

CLINICAL AND EXPERIMENTAL STUDIES IN ALLERGY

By

David Harley, B.Sc., M.B., F.I.C.
First Assistant, Allergy Clinic, Inoculation
Department, St. Mary's Hospital, London,
Asthma Research Council Fellow 1932 - 1939.



PREFACE

Few branches of medical science hold promise of a richer harvest or are burdened by more conflicting theories and speculations than that of Allergy. Some of the confusion is due to the multiplicity of terms employed for the various types of allergic phenomena and to the different interpretations of the same term by clinicians and pathologists. Von Pirquet defined allergy as the altered capacity for reacting which follows disease or treatment with a foreign substance. Though von Pirquet had in mind particularly the hypersensitivity of infection and serum disease he appears to have included spontaneous hypersensitivity of the hay fever type as well. As his original definition did not specify the direction in which the change of reactivity takes place, the term may be taken to include all acquired immunity in addition to hypersensitivity. By investing the term allergy with such an all-embracing meaning the word in itself conveys but little, or rather its vastness prevents any attempt at a precise definition. In contrast to the fundamentalist view is the tendency, due mainly to American clinicians, to narrow down the meaning of the term to designate the hypersensitivities of the asthma-hay fever-eczema-urticaria group. This latter interpretation, however, does not help matters much, as the term allergy has been firmly established by pathologists in connection with the

hypersensitivity of infection in man and animals, the mechanism of which is of a different nature to that of the asthma group. One may cite the case of the indignant doctor from Ohio, who, wishing to pour forth his views on asthma, had come all the way to a 'Congress of Allergy' in London to do so, only to find to his disgust "Frenchmen and Germans talking about tuberculosis" (Freeman). Attempts to avoid this ambiguity have resulted in a flood of terms to describe the asthma group; thus we have, to mention but a few, Atopy (Coca), Hyperergy (Schick), Attack Diseases (Aschoff), and Toxic Idopathies (Freeman). The tendency of many in the profession to-day is to extend the popular American usage and apply the term allergy to all those conditions in man which are believed to be expressions of a state of increased reactivity, irrespective of the nature of the mechanism by which they are actuated. Indeed, I recently heard a distinguished physician describe as allergic the lowered tolerance to morphia found in patients with disease of the liver.

The conception of allergy in the general sense of increased reactivity is being widely, and at times wildly, applied to medical problems at the present time. I feel that much of the confusion and conflict of opinion, especially marked in connection with the hypersensitivity of infection and its relationship to infective and non-infective asthma on the one hand and to antibacterial immunity on the other, is due to a failure

to realize that in the group of phenomena designated allergic there are several different types of immunological mechanism involved. In bacterial allergy, for example, evidence has already been presented to show there are at least three independent types of allergy to the pneumococcus and its products, of which one type is closely related to antipneumococcal immunity.

The investigations here-in described were carried out in the Laboratories of the Inoculation Department, St. Mary's Hospital, London, during the tenure of an Asthma Research Council Fellowship, 1932-1939.

CONTENTS

Preface		ii
CHAPTER I	<u>Hypersensitivity, Anaphylaxis, Allergy: Terminology</u>	1
 <u>S E C T I O N I H A Y F E V E R</u>		
CHAPTER II	<u>Diagnosis and Etiology:</u>	
	Symptomatology	6
	Specific Diagnosis	7
	Differential Diagnosis	8
	Sex Incidence	8
	Age Incidence	10
	Heredity	10
CHAPTER III	<u>Immunology:</u>	
	The Specific Skin Reaction	12
	Pathology	12
	Mechanism	13
	The Idioceptor	14
	Passive transfer of sensitivity	15
	Immunological nature	16
	Idiotoxin-Idioceptor Mixtures	18
	Reactions in normal skins	18
	Effect of blood cells on	23
	Action of idioceptor on idiotoxin	23
CHAPTER IV	<u>The Grass Pollen Idiotoxin:</u>	
	Skin-Reactive Specificity	26
	Chemical Nature	27
	Experimental investigations	29
	Discussion	35
	Antigenic Properties	38
	re idioceptor	38
	re anaphylactin and precipitin	38
	Attempts to Modify the Idiotoxin	
	for Therapeutic Purposes	40
	Physical methods	41
	Chemical methods	41
CHAPTER V	<u>The Nature and Origin of the Allergic State:</u>	
	Origin of Idioceptor	43
	Heredity	44
	Lysis of Pollen Granules	45
	Inability of Blood to Digest Peptone	46
	Possible Biochemical Basis	46
	Failure to Sensitise Animals	47
	Animals inactivate idioceptor	47

