

PROGRESS IN PEDIATRICS

THE ALLERGIC OR HYPERSENSITIVE CONDITION

A REVIEW OF TWO YEARS' PROGRESS *

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An essential advance in the understanding of anaphylaxis and related phenomena, which occurred early in this period of two years, has been the restrictive definition of the term "anaphylaxis." For the classification of the various conditions which were thereby excluded and which had hitherto been regarded as manifestations of anaphylaxis, the terms "allergy" and "hypersensitiveness" are now in general use. The hypersensitive condition, according to Coca,¹ is one of specific or particular reactivity, with characteristic symptoms, to the administration of or contact with, any substance in a quantity which, to most of the individuals of the same species is innocuous. In amplification he adds: (1) "The characteristic symptoms are generally different in the different animal species for the same group of substances." (2) "They are uniform in any one species for various substances." (3) "Where the exciting agent possesses a normal physiological action; for example, the drugs, the symptoms of this action are, with few exceptions, different from those of hypersensitiveness to that agent." This excludes the tuberculin reaction because its symptoms are the same for all species and the so-called "toxin hypersensitiveness" because the symptoms are not different from those of the normal physiological effect of the agent.

The phenomena of true hypersensitiveness, Coca says, are those of anaphylaxis and those of allergy.

Anaphylaxis is defined by the same author as hypersensitiveness induced and experimental, not inheritable, and due to the presence of specific antibodies in certain tissues.

Allergy, on the other hand, is a natural inherited condition of hypersensitiveness which affects only human beings and is not dependent in any way on immunologic antibodies. Coca and other authorities are not, however, in complete accord as to the relation of specific antibodies to allergic phenomena.

Coca points out, furthermore, that if true anaphylaxis ever does occur in man, it does so very rarely, and he believes that there is no positive evidence that it occurs at all in human beings. The allergic

* Received for publication, June 20, 1922.

1. Coca: J. Immunol. 5:363, 1920.

phenomena to which some of us are subject would, therefore, be independent of artificial sensitization and often, in fact, occur at first contact without opportunity for sensitization to have taken place in the ordinary meaning of the word.

According to Wells² the criteria for true anaphylaxis are:

(a) The observed toxicity of injected material must depend upon the sensitization of the animal; i. e., must not produce similar symptoms in non-sensitized animals.

(b) The symptoms produced must be those characteristic of anaphylactic intoxication, and therefore the same for all antigens with the same test animal, but differing characteristically with each species.

(c) It should be possible to demonstrate passive sensitization with the serum of sensitized animals.

(d) It should be possible to demonstrate typical reactions in a strip from the virgin guinea-pig uterus.

(e) It should be possible to demonstrate amelioration or prevention of the bronchial spasm in guinea-pigs by the proper use of atropin and epinephrin.

(f) The possibility that the observed symptoms are caused by capillary thrombosis or embolism must be excluded.

(g) After recovery from anaphylactic shock there should be exhibited a condition of desensitization under proper conditions.

Wells also states that there is no satisfactory proof that anything except proteins can act as anaphylactogens (antigens of anaphylactic reactions). The only soluble proteins as yet found not to be antigenic are those which are, from the chemical sense, incomplete proteins, and there is evidence that lack of certain amino-acids may be the essential deficiency. Solubility is essential since, although insoluble proteins may eventually be brought into solution in the animal body, the process is too slow to bring about anaphylactic reactions, and is probably also accompanied by a disintegration of the protein molecule. Heating to a degree that does not disintegrate the proteins affects them only to the extent that it makes them insoluble. Among the few proteins not made insoluble by heating are casein and ovomucoid, and these are antigenic despite boiling.

There is disagreement and doubt as to the true nature of serum disease allergy in relation to anaphylaxis. Drug hypersensitiveness seems undoubtedly a distinct phenomenon. Schloss³ has been able to transfer sensitization to guinea-pigs by the injection of serum from patients in four cases, and Ramirez⁴ reports an interesting case which appears as an example of passive sensitization to horse dander from man to man by transfusion of 600 c.c. of blood. Coca, however, feels that the evidence is not conclusive in this case, that the transfused patient was not already allergic toward dander and has found in addition that the same donor previously gave 800 c.c. of blood to another patient in whom no symptoms of sensitization appeared.

2. Wells: *Physiol. Rev.* **1**:44, 1921.

3. Schloss: *Am. J. Dis. Child.* **19**:433 (June) 1920.

4. Ramirez: *J. A. M. A.* **73**:589 (Sept. 27) 1919.

Zinsser,⁵ in determining the relation of the tuberculin reaction to anaphylaxis, states that in guinea-pigs two fundamentally different types of intradermal reactions can be produced; one immediate and transitory, which develops in animals sensitized against proteins and is true anaphylaxis; and one, the tuberculin type, which develops more slowly, leads to more profound injury of tissues, and is independent of anaphylaxis. Tuberculin sensitization is easily accomplished only with live infections, and reactions follow intradermal injections of extracts of bacteria from which all coagulable proteins, nucleoproteins and Bence-Jones bodies have been removed as far as possible by boiling with acid. Anaphylactic sensitization developed by injections of dead bacterial material is not as quickly developed as tuberculin sensitization. Manifestations of tuberculin sensitiveness also differ in animals and man from those characteristic of anaphylaxis in each species.

Attempting to produce tuberculin sensitiveness with constituents of dead bacteria, Zinsser has obtained hopeful results only with massive injections, and these of substances precipitated with acid.

Fleishner, Meyer and Shaw⁶ have shown by experiment that bacterial proteins, whether insoluble or soluble, which sensitize guinea-pigs in an anaphylactic sense will not sensitize its skin. The observations of Auer⁷ on the effect of independent local irritants are of interest in this connection. He determined that xylol, when applied to the ears of nonsensitized rabbits, produced no very marked amount of inflammation. If sensitized animals were used, however, the application of this substance, when followed by the injection of otherwise ineffective amounts of the antigen to which the animals were sensitized, caused necrosis. He concluded that this result was due to the accumulation of effective amounts of antigen in the treated area, owing to the inflammatory reaction initiated by the xylol. This suggests a possible relation between drug idiosyncrasy and anaphylaxis.

