

Allergic Reactions to Insulin

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Two of five patients with acute systemic allergic reactions to insulin injection required desensitization. Immunologic studies consisted of direct skin testing with a variety of insulins which included human and synthetic insulins. Passive cutaneous transfer, leukocyte histamine release, and radioimmunodiffusion studies were also performed. Fifty diabetic patients without symptoms of insulin allergy were also selected for skin testing with a variety of insulin preparations. Results indicated that insulin allergy may be directed against the insulin molecule itself or against protein contaminants in the commercially available preparation, and that it can be mediated by IgE. Desensitization resulted in precipitous drops in reaginic antibody titers and cutaneous sensitivity, with the simultaneous induction of tolerance to insulin.

Immediate allergic reactions to insulin injection have been described repeatedly.¹ The immunologic mechanisms involved in these reactions are not clear. However, the immunoglobulin class IgE, responsible for most if not all such immediate hypersensitivity reactions,² is believed to play a major role in insulin allergy as well. The first experimental evidence of insulin hypersensitivity involving an IgE mediated response to antigenic components on the insulin molecule itself, and not to contaminants in the preparation, was recently reported.³

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Read before the Section on Allergy at the 119th annual convention of the American Medical Association, Chicago, June 22, 1970.

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In the present study, the clinical and immunologic characteristics of insulin allergy are evaluated further. Five patients with systemic manifestations of insulin allergy are described. In addition, in order to evaluate the local urticarial reaction often observed after insulin injection, 50 diabetic patients receiving insulin were selected at random for skin testing with a variety of insulin preparations.

This study has provided information regarding certain aspects of insulin allergy. The information includes observations on the duration of sensitivity, on the nature of the antigen and antibody involved, and on certain diagnostic and therapeutic procedures which may be useful in the treatment of patients with insulin allergy.

Materials and Methods

Insulin Preparations Used for

Testing.—Various preparations of insulin were used for intradermal testing: beef-pork isophane insulin suspension, crystalline beef insulin, crystalline pork insulin, crystalline sheep insulin, desalinated pork insulin, beef insulin purified by chromatography, and extracted human insulin. Boiled beef and boiled pork insulins were prepared by the method of Dolger.⁴ Recrystallized beef insulin was prepared by the method of Carpenter and Baum.⁵ Human synthetic insulin was supplied by P. G. Katsoyannis, PhD.^{6,7} Soluble beef protein and pork protein antigens were also supplied for allergy skin testing.

Intradermal Tests.—Direct tests were performed by injecting intradermally 0.1 ml of each insulin preparation. These preparations contained varying concentrations of insulin. Reactions were graded on the size of the wheal and erythema responses.⁸ Intradermal control solutions were buffered saline solution, pH of 7.2, and insulin diluent fluid, pH of 2.8.

Passive Cutaneous Sensitivity Testing (Pausnitz-Küstner [P-K]).—Pausnitz-Küstner testing was performed by the injection of 0.1 ml of the patient's reaginic serum intradermally into the skin of normal volunteers. Normal serum was injected in a similar fashion as a control. Twenty-four hours later, these sites were injected intradermally with 0.1 ml of insulin preparations containing varying concentrations of insulin. Pausnitz-Küstner reactions were graded in the same manner as in the direct tests. All tests for P-K reaction were performed a second time after the reaginic sera

Table 1.—Clinical Summary of Patients Allergic to Insulin

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, yr	76	51	26	71	37
Sex	M	M	F	F	M
Diabetic manifestations	weight loss, polyuria	weight loss	ketosis	weight loss, neuropathy	ketosis, polyuria
Fasting blood glucose, mg/100 cc	200-250	300-380	150-250	200-300	160-250
Insulin dose, units, at onset of allergic symptoms	30	40	30	32	36
Insulin type	beef-pork isophane suspension	beef-pork isophane suspension	beef-pork isophane suspension	beef-zinc suspension	beef-pork isophane suspension
Allergic manifestations	urticaria	urticaria	urticaria	urticaria, angio-neurotic edema	urticaria, angio-neurotic edema
Treatment gap in insulin therapy	yes	yes	yes	yes	yes
Preceding local reaction	yes	yes	yes	yes	yes
No. of injections prior to onset of symptoms	6	3	5	8	10
Personal or family allergy history	no	no	no	no	no
Direct intradermal skin test reaction to insulin	positive	positive	positive	positive	positive
Serum transfers reactivity to normal recipients	yes	yes	yes	yes	yes
Course	treated with oral agents	treated with oral agents	desensitized to pork insulin during pregnancy; diabetes controlled with 35 units daily; mother and child doing well	desensitized to pork insulin; diabetes controlled with 32 units daily; doing well	Treated with oral agents