CHAPTER VI	<u>Treatment:</u>	
	Phylactic Treatment	48
	Palliative	48
	Specific	49
	Prophylactic Specific Treatment	49
	Heavy desensitization	50
	Dosage and frequency of injections	52
	Reactions during treatment	53
	Self inoculation	54
	Clinical results	62
	Possibility of permanent cure	63
CHAPTER VII	<u>The Mechanism of Specific Desensitization:</u>	
	Effect of Pollen Therapy on the Skin Reactions	66
	Variations in potency of commercial extracts	70
	Effect of Pollen Therapy on Serum Idioceptor	74
	Clinical Results of Pollen Therapy	75
	Immune Bodies Engendered by Pollen Therapy	76
	Nature and origin	87
CHAPTER VIII	<u>The Mechanism of Specific Desensitization</u> (Contd.). Discussion:	
	Inactivation of Idioceptor	89
	Role of H-Substance	90
	General Reactions and Adrenaline	90
	Histamine Tolerance	91
	Non-Specific Desensitization Effect	91
	Reaction-Inhibiting-Substances	94
CHAPTER IX	<u>Allergic Rhinitis (Non-Pollen):</u>	
	Allergic Rhinitis	95
	Bacterial Sensitizations	99
	Reflex Nasal Type	101
	Mixed Types	102

SECTION II ASTHMA

CHAPTER X	<u>Introductory:</u>	
	Allergic Predisposition	104
	Development of Hypersensitivity	104
	Secondary Non-Specific Factors	105
	Hypersensitivity to Non-Bacterial Idiotoxins	105
	Hypersensitivity to Bacteria and their Products	106
	Skin reactions to vaccines	107

CHAPTER XI	<u>Bacterial Allergy. Specificity of Vaccine</u> <u>Skin Reactions:</u>	
	Experimental Investigations	109
	Methods	110
	Results	114
	Discussion	115
	Summary	119
CHAPTER XII	<u>Bacterial Allergy (Contd.). Relationship</u> <u>to Immunity:</u>	
	Experimental Investigations	120
	Methods	120
	Results	124
	Discussion	125
	Summary	127
CHAPTER XIII	<u>Types of Asthma:</u>	
	Hypersensitivity to Non-Bacterial Idiotoxins	129
	Bacterial-Sensitization Asthma	130
	Mixed Types	131
CHAPTER XIV	<u>Diagnostic Methods:</u>	
	Clinical History	138
	General Medical	139
	Skin Tests	140
	Prick method	140
	Technique	140
	Interpretation and significance	143
	Bacteriological Examination	147
CHAPTER XV	<u>Treatment:</u>	
	<u>Treatment of the Asthmatic Attack:</u>	
	Adrenaline	149
	Ephedrine	151
	Narcotics and anaesthetics	151
	Aspirin	151
	General measures	151
	Hospitalization	152
	<u>Treatment of the Asthmatic State:</u>	
	Immunological methods:	153
	Specific avoidance	153
	Specific desensitization	155
	Vaccine therapy	158
	Accessory methods:	
	General hygiene	161
	General medical measures	162
	Surgery	162
	The psychological factor	163
	Miscellaneous treatments	166
	References	168

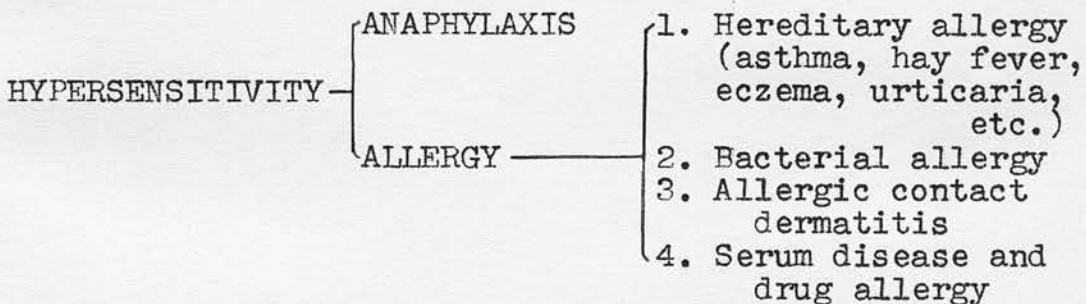
CHAPTER I

HYPERSENSITIVITY, ANAPHYLAXIS, ALLERGY

TERMINOLOGY

The term Hypersensitivity (synonyms Hypersensitive-ness, Sensitivity, Sensitiveness) is here-in used in the broad immunological sense to include all those forms of specific increased reactivity in man and the lower animals which are considered to be mediated by special mechanisms (Table 1).