It does not seem desirable to include in this review references to the literature on anaphylaxis except as they may be directly enlightening to the understanding and treatment of allergy and hypersensitiveness in man. For further information on anaphylaxis one may examine the comprehensive and authoritative treatises by Besredka,⁸ Coca⁹ and Bordet.¹⁰

It appears that the nature of anaphylaxis and the understanding of its mechanism is comparatively well established but that the nature

5. Zinsser: *J. Exper. M.* **34**:495, 1921.

6. Fleishner, Meyer and Shaw: *Am. J. Dis. Child.* **18**:577 (Dec.) 1919.

7. Auer: *Proc. Soc. Exper. Biol. & M.* **17**:93, 1919.

8. Besredka: *Anaphylaxis and Antianaphylaxis and Experimental Foundations*, C. V. Mosby, 1920, p. 156.

9. Coca: *Tice, Practice of Medicine*, New York, W. Pryor Company, 1920, p. 107.

10. Bordet: *Bull. Johns Hopkins Hosp.* **32**:269, 1921.

of the allergic or hypersensitive condition in man is more elusive to the understanding and possibly much more complex in its mechanism. As a rule, according to Longcope,¹¹ the symptoms in man appear early in life and may be observed the first time the patient comes in contact with the substance to which he is hypersensitive. There is undoubtedly a definite tendency toward the inheritance, not of specific hypersensitiveness, but of a quality of tissue that allows of the development of idiosyncrasies. This may be dependent on the condition of the body fluids or of the cells, which permits of a ready union of foreign protein with them. A striking peculiarity of these patients is that the skin reacts by the formation of an urticarial wheal, to the application of the substance or substances to which they are sensitive.

Turnbull¹² believes that sensitization may be acquired during intercurrent disease, or overexertion or worry, or by the absorption of bacterial products from foci, or by over eating or repeated eating of certain foods, or by the ingestion of certain foods too soon after illness or exhaustion. In some persons there may have been a combination of one or more of these circumstances.

The Cutaneous Reaction.—It is remarkable that in contrast to the thousands of cases reported in American medical literature, virtually no activity in the determination of the incidence of the cutaneous reaction is discoverable elsewhere. Furthermore, correspondingly little specific treatment appears to be given. Most foreign reports on the treatment of asthma and of "alimentary anaphylaxis" indicate that the injection or ingestion of peptones or other nonspecific substances is the more favored method.

Either the cutaneous or the intracutaneous method may be used for testing. Schloss³ in a comparison of the two methods, prefers the cutaneous method. His study was made on 100 infants and children not apparently suffering from disturbances due to food and on thirty who suffered definitely from this cause. His conclusions were that the intracutaneous test is more sensitive but more misleading owing to its tendency to cause pseudoreactions. Many vegetable proteins are difficult to obtain in any form soluble in physiologic sodium chlorid solution, but are soluble only in alkaline solvents and thus cannot be used intradermally. To insure sterility, the proteins used for the intradermal test solutions must be carefully prepared, which adds considerable technical difficulty. On two occasions he has seen severe infections due to such tests. Another objection is that a very sensitive patient may be made seriously ill by the injection of even a minute amount of the protein to which he reacts.

11. Longcope: J. A. M. A. **77**:1535 (Nov. 12) 1921.

12. Turnbull: Boston M. & S. J. **182**:497, 1920.

The greatest limitations of the cutaneous test, according to Schloss, are that it is not conclusive when negative. This deficiency, he suggests, may be due to lack of skin sensitization, or, possibly to temporary desensitization.

In these opinions Schloss is in agreement with Walker and a large number of other authors; nevertheless there are and have always been those who are vigorous supporters of the intracutaneous method. Larsen, Paddock and Alexander¹³ favor the intracutaneous test because it is more delicate; the dry preparations are too uncertain, and they can do more tests in less time and with less trouble. They find, however, that the solutions for the intracutaneous tests are apt to show a precipitate after a while, and lose their potency. They also find that certain points on the body, particularly the fold at the elbow, are more favorable than others to the development of a reaction.

Brown,¹⁴ commenting on Walker's selection of the cutaneous method, questions the value of his experiments with intracutaneous applications because of the use of too much fluid in the injections and because his standard for a normal reaction allowed of too many positive reactions. Using a fluid preparation prepared according to Coca's method in seventy-eight cases, he claims the superiority of the intracutaneous method on the following grounds: (1) every case known to be clinically sensitive to a protein gave a reaction. (2) The scratch method with dry powdered proteins gave positive reactions in only 50 per cent. of the cases, and with his more potent fluid preparations, in only 80 per cent. (3) The intradermal method is not so painful nor so disfiguring. (4) The intradermal method requires less time for application and for obtaining results, which is an important advantage in office work. (5) The same preparation can be used conveniently for treating and testing. (6) General reactions occasionally follow the dermal scratch application as well as the intradermal injection.

Cooke,¹⁵ writing on the danger of constitutional reactions from dermal and intradermal tests, reports one death following an intradermal test injection containing not more than 0.002 mg. of nitrogen. He refers to one instance of constitutional reaction following the scratch method of testing, and reports several in his own experience from the intracutaneous injection. Such cases have been reported by Park¹⁶ and by Gerstenberger and Davis.¹⁷ Cooke suggests that there is special danger of provoking these reactions when changing from a weak preparation to a strong one. When a constitutional

13. Larsen, Paddock and Alexander: *J. Immunol.* **7**:81, 1922.

14. Brown: *J. Immunol.* **7**:97, 1922.

15. Cooke: *J. Immunol.* **7**:119, 1922.

16. Park: *Am. J. Dis. Child.* **19**:46 (Jan.) 1920.

17. Gerstenberger and Davis: *J. A. M. A.* **76**:721 (March 12) 1921.

reaction is diagnosed, Cooke recommends, first, the application of a tourniquet to restrict, if possible, the rate of absorption of the injection; secondly, the injection of epinephrin in strong doses—from 0.4 to 0.6 c.c. in children and 1 c.c. in adults, either subcutaneously or intravenously according to the severity of symptoms. This should be repeated after a short interval if symptoms continue to progress and, in his experience, is not dangerous. There may also be indications for the use of strophanthus intravenously, up to 1 mg.

The reports quoted indicate an apparent superiority amounting to about 20 per cent. in favor of the delicacy of the intradermal method of testing, which is or is not offset by the greater liability to constitutional reactions, according to personal opinion. The inference is clear, however, that the protein preparations used by these authors may be especially potent. The method of preparing these proteins was devised by Coca and is explained in his paper on the subject.¹⁸ Vander Veer,¹⁹ testing the comparative potency of four of the best known commercial preparations of proteins, and that obtained from the Department of Applied Immunology of the New York Hospital, known as the "Cornell preparation" (Coca's method), found that none of the commercial preparations even approximated the potency of the strongest Cornell preparation. The strongest or most potent of these seemed about equal in potency to a medium strength Cornell preparation containing 0.005 mg. of nitrogen per c.c. All preparations were in the fluid form and tests were made by the ophthalmic method. They state that experience indicates that for therapeutic effects a maximum potency is desirable but that in using these preparations more caution is necessary in order to avoid constitutional reactions.