were incubated in a water bath at 56 C for 30 minutes.

Histamine Release.—Histamine release studies were performed by incubating patients' peripheral blood leukocytes with insulin. The amount of cell-bound and supernatant histamine was determined by techniques previously described.⁹

Immunologic Studies.—Immunoelectrophoresis was done by standard techniques.¹⁰ Precipitin arcs were developed with rabbit antihuman serum. Autoradiographs of immunoelectrophoretic preparations were made with the use of porcine insulin I 125. Double-gel-diffusion autoradiography¹¹ was done with the use of sheep antihuman IgE and goat antihuman IgG, IgA, and IgM.

Clinical Summaries.—Five patients with insulin allergy were seen in Northwestern University Medical Center between December 1966 and December 1969. The studies described were performed on these patients.

Fifty patients with diabetes mellitus who were receiving insulin therapy for at least one week were selected at random from the metabolic outpatients service. Wheal and erythema reactivity of these patients was determined by intradermal testing with various insulin preparations.

The clinical features of the five allergic patients are described in this communication and summarized in Table 1. Table 2 describes a repre-

sentative desensitization schedule, as followed in case 3. Results of initial intradermal tests performed with various insulin preparations are presented in Fig 1.

Report of Cases

CASE 1.—A 76-year-old man was admitted to the hospital on Dec 3, 1966, with adhesive capsulitis of both shoulders. Diabetes mellitus had been diagnosed nine years previously. At that time he was treated with 20 units of isophane insulin suspension daily. Shortly thereafter, he developed generalized urticaria. A diagnosis of insulin allergy was made, and insulin was discontinued. Subsequent treatment consisted of tolbutamide and a diabetic diet. He remained on this regimen until his admission in 1966. Because of a fasting blood glucose level on admission of 316 mg/100 cc and a history of

Table 2.—Representative Schedule for Desensitization to Insulin, as Used in Case 3*

Day	Hr	Insulin Dose, Units	Route of Administration	Type of Insulin
1	8 AM	0.00001†	Intradermal	Pure pork
	12 noon	0.0001	Intradermal	Pure pork
	5 PM	0.001	Intradermal	Pure pork
2	8 AM	0.01	Intradermal	Pure pork
	12 noon	0.1	Intradermal	Pure pork
	5 PM	1.0	Intradermal	Pure pork
3	8 AM	2.0	Intradermal	Pure pork
	12 noon	4.0	Subcutaneous	Pure pork
	5 PM	6.0	Subcutaneous	Pure pork
4	8 AM	8.0	Subcutaneous	Pure pork
	12 noon	12.0	Subcutaneous	Pure pork
	5 PM	16.0	Subcutaneous	Pure pork
5	8 AM	20.0	Subcutaneous	Pure pork
6	8 AM	25.0	Subcutaneous	Pure pork
7	8 AM	30.0	Subcutaneous	Pure pork

*Patient must be observed closely by physician for 30 minutes after each injection.
†Initial dose was based on reactivity to intradermal testing. A concentration one tenth as strong as most dilute preparation giving positive skin test was used.
‡Insulin used to desensitize was determined by results of skin testing. The least reactive readily commercially available preparation was used.

a 9.1-kg (20-lb) weight loss, insulin therapy was reinstituted. On the sixth day of treatment with 35 units of beef-pork isophane insulin suspension, generalized urticaria developed. Insulin was once again discontinued, and his diabetes was subsequently controlled with tolbutamide, phenformin hydrochloride, and diet. Cutaneous sensitivity to insulin was determined on that admission and has been evaluated serially for three years (Fig 2).