Table 1.



Hypersensitivity is divided into Anaphylaxis and Allergy. Anaphylaxis may be defined as those manifestations of hypersensitivity in the lower animals which are due to an antigen-antibody reaction, in which the sensitive state is always induced and never spontaneous, is uninfluenced by heredity, is readily established in the great majority of individuals of the susceptible species, and in which the process of desensitization is easily carried out. Anaphylaxis has not been demonstrated in man, with the doubtful exception of serum disease,

which, however, is included in the allergy group for the reason given below.

By Allergy is meant the various forms of hypersensitivity exclusive of anaphylaxis in the lower animals. This is in accordance with its current medical usage (Editorial announcement, Journal of Allergy, 1930, Vol. 1, p. 1). The term is less easy to define positively, and is indeed incapable of precise definition at present, as it contains a number of subdivisions which exhibit few, if any, common characteristics other than the general one of specific hypersensitivity. Allergy includes such apparently unrelated conditions as (i) hay fever, which appears spontaneously in a small proportion of the population, has never been induced and is subject to hereditary influences, and (ii) serum disease, which is readily induced in over 80 per cent of individuals and is not subject to heredity.

At least four main subdivisions of allergy have been recognised and are clearly separable from one another namely, (1) Hereditary allergy (asthma, hay fever, and allied conditions), (2) Bacterial allergy, (3) Allergic contact dermatitis, and (4) Serum disease with which may be grouped tentatively drug allergy.

(1) Hereditary allergy (synonyms atopy, toxic idiopathies, attack diseases, etc.) or more simply referred to as the asthma-hay fever-eczema group, includes those forms of hypersensitivity that do not

occur, as far as is known, in the lower animals, and which are subject to hereditary influences. Some of them (for example hay fever) are characterized by skin reactions of the 'immediate' type, the state of sensitivity is passively transferable to normal individuals by the injection of serum from the sensitive person through the mediation of special sensitizing antibodies in the serum, and the chief pathological basis of their manifestations is spasm of smooth muscle and increased permeability of blood capillaries. Others, such as angio-neurotic oedema, urticaria, gastro-intestinal allergy, etc., usually fail to exhibit skin reactions or sensitizing antibodies in the serum; they are included in this group however because of their hereditary nature and their clinical and pathological relationship to the hay fever type.

The clinical variations in this group are considered to be due more to the route by which the particular reaction-exciting substance gains access to the sensitive tissues, and to the degree of sensitivity of the various tissues, than to any fundamental immunological differences. In hay fever the symptoms are chiefly nasal, the comparatively large pollen grains being filtered out of the inspired air to a great extent in the nose. In 'horse-asthma' the finely suspended particles of horse dandruff reach lower down and bronchial symptoms predominate. In food allergy we have gastro-intestinal symptoms with or without symptoms in

distal tissues depending on the amount of specific irritant absorbed into the blood stream. In any one of these types the injection of the specific irritant parenterally may produce asthma, hay fever, urticaria, etc., simultaneously, as occasionally happens in hay fever, for example, when an overdose of pollen extract is given in the course of desensitization treatment.

The specific desensitization chosen from this group for the majority of the immunological studies detailed in this thesis was hay fever (grass-pollen-hypersensitivity). The abundance of the available clinical material, the clear-cut specific sensitization, and the seasonal nature of the disease, offered the best conditions for experimental investigations.

The specific reaction-exciting substance is variously designated allergen, atopen, idiotoxin, etc., depending on the system of nomenclature favoured (allergy, atopy, toxic idiopathy) and the corresponding sensitizing antibody is named the allergin, reagin, or idioceptor. In this thesis the terms Idiotoxin and Idioceptor are employed for the reason that they are more or less self explanatory, are less confusing than the allergen-allergin pair and therefore are more suited to immunological discussion.

(2) Bacterial allergy, or hypersensitivity accompanying infection as it has been called, was at one time considered to be engendered exclusively by an infective

process, but as will be shown, it can be produced also by treatment with dead bacteria and their products. Within this group there are several separate and distinctive immunological mechanisms involved.