Mackenzie and Baldwin,²⁰ experimenting to determine the exhaustibility of the skin reaction after repeated reactions on the same site, conclude: (1) that in persons manifesting a cutaneous reaction, the reactivity of the skin may be locally abolished by repeated applications to the same area; (2) The reactivity of the skin at the exhausted site may not return for three days or longer. (3) The exhaustion appears to be specific and is not apparent when some other substance is used. (4) The extent of the area of exhaustion is strictly limited to the site of the reaction. (5) Nonspecific cutaneous reactions produced by non-antigenic substances such as histamin are not only inexhaustible but progressively increase with each repetition of the application to the same site. (6) From these results they suggest the possibility of genuine local desensitization and suggest its application in the treatment of hay fever and allergic rhinitis. Larsen, Paddock and Alexander¹³

18. Coca: *J. Immunol.* **7**:163, 1922.

19. Vander Veer: *J. Immunol.* **7**:113, 1922.

20. Mackenzie and Baldwin: *Arch. Int. Med.* **28**:722 (Nov.) 1921.

attempted to confirm these results by repeated injections in two persons at intervals of one hour. With this technic nine intracutaneous injections in one person and four in the other in the same skin area failed to abolish the reaction of the skin. After the eighth injection, the first patient had symptoms of hay-fever, and his eighth and ninth reactions were locally the largest and his arm became much swollen. The next day a typical reaction was obtained again on the same site. When tests were made at intervals of one week, however, these two cases showed a definitely decreased reactivity, the duration of which was not accurately tested, but at the end of three weeks the reaction was again produced as strongly as ever. Their experiments, therefore, are partially confirmatory to those of Mackenzie and Baldwin.

Desensitization and "Hyposensitization".—Cooke,²¹ comparing diminished sensitization in allergic conditions in man with desensitization in experimental anaphylaxis, believes that the uniform failure to induce complete insensitiveness in allergy indicates that the relative insensitiveness is of a nature different from that of desensitization in anaphylaxis. He proposes that this distinction be made by designating such a modification of allergic sensitiveness "hyposensitization." He has studied the phenomena of "local exhaustion" of the allergic cutaneous reaction described by MacKenzie and Baldwin, and finds in disagreement with these authors that the exhaustion is nonspecific.

Incidence of the Cutaneous Reaction.—That evidence of sensitization can be obtained by the cutaneous or scratch method in patients whose history is free from the consequences of such sensitization is shown by Baker²² and by Peshkin and Rost.²³ Baker obtained ten positive and eleven doubtful reactions in twenty-five children whose history indicated no allergic conditions. In comparison with these he reports fifty-five positive and fifty-three doubtful reactions in seventy-four children with symptoms of a probable allergic nature. Peshkin and Rost tested 502 children who were carefully selected as giving in their histories no symptoms which could be attributed to allergy. They report positive reactions in only five, all of whom were more than 5 years of age. They also contained sixty-seven doubtful reactions. The total number of tests done on these 502 children was 9,406, an average of only nineteen per patient. Baker concludes that the incidence of sensitization in apparently normal children is almost negligible, but unless his ten positive reactions were all obtained from one or two of his twenty-five normals, one can hardly agree with this estimate. Peshkin and Rost conclude that 10 per cent of apparently normal children show doubtful or positive reactions which decrease as their age

21. Cooke: J. Immunol. **7**:219, 1922.

22. Baker: Am. J. Dis. Child. **19**:114 (Feb.) 1920.

23. Peshkin and Rost: Am. J. Dis. Child. **23**:51 (Jan.) 1922.

increases, indicating progressive desensitization. On the basis of their own figures, especially in consideration of the small average number of tests, this percentage seems too conservative. Baker's tests were confined to food proteins.

The articles of diet found by Baker to be most commonly the source of allergic symptoms were in the order mentioned: oatmeal, potato, egg, peas, rice, casein, beef juice and chicken.

Rackemann²⁴ reports the results of cutaneous tests in 939 patients presenting various clinical conditions. He obtained positive reactions in about 100 cases in which nothing compatible with this reaction appeared in the history. Subsequently, in following these patients, thirteen developed conditions in relation to which the reaction obtained proved important.

Of 118 cases of hay-fever and pollen asthma, forty-eight gave reactions to proteins other than pollens. Of forty-five cases of horse asthma, fifteen gave positive results with other proteins. Of thirty-one cases of dust asthma, there were many complicating reactions. Of nineteen cases of food asthma, four gave numerous reactions to other proteins. Of 156 bacterial asthmas, 103 with fairly complete skin tests showed positive reactions to other proteins. It is desirable, according to Rackemann, to make a wide variety of tests and to so limit the patients' life and habits that they will come in contact only with negatively reacting proteins. Positive reactions, however, should not be taken very seriously unless compatible with the patient's history, or if further study proves their importance as etiological agents.

Coca²⁵ states that the age incidence of natural allergies increases rapidly in the early age periods but probably does not greatly exceed 10 per cent. in any period. Coca, Deibert and Menger²⁶ find that the American Indian is apparently much less frequently affected by the allergies than is the white race.

Sensitization in Hay-Fever.—In this disorder skin sensitization is so nearly universally present that although tests are useful as confirmatory evidence and, as Walker suggests, to determine the strength of immunizing doses, it is, perhaps, more essential to know the usual offending pollens, their regional distribution, and their season of pollination. There are, however, cases in which symptoms are perennial rather than seasonal.

The frequent causes of perennial hay-fever, according to Walker²⁷ are animal emanations, particularly dander and cat hair, ingested foods, inhaled cereal grains, and sometimes pollens, these last being usually

24. Rackemann: Am. J. M. Sc. **163**:87, 1922.

25. Coca: J. Immunol. **7**:193, 1922.

26. Coca, Deibert and Menger: J. Immunol. **7**:201, 1922.

27. Walker: J. A. M. A. **75**:782 (Sept. 18) 1920.

relieved by the ordinary pre-season treatment. Recurring head colds are sometimes due to sensitization which renders the nasal mucous membrane more irritable. Nonsensitive patients with perennial hay-fever, provided there are no demonstrable abnormalities, growths, and the like in the nasal cavities or sinuses, are sometimes benefited or relieved by autogenous vaccines from nasal secretions. A pseudo hay-fever caused by mechanical, thermal or odorific irritants is not uncommon.

Of seasonal hay-fever in New England the dwarf ragweed is practically always the cause of late symptoms—in August and September, and timothy causes 90 per cent of the early cases of hay-fever, in June and July. Rose and redtop occasionally cause early hay-fever and when their season happens unusually early it may interfere with the course of treatment.