CASE 2.—A 51-year-old man with diabetes of eight years' duration was admitted to the hospital on April 27, 1968, complaining of polyuria, polydipsia, and weight loss. Following a brief trial with insulin eight years previously, his therapy was changed to tolbutamide, which had been continued to the current admission. A fasting blood glucose level of 384 mg/100 cc was obtained on this admission. Because of the poor diabetic control, insulin therapy was reinstituted with 40 units of beef-pork isophane insulin suspension. Seventy-two hours after the first injection, a severe, generalized urticarial reaction occurred. Insulin was discontinued, and the skin lesions subsided in 24 hours. Cutaneous sensitivity to insulin, as determined by intradermal testing, has now persisted for a period of 20 months (Fig 2).

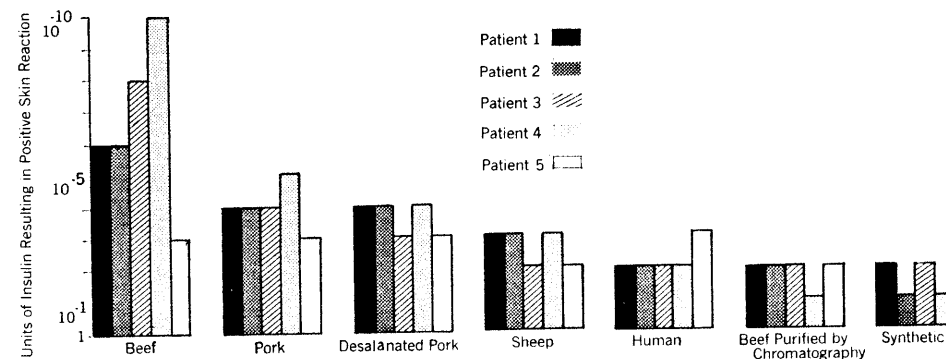
CASE 3.—A 26-year-old pregnant housewife was hospitalized on Sept 2, 1969, because of severe generalized urticaria and angioneurotic edema.

Diabetes mellitus had been diagnosed during her first pregnancy ten years previously. She had been treated intermittently with oral hypoglycemic agents and had received insulin during one pregnancy without evidence of hypersensitivity. Five days prior to admission, a fasting blood glucose level of 288 mg/100 cc and ketonuria were discovered. Treatment with 30 units of beef-pork insulin zinc suspension daily was initiated. During the first four days of insulin injections, progressively increasing local reactions at the injection sites were produced. After the fifth injection, a very large local reaction, generalized urticaria, and angioneurotic edema appeared. Following discontinuation of insulin, the reaction subsided. An initial attempt to control the patient's diabetes with oral hypoglycemic agents was unsuccessful. Because of persistent elevation of blood glucose, the pregnancy, and the possibility of future ketosis, the endocrinology consultants recommended that insulin therapy be resumed. Desensitization to pork isophane insulin suspension was accomplished over an interval of seven days (Table 2). The patient was treated throughout her pregnancy with 25 to 35 units of pork isophane insulin suspension without complication. Delivery was performed by cesarean section, and the infant and mother have done well.

CASE 4.—A 71-year-old white woman was admitted to the hospital on Dec 7,

1969, with urticaria and angioneurotic edema involving the hands, feet, periorbital area, and trunk. The symptoms appeared after the eighth injection of 30 units of beef insulin zinc suspension. Diabetes mellitus had developed 12 years previously, but had been managed with orally administered hypoglycemic agents, except during two brief periods prior to the current admission. Six years earlier, she had received beef-pork isophane insulin suspension for 12 days while undergoing a mastectomy for carcinoma of the breast. No adverse reaction occurred during that interval. However, two years prior to admission, an attempt to treat her again with beef-pork insulin resulted in urticaria and angioneurotic edema. Insulin was therefore discontinued until prior to this admission. Resumption of insulin therapy was prompted by weight loss, findings of diabetic neuropathy, and elevated blood glucose levels ranging up to 260 mg/100 cc. After eight injections of beef insulin zinc suspension, severe urticaria and angioneurotic edema appeared. The symptoms subsided 48 hours after insulin was discontinued. Further attempts to treat her diabetes with diet and orally administered agents were unsuccessful. For this reason, and because of the peripheral neuropathy, the endocrinology consultant advised that insulin was necessary for her treatment. Desensitization was accomplished successfully. The patient is now receiving 32 units of pork isophane insulin suspension daily.