The remaining groups of allergic conditions — (3) Allergic contact dermatitis, and (4) Serum disease and drug allergy — are not further considered as they are outside the scope of the investigations described below. However, it is worthy of note that serum disease, which is possibly the only doubtfully anaphylactic-like type of human allergy, is retained in the allergy group chiefly for the reason that it was one of the conditions von Pirquet had in mind when he coined the word allergy.

S E C T I O N I H A Y F E V E R

CHAPTER II

DIAGNOSIS AND ETIOLOGY

Hay fever is a type of paroxysmal rhinitis due to hypersensitivity to the pollen of the grasses. The well-known symptoms are produced in the sensitive subject by the application of pollen to the upper respiratory tract and eyes. Normally this occurs only during the pollinating season of the grasses when the widely disseminated air-borne pollen reaches the sensitive person, but the same symptoms can be produced artificially at any other time of the year by applying preserved pollen or pollen extract to the mucous membrane.

In the average case of uncomplicated hay fever the symptoms begin about the third week in May and continue until the middle of July, the patient being symptom-free the remainder of the year. The symptoms consist of intense irritation and swelling of the mucous membrane of the nose, with paroxysms of violent sneezing — frequently as many as 30 or 40 in rapid succession — accompanied by profuse serous discharge, which leaves the patient quite exhausted. There is often present some nervous irritability or ever prostration in the more severe cases. There is also itching of the eyes with congestion of the conjunctivae, and lachrimation, in varying degree. Asthmatic symptoms are not infrequently

present, especially towards the end of the season, and these tend to increase in severity and duration with each successive hay fever season. The intensity of the symptoms varies considerably with the weather and the locality; dry sunny weather and the proximity of pollinating grass increasing it, while the rain and the still air in closed rooms, etc., tend to lessen it by reducing the amount of pollen in the air. Grass pollen, being very light and carried by the air for long distances, makes it almost impossible for the sufferer to escape contact under normal conditions.

This syndrome is frequently referred to as 'seasonal' hay fever in contradistinction to 'perennial' hay fever, a type of allergic rhinitis due to non-seasonal products such as animal dandruffs, orris root (face powder) etc.; this loose usage seems undesirable and the term hay fever (i.e. grass-pollen hay fever) should be confined to grass-pollen-hypersensitivity, as Noon & Freeman originally recommended. True, the term is often applied in America and some other countries to allergic rhinitis caused by the ragweeds (absent in this country) but this is usually and more fittingly designated ragweed hay fever. Tree, weed, and flower pollens are rarely a cause of allergic rhinitis in this country, although the autumn compositae (particularly the Michaelmas daisy) and heather do produce a few cases.

Specific Diagnosis. The diagnosis is confirmed by producing a skin reaction with grass pollen extract

(see Technique of Skin Testing, Chapter XIV, p.139). For routine purposes it is sufficient to make a test with timothy (*Phleum pratense*) pollen extract. (The polyvalency of the grass pollens is discussed in Chapter IV, p.26).