Watson and Kibler²⁸ have investigated the etiology of hay-fever in Arizona and the Southwest. They find that of the wind pollinated flora of these regions the artemisias, or wormwoods, have little, if any, importance. Amaranths are an important factor and their pollen is very active. As a predominating cause of hay-fever in the Southwest they take the place of ragweed in the east and the artemisias in the Rocky Mountains. In some seasons *Atriplex wrightii* will probably take the place of *Amaranthus palmeri*. *Capriola dactylon* (Bermuda grass), causing spring, summer and fall types, will probably prove to be the common grass causing hay-fever at altitudes up to 4,500 feet, and *Poa pratensis* (June grass) above that altitude.

Gaertneria dactylon (rabbit bush) and *Atriplex canescens* (shad scale) are probably the most important plants causing the spring type of hay-fever. Trees are probably not an important cause, but when they do cause hay-fever it will be of a very early type, and the most important are cottonwoods and the ash. The principle of group reactions is not applicable to hay-fever in Arizona and the Southwest.

Heredity in Hay-Fever.—Scheppegrell,²⁹ investigating the incidence of heredity in 1000 cases of hay-fever, found that 358 patients had relatives of the first degree who also suffered from hay-fever. In view of the heterogeneous nature of the heredity reported in other allergic conditions, the fact that the hypersensitiveness should be manifested in the same way in so many cases seems especially remarkable.

Results and Methods of Treatment of Hay-Fever.—Most of the reported cases of hay-fever have been treated by the pre-seasonal immunization process of Walker, that is, by the injection of increasing doses of the specific pollen protein, beginning considerably before the season of pollination and being completed shortly previous to the

28. Watson and Kibler: J. A. M. A. **78**:719 (March 11) 1922.

29. Scheppegrell: Med. Rec. **98**:216, 1920.

opening of the season. There is unanimity of opinion that the specific protein must be used in order to obtain success rather than the preparations of mixed pollen proteins distributed by commercial houses.³⁰ These are open to the same criticism that is justly leveled at mixed vaccines or "shot-gun" drug prescriptions. Scheppegegrell³¹ finds that some cases do not give a marked skin reaction while others do. In the first group the dose of protein may safely be increased rapidly and it is necessary to reach a much higher number of units in order to be effective. In the strongly reacting group, the dosage should be increased cautiously but treatment should be given as intensively as possible.³²

In view of reports previously quoted of the greater potency of certain protein solutions, particularly the Cornell preparations of Coca, it seems advisable that all such solutions or dry proteins should be compared with some suitable standard before using.

That treatment during the hay-fever season cannot be given with as much chance of success is indicated by Williams,³³ who reported that twenty-seven cases due to ragweed were not benefited by treatment after the onset of symptoms. Of five cases due to goldenrod, there resulted some benefit in two and much improvement in one. Walker³⁴ reported, however, that 32 per cent. of twenty-two grass pollen hay-fever patients were made practically free from symptoms by treatment given during the season; 18 per cent. more were benefited to the extent of 75 per cent.; 13 per cent. were 50 per cent benefited; and 13 per cent. were 25 per cent benefited. Of twenty-seven cases due to ragweed, 14 per cent. were made free from symptoms, or practically so; 11 per cent. were 75 per cent. improved; 25 per cent. were 50 per cent benefited, and 44 per cent. were not benefited. He adds that bacterial vaccine treatment during the season occasionally seems to be beneficial. Late preseasonal treatment gives better results than treatment during the season.

Rackemann,³⁵ reporting the results of preseasonal treatment, found that 9 per cent. of ninety-one patients with fall ragweed hay-fever were made entirely free from symptoms; 62 per cent. were considerably relieved. The best results were obtained by moderate amounts of specific treatment since even after more considerable preparation the tolerance for ragweed remained at a very low level. Systemic reactions occur after 2 per cent. of injections and are not always due to an

30. Editorial, *J. A. M. A.* **77**:791 (March 19) 1921.

31. Scheppegegrell: *Med. Rec.* **100**:191, 1921.

32. Caulfield: *J. A. M. A.* **76**:1071 (April 16) 1921.

33. Williams: *Mil. Surg.* **46**:199, 1920.

34. Walker: *Arch. Int. Med.* **28**:71 (July) 1921.

35. Rackemann: *Boston M. & S. J.* **182**:295, 1920.

overdose. Hay-fever, he believes, depends on a mechanism which is not anaphylactic, but which is perhaps closely related to that of drug idiosyncrasies.

Walker³⁴ finds that preseasonal treatment with ragweed pollen was the cause of complete freedom in 22 per cent. of 202 patients; 30 per cent. more were benefited at least 75 per cent.; more than 23 per cent. were only 50 per cent. improved, and 6 per cent. were not benefited at all. Of fifty-two patients whose hay-fever was due to grass pollens, 40 per cent. became free from symptoms; more than 17 per cent. were made practically free; 19 per cent. were 75 per cent. benefited; 17 per cent. were 50 per cent. benefited, and about 6 per cent. were not improved.

For seventy-three patients having ragweed hay-fever who received the preseasonal treatment two years in succession, Walker gives the following figures:

	First Year, Per Cent.	Second Year, Per Cent.
Symptom free	38	16
Practically free	22	22
75 per cent. benefited.....	19	45
50 per cent. benefited.....	16	12
Not benefited	6	4

He believes the poorer results obtained the second year in the first group were due to the fact that these patients were apt to get less treatment. He believes that the greater amounts of preseasonal treatment give the better results.

Caulfield,³¹ with a small group of thirteen fully treated patients, that is, receiving at least 0.05 c.c. of 1:5 dilution, found that all were very much improved. Walter³⁶ finds that preseasonal inoculation against ragweed has not helped his cases, while in hay-fever due to rose, timothy, daisy, etc., there has been success. He believes that ragweed hay-fever is a different problem and suggests alkaline therapy and fractional doses of the pollen during the season.

The most interesting divergence from the subcutaneous method of immunizing is that MacKenzie³⁷ who, having in previous experiments with Baldwin²⁰ observed the exhaustion of local skin reactivity following repeated applications of specific protein to the same area in a sensitive subject, attempted to exhaust the reactivity of the nasal membranes by the instillation of pollen solutions. He quotes Dsergowsky³⁸ and Blumenau³⁹ as producing an active immunity by applications of diphtheria toxin to the mucosa of the nose, throat and trachea, and Ehrlich on the production of immunity by applications of the

36. Walter: J. A. M. A. **75**:670 (Sept. 4) 1920.

37. Mackenzie: J. A. M. A. **78**:787 (March 18) 1922.

38. Dsergowsky: Ztschr. f. Immunol. **2**:602, 1910.

39. Blumenau: Ztschr. f. Immunol. **3**:196, 1911.

antigens ricin and abrin to the upper air passages or to the alimentary tract. He also quotes Sewall and Powell⁴⁰ who obtained either sensitization or immunization in guinea-pigs, depending on the dosage, by intranasal instillation.