CASE 5.—A 37-year-old man was hospitalized on Dec 28, 1969, with angioneurotic edema of the hands and periorbital area which occurred after the tenth injection of 36 units of beef-pork isophane insulin suspension. A diagnosis of diabetes mellitus had been made two years previously, when the patient was admitted to the hospital in diabetic acidosis. Insulin therapy was begun at that time, and he continued with this treatment, requiring 50 to 60 units of beef-pork isophane insulin suspension daily, for one year. Insulin was then discontinued for unknown reasons, and treatment with tolbutamide was begun. Because of polyuria, polydipsia, and blood glucose levels ranging from 150 to 250 mg/100 cc, insulin was reinstituted at a dose of 36 units of beef-pork isophane insulin suspension daily. This treatment resulted in the angioneurotic edema, which subsided 24 hours after discontinuation of insulin. Angioneurotic edema reoccurred one hour after intradermal testing with insulin. With rigid dietary control and therapy with



1. Results of initial intradermal tests in five patients allergic to insulin. Seven varieties of insulin were used for testing.

tolbutamide, 2 gm daily, the patient has done well.

Results

Cutaneous Reactivity.—All five patients were tested directly with seven varieties of insulin. Tests for P-K reaction were performed in each instance, except for in case 4. Passive transfer was not done with this patient's serum because of the history of carcinoma of the breast.

All patients demonstrated immediate wheal and flare activity to each insulin type used in the study (Fig 1). All patients were most reactive to beef insulin and least reactive to human, sheep, and synthetic insulins, except for patient 5, who was equally reactive to beef, pork, and human insulin.

Passive transfer of skin reactivity was successfully accomplished in four patients. Reactivity of the reaginic sera was destroyed by incubation in a water bath at 56 C for 30 minutes.

Direct cutaneous tests (Fig 2) and passive transfer tests (Fig 3)

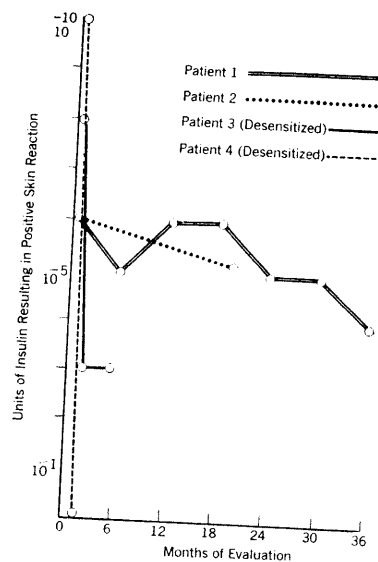
were repeated serially in all patients available for study. Patients 1 and 2 were tested periodically for 36 and 20 months, respectively. Patients 3 and 4 were tested before and after desensitization. Direct cutaneous reactivity decreased markedly in both patients following desensitization. Patient 4 became completely non-reactive to the intradermal injection of insulin after desensitization. Following desensitization, the serum of patient 3 lost the ability to transfer reactivity to the skin of a normal donor. In contrast, patients 1 and 2, who were not desensitized, have shown a persistence of both direct cutaneous reactivity and passive transfer capability.

Histamine Release.—When insulin was added to the peripheral leukocytes of the five patients, no specific release of histamine was demonstrated.

