255, 1954.
71. Walker, N.: Iododerma, or Dermatitis Tuberosa, Due to the Ingestion of Iodide of Potassium, *Lancet*: p. 571, 1892.
72. Lindsay, S. S.: Acute Edema of the Face Due to Potassium Iodide, *Lancet* 2: 217, 1919.
73. Rackemann, F., and Greene, F.: Periarthritis Nodosa and Asthma, *Tr. Am. A. Physicians* 54: 112, 1939.
74. Joffe, J. J.: Erythema Iodicum Bullosum Haemorrhagicum With Fatal Termination, *Arch. Dermat. u. Syph.* 163: 517, 1931.
75. Bechet, P. E.: Role of Iodized Table Salt in Iododerma, *J. Invest. Dermat.* 8: 409, 1947.
76. Alcan, D. N.: Sensitivity to Iodides and Bromides in Dermatoses Other Than Dermatitis Herpetiformis, *J. Invest. Dermat.* 7: 287, 1947.
77. Churg, J., and Strauss, L.: Allergic Granulomatosis, Allergic Angiitis and Periarthritis Nodosa, *Am. J. Path.* 27: 277, 1951.
78. Ophils, W.: Periarthritis Acuta Nodosa, *Arch. Int. Med.* 32: 870, 1923.
79. Zeek, P. M.: Periarthritis Nodosa: A Critical Review, *Am. J. Clin. Path.* 22: 777, 1952.
80. Zeek, P. M., Smith, C. C., and Weeter, J. C.: Studies on Periarthritis Nodosa; Differentiation Between Vascular Lesions of Periarthritis Nodosa and of Hypersensitivity, *Am. J. Path.* 24: 889, 1948.
81. Blankenhorn, M. A., and Knowles, H. C., Jr.: Periarthritis Nodosa: Recognition and Clinical Symptoms, *Ann. Int. Med.* 41: 887, 1954.
82. Zeek, P. M.: Periarthritis Nodosa and Other Forms of Necrotizing Angiitis, *New England J. Med.* 248: 764, 1953.
83. Rich, A. R.: Personal Communication.
84. Castleman, B. J.: Personal Communication.
85. Nuzum, J. W.: Polyarteritis Nodosa, *Arch. Int. Med.* 94: 942, 1954.
86. Wilson, K. S., and Alexander, H. L.: The Relationship of Periarthritis Nodosa to Bronchial Asthma and Other Forms of Human Hypersensitivity, *J. Lab. & Clin. Med.* 30: 195, 1945.
87. Danowski, T. S., Johnston, S., and Greenman, J. H.: Alterations in Serum Iodine Fractions Induced by the Administration of Inorganic Iodide in Massive Dosage, *J. Clin. Endocrinol.* 10: 519, 1950.
88. Danowski, T. S., Mateer, F., Wergard, F. A., Peters, J. H., and Greenman, J. H.: Serum Iodine Fractions in Subjects Receiving Potassium Iodide in Small Dosage, *J. Clin. Endocrinol.* 10: 532, 1950.
89. Landsteiner, K.: The Specificity of Serological Reactions, Cambridge, 1945, Harvard University Press.
90. Goldstein, A.: The Interaction of Drugs and Plasma Protein, *Pharmacol. Rev.* 1: 102, 1949.
91. Salter, W. T.: The Endocrine Function of Iodine, Cambridge, 1943, Harvard University Press.
92. Riggs, D. S.: Quantitative Aspects of Iodine Metabolism in Man, *Pharmacol. Rev.* 4: 284, 1952.
93. Cole, V., Dunn, R., and Curtis, G.: The Intrapulmonic Absorption of Iodine, *J. Pharmacol. & Exper. Therap.* 53: 327, 1935.
94. Cohn, B. N. E.: Absorption of Compound Solutions of Iodine From the G. I. Tract, *Arch. Int. Med.* 49: 950, 1932.
95. Sollman, T.: The Fate of Iodin, Iodids, and Iodates in the Body, *J. Pharmacol. & Exper. Therap.* 9: 269, 1917.
96. Roche, J., and Michel, R.: Natural and Artificial Iodoproteins, *Advances Protein Chem.* 4: 253, 1951.
97. Cohn, E. J., Salter, W. T., and Ferry, R. J.: Society Proceedings, *J. Biol. Chem.* 123: 24, 1938.
98. Wormall, A.: Immunological Specificity of Proteins, *J. Exper. Med.* 51: 295, 1930.
99. Jacobs, J.: Serological Studies on Iodinated Sera I: Precipitins and Precipitinogens, *J. Immunol.* 23: 361, 1932.
100. Jacobs, J.: Serological Studies on Iodinated Sera. II: Anaphylaxis, *J. Immunol.* 23: 375, 1932.
101. Klecykowski, A.: Quantitative Investigation of Changes in Antigenic Properties in the Course of Iodination of Horse-Serum Globulin, *Brit. J. Exper. Path.* 21: 98, 1940.

102. Scatchard, G., Scheinburg, I. H., and Armstrong, S., Jr.: Physical Chemistry of Protein Solutions. IV: The Combination of Human Serum Albumin With Chloride Ion, *J. Am. Chem. Soc.* **72**: 535, 1950.
103. Scatchard, G., Scheinburg, I. H., and Armstrong, S. Jr.: Physical Chemistry of Protein Solutions V: The Combination of Human Serum Albumin With Thiocyanate Ions, *J. Am. Chem. Soc.* **72**: 540, 1950.
104. Wyngaarden, J. B., Stanbury, J. B., and Dutoit, C. H.: On the Mechanism of Iodide Accumulation by the Thyroid Gland, *J. Clin. Endocrinol.* **11**: 1259, 1951.
105. Lerman, J., and Salter, W. T.: Iodinated Protein in Human Athyreosis, *J. Clin. Invest.* **18**: 493, 1939.
106. Chase, M. W.: Studies on the Sensitization of Animals With Simple Chemical Compounds X: Antibodies Inducing Immediate-Type Skin Reactions, *J. Exper. Med.* **86**: 489, 1947.
107. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, 1948, J. B. Lippincott Company.