In his report eight patients were treated by subcutaneous injections only; twenty by local applications only, and twenty by combined methods. His results were:

	Injections	Spray	Both
Complete relief	0	1	3
Almost complete	3	2	9
Considerable	4	6	6
No relief	1	1	2

Although the number of cases was unfortunately very small, the use of the spray in this manner combined with treatment by injections seems attractive.

Sensitization in Asthma.—Unfortunately, the large numbers of cases which Caulfield⁴¹ and Sanford⁴² have reported are not so grouped that asthma cases can be separated from those of hay-fever. In Sanford's report 100 cases, presumably asthmatics, reacted to one or more of the proteins derived from foods, particularly to egg white, to which eleven patients reacted. To proteins of various grains, twenty-five persons reacted, and twenty-eight reacted to vegetable proteins, but these twenty-eight were, on the whole, negative to the therapeutic test. Fruits had apparently little to do with his cases of asthma, although banana, which produced several positive reactions, was twice shown to be a causative agent. In 365 tests with preparations of *Staphylococcus pyogenes aureus* and *S. pyogenes albus* there was not a single reaction. Caulfield also found bacterial skin tests consistently negative and has virtually discarded these proteins in his tests. The experiments, previously mentioned, of Fleishner, Meyer and Shaw are of interest in this connection. Rackemann,⁴² however, reports somewhat differently concerning their importance: In forty cases of asthma, he isolated from the sputum 129 different organisms on blood agar. These consisted of: 72 nonhemolytic streptococci, or 60 per cent.; 17 hemolytic streptococci, or 13 per cent.; 17 staphylococcus albus, or 13 per cent.; 7 gram-negative cocci; 5 staphylococcus aureus; 3 pneumococci; 2 gram-negative bacillus; 1 diphtheroid bacilli; 11 others. The percentages, according to Rackemann, would vary with different technic and with mice passages the pneumococci would have been more prominent.

Intradermal tests with proteins from these were done on thirty-nine patients to whom they were autogenous, and twenty-five gave positive

40. Sewall and Powell: J. Exper. Med. **24**:69, 1916.

41. Sanford: Minnesota Med. **3**:180, 1920.

42. Rackemann: J. Immunol. **5**:373, 1920

skin tests. Some gave reactions to heterologous preparations and in all, out of fifty-six patients, thirty-four gave positive reactions.

Treatment was successful in fairly close accordance with the positive tests, ten patients treated with injections of a positively reacting autogenous protein were benefited. It was also true that four out of six treated with positively reacting heterologous preparations were benefited. No negatively reacting patients were improved.

Rackemann concludes that asthma due to bacteria depends on a condition of specific cellular sensitiveness, either to the bacteria themselves or to the products of their action in the body. Caulfield, on the other hand, feels that the failure of vaccine therapy is sufficiently marked in contrast to protein therapy to cause one to question that both are etiologic agents acting in a comparable fashion. Cooke⁴³ questions the specific value of vaccines in allergy and has failed to find proof that bacterial extracts will act as allergens. He, therefore, does not make the diagnosis of bacterial asthma. For some of these cases he believes that dusts are responsible, and names particularly hay dust and house dust as containing specific nitrogenous factors.

Coke⁴⁴ mentions, among other interesting instances of sensitization, certain married patients who are hypersensitive to human hair and whose health is better when sleeping apart. This author, using the scratch tests for diagnosis, finds that 50 per cent. of all asthmatics and 90 per cent. of asthmatic children give reactions. These percentages seem very high in consideration of the extensive reports by American authors. He also concludes that much can be done for nonreacting cases by nonspecific protein therapy.

Pines⁴⁵ reviewing 150 cases of asthma, concludes that it is due to protein sensitization and that it is possible with cutaneous tests to determine the etiology in about 50 per cent. of the cases. Cunningham⁴⁶ tested thirty-six children with asthma, found positive reactions in eleven, or 30 per cent., but was able to confirm this relationship in only six, or 17 per cent.

Other Causes of Asthma.—Gerdon⁴⁷ discusses his experiences with asthma in fur dye workers. The dyes used were ursol dyes, and derivatives of p-phenyldiamin. There seemed to be a distinct relation between the asthma and exposure to this dye and in addition patients suffered from salivation, edema, diarrhea and exophthalmos. Asthma would sometimes recur at the mere odor of the dye. He believes that the indications in these cases point to sensitization.

43. Cooke: J. Immunol. **7**:147, 1922.

44. Coke: Brit. M. J. **1**:372, 1921.

45. Pines: California State M. J. **19**:29, 1921.

46. Cunningham: Boston M. & S. J. **186**:876, 1922.

47. Gerdon: Zentralbl. f. Gewerbehygiene **8**:201, 1920.

Sluder⁴⁸ considers that in some cases asthma may be the result of a nasal reflex and mentions six examples. Knapp⁴⁹ believes the disease to be due to insufficiency of the pylorus with long continued pressure of the diaphragm against the lungs. The remarkable case reported by Ramirez, which was apparently due to passive sensitization by transfusion, has already been mentioned.

Pathology of Asthma.—Kamchorn and Ellis⁵⁰ report the necropsy findings in an additional case of death from asthma, making two such cases in their own experience, and review the reports of ten similar cases reported by other observers. They conclude that the histology of the bronchi shows simply acute catarrhal bronchitis and does not explain the course of bronchial asthma. The length of time a person suffers from the disease and the number of attacks he has are apparently without effect on the bronchi (The patient reported on had had asthma all his life). The theory of spasm is favored by these findings. In addition to the bronchial findings the cases showed hypertrophy and dilatation of the heart.

Treatment of Bronchial Asthma.—This may be considered first from the specific standpoint, including the diagnosis of protein sensitization and consequent elimination of the indicated proteins, or the diagnosis of an infectious etiology and treatment by immunization. It is the general opinion, and Caulfield states that the results of elimination of allergic substances surpass in promptitude and completeness the results of other methods of treatment.

Hutcheson and Budd⁵¹ treated ninety asthmatics with autogenous vaccines and by removal of diseased foci. Most of the cases were chronic. In fifty-three, or 75 per cent., either complete freedom from attacks or the longest interval of freedom since the disease began was obtained. In the remainder there was no improvement. Walker has previously reported considerable success from the use of autogenous vaccines. Cunningham⁴⁶ obtained relief in seven of twenty children so treated. Rackemann's results from the use of autogenous, positively reacting bacterial proteins has already been mentioned.