Immunoelectrophoresis, Double-Gel Precipitin Reaction, and Autoradiography.—The sera of patients 1 through 4 were studied for evidence of antibodies against insulin by auto-

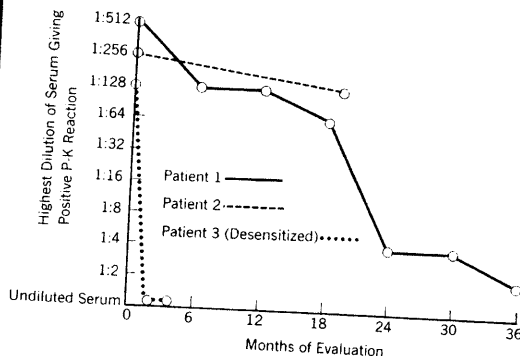
radiography. Serum samples obtained both before and after desensitization and during insulin therapy were studied in this manner. Autoradiographs of double-gel precipitin reactions were made with the use of goat antihuman IgG, IgA, and IgM, and sheep antihuman IgE, and were developed with the use of insulin I 125. These were all negative. Insulin-binding by IgG and IgA was demonstrated in patient 1 by autoradiographic immunoelectrophoresis with the use of rabbit anti-normal-human serum and with the use of insulin I 125 for development. The same procedure repeated in the other patients resulted in negative autoradiographs in all instances.

Cutaneous Testing in 50 Diabetic Patients With no History of Insulin Allergy.—Positive reactions of the wheal and erythema type were obtained in 20 of the 50 patients tested. Insulins used to test for reactivity in these patients were the insulins being used for therapy at the time; boiled beef insulin, boiled pork insulin, and beef insulin purified by chro-



2. Results of serial intradermal tests with beef insulin in four insulin allergic patients available for continued observation.

3. Results of serial passive transfer tests with beef insulin in three insulin allergic patients available for continued observation.



matography. The insulins being used for therapy gave positive reactions in 19 of the 20 reactors. Beef insulin purified by chromatography caused reactions in only four of the 20 reactors. Boiled beef and boiled pork insulin were responsible for positive reactions in 13 and 10 of the 20 reactive patients, respectively.

Thirteen of the 20 reactive patients available for further study were tested with sheep, desalinated pork, recrystallized beef, and human insulins, and with beef and pork protein (Fig 4). Beef insulin purified by chromatography and human insulin were the least reactive of the insulin varieties used.

Comment

The five cases of systemic reactions to insulin represent, to our knowledge, the largest such series reported. Each case was diagnosed by the presence of urticaria or angioneurotic edema or both, which subsided within 24 hours after in-

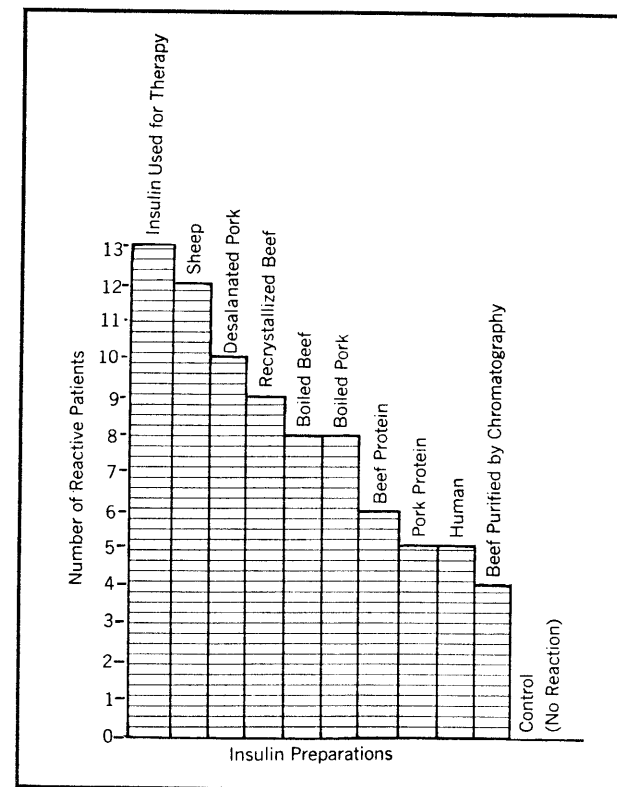
sulin was discontinued. In all instances, the generalized symptoms were preceded by progressively enlarging local reactions, consisting of wheal and erythema reactions at the site of injection. Two of the patients were successfully desensitized to insulin, while three were treated with oral hypoglycemic agents. In all cases, there had been a discontinuation of previous insulin injections, resulting in a time lapse in insulin therapy. The systemic reactions occurred from three to ten days after insulin was resumed. Skin sensitivity was shown to persist for as long as three years in one patient. Therefore, the danger of anaphylaxis must always be considered whenever insulin therapy is resumed, even after a prolonged period with no treatment.