Gottlieb⁵² reported the relief of symptoms in fifteen of thirty-two asthmatics by the elimination of positively reacting proteins. In a second paper⁵³ he recommends the use of bacterial vaccines prepared from the stools. He reports one case of colon bacillus allergy and states, furthermore, that in hay-fever and asthma, the normal intestinal

48. Sluder: J. A. M. A. **73**:589 (Sept. 27) 1919.

49. Knapp: Med. Rec. **101**:55, 1921.

50. Kamchorn and Ellis: Am. J. M. Sc. **161**:525, 1921.

51. Hutcheson and Budd: Virginia M. Month. **46**:281, 1919.

52. Gottlieb: J. A. M. A. **75**:814 (Sept. 18) 1920.

53. Gottlieb: J. A. M. A. **74**:931 (April 3) 1920.

flora is often replaced by the predominance of unusual bacteria for these locations, which indicates an intestinal disturbance probably of bacterial origin. This may play a part in the etiology.

Auld⁵⁴ in the most recent of several papers on the use of non-specific protein therapy, reports very successful results. He uses injections of Witte's peptone. The patients ought always to be placed in the best possible surroundings and should have specific skin tests before attempting this form of treatment. Cunningham⁴⁶ has had good results from a change of climate and believes that for asthmatic children residing in our Atlantic coast cities particularly, the removal inland is indicated when the cause seems to be bacterial.

Sensitization in Eczema.—Fox and Fisher,⁵⁵ in sixty cases of eczema in adults, found nineteen giving positive reactions. O'Keefe^{56, 57} found that 35 per cent. of 131 bottle fed babies and older children showed sensitization to one or more of the common food proteins. In the order of frequency these foods are egg, milk, potato, wheat and oat. In these cases also, fat or carbohydrate indigestion was more often found than would be the case in an unselected group of children. He suggests that these forms of indigestion make protein sensitization more likely to occur and so produce eczema.

In forty-one exclusively breast fed babies having eczema, he was surprised to find that more than 60 per cent. showed sensitization; 40 per cent. of these being sensitive to egg, 39 per cent. to cow's milk, 5 per cent. to oat, and about 2 per cent. to wheat. None showed a reaction to human milk protein. The conclusion is that human milk must often contain foreign proteins which the babies may absorb in an unbroken form, thus becoming sensitized. The treatment of removing such positively reacting foods from the mothers' diets, together with external remedies, resulted in a cure in seventeen of forty-one treated. Whenever milk or eggs were so limited or omitted, cod liver oil and green vegetables were especially prescribed.

In bottle fed babies those sensitive to casein were fed with whey and cream mixtures. Those sensitive to lactalbumin received milk prepared by boiling and skimming off the coagulated material; for those sensitive to both casein and lactalbumin, the formulae were peptonized or were restricted to the minimum in protein. In nearly 20 per cent. of the seventy cases reported in the first of these two papers there was evidence of heredity.

Sidlick and Knowles,⁵⁸ using the intracutaneous method of testing, found that of twenty-five children with eczema, fifteen gave positive

54. Auld: Brit. M. J. **1**:696, 1921.

55. Fox and Fisher: J. A. M. A. **75**:907 (Oct. 2) 1920.

56. O'Keefe: Boston M. & S. J. **183**:569, 1920.

57. O'Keefe: J. A. M. A. **78**:483 (Feb. 18) 1922.

58. Sidlick and Knowles: Am. J. Dis. Child. **23**:316 (April) 1922.

reactions. Of these fifteen, six were either cured or much improved by the removal of the reacting proteins. Of twelve cases with papular eczema, nine reacted to one or more proteins and seven of these patients were either cured or very much improved. We assume that external treatment was also employed. Engman and Wander⁵⁹ found skin reactions in 78 per cent. of thirty-six cases of infantile eczema and in every instance where control could be exercised got excellent results from the indicated treatment.

Schloss,³ in fifty-three cases of infantile eczema, found forty giving cutaneous reactions, thirty-four to egg white which had never been eaten but which nevertheless produced symptoms. Thirty-six gave reactions to cow's milk, and although it was difficult to omit this food at this age, six were fed on an artificial milk and, by the the improvement in their eczema, confirmed the indicated etiology of milk protein. Schloss feels that infantile eczema is also often due to the fat or sugar in the food.

In a second group consisting of twenty-four children more than 16 months of age, ten gave positive reactions. In these the type of eczema was rather definite, the patients showing a dry, scaly skin, with weeping areas occurring only in periods of marked exacerbation. The distribution in these cases usually included the hands, forearms, bends of the elbows, and the popliteal spaces. Six of them reacted to so many proteins that therapeutic confirmation of the relation of any one of them was impossible. The remaining four were greatly improved when the protein indicated was removed.

Schloss' figures for children of all ages would show 65 per cent. giving positive cutaneous (scratch) tests. Sidlick and Knowles tested thirty-five children, using the intracutaneous method, and 68 per cent. reacted. With the scratch method in 131 children O'Keefe had only 35 per cent. positives.

The infantile cases of Schloss and of Engman and Wander gave positive reactions in about 77 per cent. of eighty-nine children. O'Keefe's group of breast fed babies, numbering forty-one, were 60 per cent. positive. Allowing for O'Keefe's uniformly lower results, it would appear that breast fed babies may give positive skin tests as often as the bottle fed.

Sensitization in Other Skin Diseases.—Engman and Wander,⁵⁹ in ten cases of urticaria, found positive skin reactions in 79 per cent. In chronic general eczema (distinguished from infantile eczema) 38 per cent. of twenty-one patients gave skin reactions. The percentage of reactions was almost negligible in eleven cases of dermatitis herpetiformis, six of erythema multiforme, four lichen urticarius, two of

59. Engman and Wander: Arch. Dermat. & Syph. 3:223 (April) 1921.

pemphigus, and three of purpura hemorrhagica. Acne vulgaris was negative in eighteen cases, and two others, which were slightly positive, did not respond to specific treatment. Schloss,³ in sixty children with urticaria, found only ten giving skin reactions, and only four of these were helped by the indicated treatment. The same negligible results were obtained in angioneuritic edema and erythema multiforme. Three cases of acute dermatitis all proved to be due to pollens.

Spain,⁶⁰ investigating the nature of ivy poisoning or dermatitis venenata, concludes that typical vesicular lesions can be produced by alcoholic or chloroform extracts of fresh leaves of *Toxicodendron radicans* applied to the skin surface. Such lesions could not be produced by the intradermal injection of the extract, thus indicating that poisoning is not due to allergic sensitization. The age incidence of susceptibility to this irritant is indicated by the fact that 65 per cent. of persons more than 8 years old are susceptible, whereas no reaction could be produced in eighteen infants.