The antibody in one patient, which was previously studied by specific absorption techniques, was found to be IgE.² This finding is in agreement with findings of other in-

vestigators.^{1,2} However, in vitro confirmation of an IgE antibody against insulin was not demonstrated by autoradiographic techniques in any of the patients reported herein. The explanation for this probably lies in the small quantities of the antibody present.

None of the five patients demonstrated in vitro histamine release when their leukocytes were incubated with insulin. This cannot be explained.

The desensitization accomplished in two patients permitted the resumption of insulin therapy without untoward effects. Following desensitization, there was a rapid fall in skin reactivity in both patients. Patient 4 became entirely nonreactive to intradermal testing. Patient 3 became nonreactive upon P-K testing, and showed a marked drop in reactivity on direct testing. This is in contrast to patients 1 and 2 who were not desensitized, and who continued to maintain skin reactivity



4. Results of direct intradermal tests with ten varieties of insulin in 13 diabetic patients, showing skin reactivity to insulin. No subject showed systemic reactivity.

over long time periods. In contrast to the results in a previous report,¹² no IgG insulin-binding activity was demonstrated after or during desensitization. The rapidity of the desensitization process and the absence of insulin-binding IgG antibody may indicate that gradual antibody neutralization, and not the presence of blocking antibody, was responsible for desensitization.

The decision to desensitize a patient who has systemic allergic

symptoms to insulin should be made with careful consideration. The possibility of anaphylaxis during the desensitization procedure is always imminent. In each case of desensitization reported herein, the decision that insulin was essential for the well-being of the patient was made by the endocrinology consultant. The representative desensitization schedule shown in Table 2 is not rigid. The initial dose, the dosage increment, and the time interval be-

tween doses are flexible, and must be based upon the physician's assessment of the clinical situation. In selecting doses and dose intervals, precautions against hypoglycemic reactions may be necessary if several doses are given during the same day.

Because all of the patients reacted to synthetic and human insulins and none reacted to noninsulin beef and pork protein, it is felt that each patient exhibited hypersensitivity to the insulin molecule per se and not to contaminating proteins in the commercially available preparations. The acid-alcohol extraction process used in preparing commercial as well as synthetic insulin presumably accounts for its allergenic properties, thus explaining why the patients did not react to endogenous insulins.

Twenty (40%) of the 50 diabetic patients selected at random for skin testing showed a wheal and flare response for intradermally administered insulin. This frequency is similar to that found by other investigators.¹³ None of these 20 patients exhibited systemic reactions. The frequency of such reactions to a variety of insulin preparations indicates that reactivity can be due not only to the insulin molecule but also to protein contaminants present in the preparations. Purifying the insulin preparations chromatographically or by boiling decreased the incidence of reactions. However, beef insulin purified by chromatography and human insulin still elicited positive skin tests in some patients.

This investigation was supported in part by Public Health Service research grant 5 T01 AI 00057 from the National Institute of Allergy and Infectious Diseases, and in part by the Ernest S. Bazley research grant to Chicago Wesley Memorial Hospital and Northwestern University, Chicago.

Beef-pork isophane insulin suspension, crystalline pork insulin, desalinated pork insulin purified by chromatography, extracted human insulin, and insulin diluent fluid were supplied by Eli Lilly and Co, Indianapolis; soluble beef protein and pork protein antigens were supplied by Holli-

ster-Stier Laboratories, Downers Grove, Ill; sheep antihuman IgE was supplied by the World Health Organization, Switzerland; and goat antihuman IgG, IgA, and IgM were supplied by Hyland Laboratories, Chicago.

Nonproprietary and Trade Names of Drugs

Insulin I 125—Inusay-125.
Phenformin hydrochloride—DBI, DBI-TD.

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Just Words

Corns are as old as footwear. They have been consistently painful and harmless, and their hilarigenic potential is universally recognized.