Allergy, Serum Disease and Dermatitis Venenata.—Coca²⁵ draws the following comparisons: (a) Serum disease differs from other forms of human sensitization in the almost constant period of incubation and the high incidence of susceptibility. (b) Dermatitis venenata differs from other forms of human hypersensitiveness in which the skin is affected by the constant and characteristic nature of the lesion. (c) The age incidence of natural allergies increases rapidly in the early age periods but probably does not greatly exceed 10 per cent. in any period. (d) The age incidence of dermatitis venenata increases greatly from childhood to adult life and reaches a very high percentage—probably 90 per cent. (e) The age incidence of serum disease seems not to change during life.

Serum Disease.—Gurd and Roberts⁶¹ report a fatal case resulting from the injection of antitetanic horse serum. Kraus et al.,⁶² and Krause⁶³ recommend the use of bovine serum instead of horse serum as a vehicle for diphtheria, tetanus, or other antitoxins, on the ground that it is less liable to cause serum sickness.

Bouche and Huston,⁶⁴ studying the reactions in man to from 0.5 to 2 c.c. of horse serum subcutaneously, conclude that both the local and general reactions vary in different persons. There is usually a vascular or sympathetic reaction at first, followed by a trophic or autonomic reaction, and the manifestations of the two phases are those seen in anaphylactic shock.

60. Spain: J. Immunol. **7**:179, 1922.

61. Gurd and Roberts: Lancet **1**:763, 1920.

62. Kraus et al.: München. med. Wchnschr. **68**:1244, 1921.

63. Krause: Rev. d. Inst. Bact. **2**:1, 1919.

64. Bouche and Huston: Presse méd. **29**:801, 1921.

Davidson⁶⁵ finds that the rashes of serum disease differ in relative frequency and in the order of occurrence, the order in either respect being urticarial, morbilliform and circinate. He suggests the possibility of a distinct mechanism for each. The most important symptoms accompanying such rashes are pyrexia, joint pains, edema, adenitis, and increased cardiac dulness.

Cowie and Greenthal⁶⁶ found that normal horse serum always protects guinea-pigs against lethal doses of diphtheria toxin if injected in sufficient quantity and question the superior value of serum from immunized horses.

Lewis⁶⁷ believes that the rate of absorption of subcutaneously injected serum or protein solutions is so slow that even when the site of the injection is massaged it could not account for the cases of sudden death occasionally reported. By intravenous injection, on the other hand, animal experiments indicate that extremely small amounts of antigenic protein will bring on fatal anaphylactic spasms. It is by the accidental entering of small veins, therefore, that Lewis accounts for these fatalities in human beings. Cook⁶⁸ mentions influences increasing or delaying the rate of absorption.

MacKenzie and Leake,⁶⁹ in studies on nineteen patients injected with foreign serum, conclude that their results support the antigen-antibody conception of serum disease.

Intestinal Allergy.—The surprising results of skin tests in exclusively breast-fed babies reported by O'Keefe, 60 per cent. of whom showed positive reactions to proteins other than those of human milk, have been mentioned. The sensitizing capacity of human milk thereby suggested is also pointed out by Shannon.⁷⁰ In this report the author mentions three cases, one each of urticaria, indigestion, and papular eczema, all being in nursing babies. In each case he was able to demonstrate by the anaphylactic reaction that egg protein had passed into the mothers' milk. All three babies were relieved of symptoms after the mothers had omitted egg from their diets. In one baby the skin test for egg yolk was positive.

Schloss³ presents experiments showing that the ingestion of foreign protein, both milk and egg, by guinea-pigs causes the development of immune reactions. Furthermore, Grulee and Bonar⁷¹ examined 136 specimens of urine from twenty-five infants selected only in being from 1 to 13 days old. These babies differed from controls in that they

65. Davidson: Glasgow M. J. **92**:20, 1919.

66. Cowie and Greenthal: J. M. Research **41**:261, 1919.

67. Lewis: J. A. M. A. **76**:1342 (May 14) 1921.

68. Cook: J. Immunol. **5**:39, 1920.

69. MacKenzie and Leake: J. Exper. M. **33**:601, 1921.

70. Shannon: Am. J. Dis. Child. **22**:223 (Sept.) 1921.

71. Grulee and Bonar: Am. J. Dis. Child. **21**:89 (Jan.) 1921.

received egg albumin water between feedings instead of plain water. Of the twenty-five test cases, eighteen showed a positive precipitin reaction to egg white in their urines at some time during these thirteen days of life. From seventeen control babies, forty-one urines gave no positive reactions. These results indicate that the intestinal wall of the new-born infant from the fourth to the tenth day, inclusive, is permeable to egg white in quantities sufficient to be determined by the precipitin reaction in the urine. It seems likely that this is not a peculiarity of specific cases but is a general characteristic of this period of life and suggests an explanation of the frequent sensitization to egg and other foreign proteins. In a previous paper,⁷² Grulee had determined that egg albumin is usually completely broken down by the digestive processes in infants and children, as indicated by the infrequency with which he had obtained positive precipitin reactions to this substance in the stools.

Zubizarreta⁷³ believes that the feeding of cow's milk to babies sensitizes them occasionally against cow's lymph and so accounts for the cases sometimes seen of severe disturbances following vaccination. Wells and Osborne⁷⁴ isolated four chemically distinct proteins from cow's milk by the use of the anaphylactic reaction in guinea-pigs. These are casein, lactalbumin, lactoglobulin, and an alcohol soluble protein. Lactalbumin and serum globulin appear to be chemically indistinct and produce mutual sensitization in guinea-pigs.

Duke⁷⁵ mentions six cases of abdominal pain apparently the result of food allergy. He believes that food allergy is observed more frequently in persons who have had lesions of the gastro-intestinal tract than in normal persons. Zubizarreta⁷³ believes that if food is not completely "homologized" in the upper intestinal tract it is likely to produce sensitization. He also believes that eggs are more easily digested after being kept for a while, and is in favor of extracts of the stomach or of upper intestinal tissues rich in the ferments of digestion and "homologization" or of peptone or of beef extract given in 0.5 gm. doses one half hour before meals as an anti-anaphylactic.