It is, therefore, surprising that our language has treated corns so very niggardly. Corns are corns; from the chiropodial expert to the ultimate hippie (with slangsters and common folk in between), all speakers of English call them corns (which suggests that they are horny and is not a particularly imaginative term).

A similar monotony prevails in our western fellow languages, though in most the terms in common use are at least visually suggestive. Corns are called "eyes," always—interestingly—with the specification of the eyes' owner and always—most interestingly—with the specification

that the owner is a bird. So we find in the pan-occidental synonymicon that a corn is a "rooster's eye" (Spanish), a "partridge eye" (French, Italian), a "magpie eye" (Dutch), a "hen's eye" (German), and so on.

What accounts for this avian versatility in combination with such ocular regimentation?

There are, in all the languages listed, fanciful explanations of *Hühnerauge*, *oeil de perdrix*, *ojo de gallo*, *eksteroog*, *occhio di pernice*, etc, but none of them considers the documented fact that medieval Latin used *oculus pullinus* as early as the seventh century. This must be the ancestral form of all the modern birds' eyes, for *pullinus* was any animal young (including, by the way, a colt).

Alexander Gode, PhD

Early Fingertip Changes in Scleroderma

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Roentgenographs of the hands of 52 patients with scleroderma were compared with those of 43 patients with other collagen diseases and 22 patients with primary Raynaud's disease. Abnormal roentgenographic findings were noted in 33 (63%) of patients with scleroderma as compared to 5% (2) of patients with other collagen disease and 41% (9) of patients with primary Raynaud's disease. In scleroderma roentgenographic changes are commonly seen early in the course of the disease. Soft tissue atrophy of the fingertips is usually associated with neurovascular manifestations (Raynaud's phenomenon). Calcifications of the pulp of the fingertip and bone erosion are commonly seen in scleroderma and are not necessarily associated with the presence or absence of Raynaud's phenomenon.

The hands are frequently involved in collagen diseases. This involvement may vary from arthropathy to neurovascular manifestations. It is well appreciated that these collagen disorders show a considerable overlap in their manifestations and, because of this, are not always separable into distinct clinical entities.

The roentgenographic changes in the hands of patients with scleroderma are thought to be highly characteristic and virtually diagnostic.¹⁻³

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Read before the 119th annual convention of the American Medical Association, Chicago, June 22, 1970.

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To determine the sequence, frequency, and specificity of roentgenographic changes in scleroderma, we have reviewed all available films of the hand obtained in patients with collagen diseases at our institutions during the last 17 years. This report will summarize our findings.

Material and Method

The records of 428 patients with various collagen disease exclusive of rheumatoid arthritis and 80 patients with primary Raynaud's disease were reviewed. The type of collagen disease was based on clinical or laboratory findings or histological study or both. A total of 132 of these patients had scleroderma, 296 had other forms of collagen disease (lupus erythematosus, dermatomyositis, and polyarteritis nodosa).

Roentgenographs of the hands were reviewed in 95 patients with collagen disease with and without Raynaud's phenomenon. They were compared with 22 patients with primary Raynaud's disease (neurovascular signs and symptoms without other manifestations of collagen disease). The patients were subdivided into the groups shown in Table 1. The roentgenographs of the hands of 50 normal patients served as controls.

The incidence of various roentgenographic abnormalities of fingers was tabulated according to the group and duration of the disease.

Bone changes

Erosion of the distal ungual tufts
Erosion of the margin of the distal interphalangeal joint

Soft tissue changes

Calcifications limited to the pulp of the fingertips or associated with interphalangeal joint capsule calcifications
Atrophy of the fingertip soft tissue

Results

Results are shown in Table 2.

Bone Changes.—Erosion of bone was present in 21 (40%) of 52 patients with scleroderma (Fig 1, top left and bottom right). Three of these cases had concurrent dermatomyositis and one had systemic lupus erythematosus. Bone erosion was noted in only one of 43 patients with other collagen diseases. This patient had polyarteritis nodosa. Bone erosion was noted in three of 22 patients with primary Raynaud's disease. Patients with scleroderma may have bony erosion whether they