Schloss³ states that the usual gastro-intestinal disturbances consist of vomiting and diarrhea; that infants showing these symptoms acutely, together with urticaria and edema, always give a cutaneous reaction to cow's milk protein and their symptoms occur after the ingestion of very small amounts of milk. In another group symptoms are less acute and may not occur until the milk has been taken for several days. These rarely show positive reactions to cow's milk, but

72. Grulee: *Am. J. Dis. Child.* **20**:15 (July) 1920.

73. Zubizarreta: *Semana méd.*, Buenos Aires **27**:513, 1921.

74. Wells and Osborne: *J. Infect. Dis.* **29**:200 (Aug.) 1921.

75. Duke: *Arch. Int. Med.* **28**:151 (Aug.) 1921.

that the conditions may, nevertheless, be caused by protein sensitization is indicated by the good results of feeding boiled or evaporated milk and by the fact that infants suffering from identical symptoms may show positive reactions to milk protein. Immunity to certain foods can be developed by the ingestion of graduated doses. In twenty cases of cyclic vomiting he found only two giving positive skin tests. Blackfan ⁷⁶ believes that the absolute omission of offending foods may be unnecessary, since some patients can tolerate them in small quantities. A high temperature is, in his experience, apt to prevent these disturbances. He considers desensitization by all means the most satisfactory method of procedure, and feels that in young infants and children this is best done by mouth rather than by subcutaneous injection. Cunningham ⁴⁶ feels that by the omission of these foods for varying periods sensitization often disappears spontaneously, and for this reason recommends postponing artificial measures of desensitization when possible until it is determined after two or three months that this will not occur. Park ¹⁶ mentions an interesting case of food allergy resulting in the spontaneous disappearance of the hypersensitive condition.

Other Conditions Due to Allergy.—Pagniez and Leutand ⁷⁷ refer to cases of epilepsy apparently due to sensitization, but base their diagnoses on the observed results of ingestion of or contact with the proteins, rather than on the results of skin tests.

Drug Idiosyncrasy.—Cooke ⁷⁸ states that in fifteen cases of drug reactions a positive history of family hypersensitiveness occurred in twelve. In the remaining three cases the evidences of sensitization were multiple and included such conditions as asthma, urticaria, and hay-fever occurring in the same individual. Occasionally with the antipyretics hyperpyrexia occurs, or cardiac collapse. In virtually all cases there was a marked eosinophilia. Acetylsalicylic acid reactions were the most frequently encountered by this author. Symptoms begin in from fifteen to twenty minutes after the ingestion of 10 grains and may last from eight to thirty-six hours. Positive cutaneous reactions do not occur except in those cases giving a history of urticaria.

Cooke classes the types of drug action as follows: (a) Normal action—side action and toxic action. (b) Idiosyncrasic action—either exaggerated normal or exaggerated side action, or lessened normal action (tolerance). (c) Allergic action—abnormal.

Labbe and Hagenau ⁷⁹ report a case of antipyrin sensitization, and Peshkin ⁸⁰ cites one of ipecac idiosyncrasy with asthma.

76. Blackfan: Am. J. M. Sc. **160**:341, 1920.

77. Pagniez and Lieutand: Presse méd. **27**:693, 1920.

78. Cooke: J. A. M. A. **73**:759, 1919.

79. Labbe and Hagenau: Bull. et mém. Soc. méd. d. hôp. de Paris **43**:549, 1921.

80. Peshkin: J. A. M. A. **75**:1133 (Oct. 23) 1920.

Lane⁸¹ reports three cases of susceptibility to procain in dentists, confirming the diagnosis by skin tests, and suggests the possibility of general reactions to this substance.

Stuart and Maynard⁸² report an interesting case of hypersensitive-ness to arsphenamin following an exfoliative dermatitis which gave a marked intracutaneous skin reaction. They examined in this way ten other cases treated with arsphenamin and sixteen controls. No positive skin tests were found among the controls. Of the other ten cases, seven gave no reaction. Two patients gave positive reactions and had lumbar pain beginning four days after an injection of arsphenamin and lasting four weeks. The third patient exhibited the same lumbar pain following the last injection but gave no skin reaction, possibly because the most recent therapeutic dose had been given as long as nine months previously.

Nonspecific Treatment.—Most of this treatment is given either by mouth or intravenously. Commenting on the use of intravenous treatment, Hanzlik and Karsner⁸³ studied twenty-nine agents given in this way and concluded that they were distinctly harmful in varying degrees. They are, therefore, opposed to the promiscuous and unwarranted giving of drugs by the intravenous method.

Auld⁸⁴ has written several reports on the successful treatment of asthma with Witte's peptone given intravenously. Pagniez and Vallery-Radot⁸⁴ believe that "alimentary anaphylaxis" can be avoided by the preliminary injection of peptone. Van Leeuwen and Varekamp⁸⁵ tried specific skin tests but concluded that nonspecific injections (they use tuberculin) give better results. Shulman⁸⁶ reports good results in the treatment of sixty cases of arthritis, and especially arthritis of gonorrheal origin, by the injection of milk. Snyder and Ramirez,⁸⁷ reporting on seventy cases of chronic arthritis, conclude that such patients as have not been relieved by the routine treatment with salicylates, hot packs, baking, and massage, are, as a rule, materially benefited by the intravenous administration of small doses of foreign protein. Such benefit is almost always in the joints of the upper extremities. Patients prefer secondary proteoses to typhoid bacilli because they seem to cause less discomfort. The effects in relieving pain and improving motion seem equally good.

81. Lane: Arch. Dermat. & Syph. **3**:235 (April) 1921.

82. Stuart and Maynard: Arch. Int. Med. **26**:511 (Oct.) 1920.

83. Hanzlik and Karsner: J. Pharmacol. & Exper. Therap. **14**:379, 1920.

84. Pagniez and Vallery-Radot: Ann. de méd. **8**:303, 1920.

85. Van Leeuwen and Varekamp: Lancet **2**:1366, 1921.

86. Shulman: Med. Rec. **98**:47, 1920.

87. Snyder and Ramirez: Arch. Int. Med. **28**:50 (July) 1921.

Joltrain,⁸⁸ Zubizarreta,⁷³ and Nathan⁸⁹ favor treatment by preliminary ingestion of peptone or extracts of certain of the digestive tissues to prevent "alimentary anaphylaxis."

Danysz⁹⁰ reports further successes in the treatment of nonfebrile chronic diseases by means of cultures of nonpathogenic intestinal micro-organisms. His most effective preparations seem to contain strains of *Bacillus coli*, *B. proteus*, streptococcus, staphylococcus, and enterococcus. He differs the proportions for psoriasis, enteritis, asthma, etc. His reports may be compared with those of four other authors already quoted, Turnbull,¹² Larsen, Paddock and Alexander,¹³ Cooke⁴³ and Gottlieb.⁵³

88. Joltrain: Bull. et mém. Soc. méd. d. hôp. de Paris **43**:556, 1921.

89. Nathan: Bull. méd., Par. **34**:59, 1920.

90. Danysz: Bull. méd., Par. **34**:657, 1920.