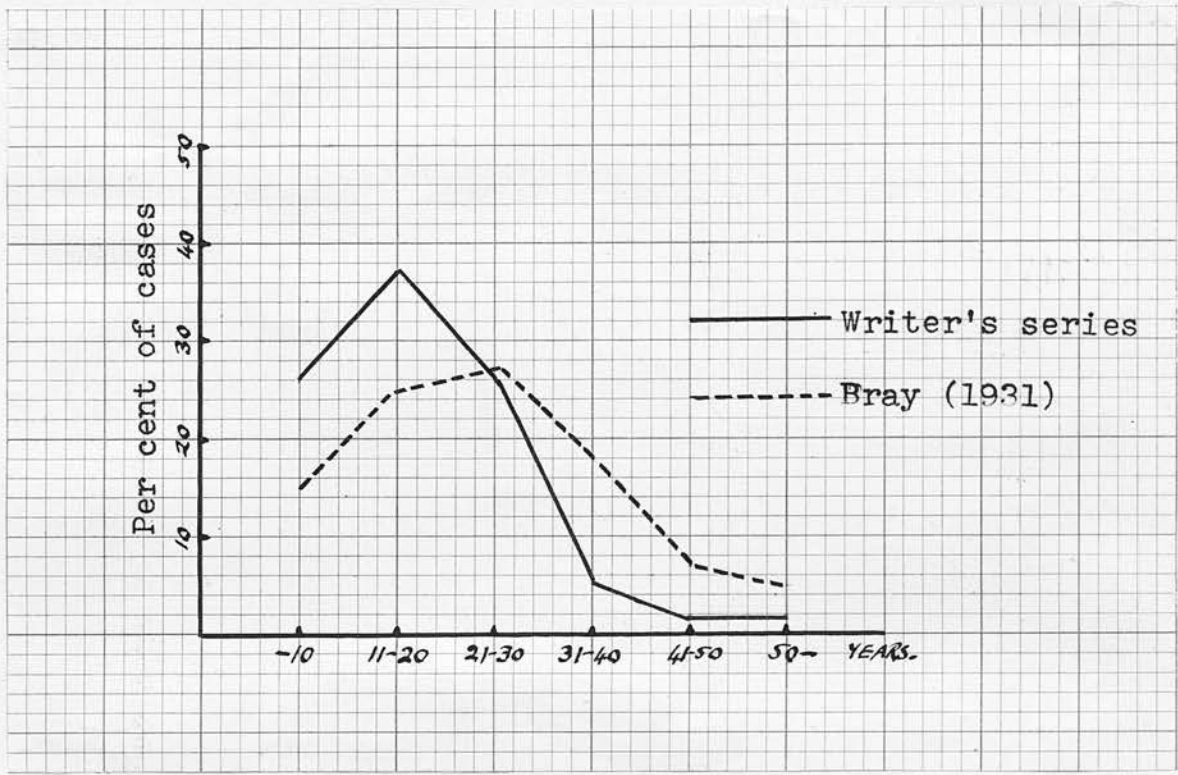
Differential Diagnosis. The characteristic symptom-complex, the periodicity, and the evidence of the skin test, usually make it easy to differentiate hay fever from the common cold, chronic infective nasal catarrh and sinusitis, vernal conjunctivitis, and allergic rhinitis due to idiotoxins other than grass pollen.

Sex Incidence

Sex appears to have little or no influence, though many observers have reported a slight preponderance of males. Scheppegrell (1916-17) reported 63 per cent males and 37 per cent females in a series of observations based on questionnaires to general practitioners in Louisiana, U.S.A., but elsewhere (1918) gives 48 per cent males and 52 per cent females in a group of clinic patients, explaining the discrepancy as due to the fact that among the clinic type of patient the women have more leisure than the men to have the complaint treated.

A representative sample of 200 patients attending the St. Mary's Hospital Hay Fever Clinic in 1940 gave 52 per cent males and 48 per cent females.

Figure 1.



Age Incidence of Hay Fever

Age Incidence

The age incidence by decades in a group of 200 patients seen in the writer's clinic in 1940, together with Bray's figures published in 1931, is given in Fig. 1. In the writer's series 7 per cent occurred before the age of 5 years and 63 per cent before the age of 20 years. These figures suggest a lower age incidence than most of the older published data indicate. This may be due, in part at least, to the fact than modern facilities enable the diagnosis to be established earlier in the type of case which in the past was labelled 'summer cold' etc. and not referred for investigation.

Heredity

As a predisposing factor in the development of hay fever, and of allied conditions, heredity is generally accepted as playing a vital part. The particular clinical sensitization is not necessarily inherited but rather the capacity to develop the hyper-sensitive state, which is usually called the allergic diathesis or predisposition for want of a more informative name. There has been much discussion concerning the mechanism of the allergic inheritance; many workers claim that their figures support the hypothesis that the allergic character is inherited as a mendelian dominant, while admitting that the figures fall short

of the theoretical expectation; a few favour the theory that the character is a recessive one.

While the general influence of heredity is established beyond doubt, the results of the study of actual figures and their interpretation as supporting either the dominant or recessive hypothesis depends to a great extent on the bias of the individual worker and must be treated with reserve. The figures may have been examined with the greatest care and according to the accepted statistical manipulations, but the figures themselves are not necessarily accurate — whether an aged grandparent with 'bronchial trouble', and other borderline cases not available for personal examination, are to be classified as allergic, depends largely on the enthusiasm of the investigator. However, it is generally accepted that the stronger and clearer the allergic hereditary background, the greater is the likelihood that the individual will develop manifestations of clinical allergy.

CHAPTER III

IMMUNOLOGY

1. THE SPECIFIC SKIN REACTION

When grass pollen or an extract of pollen[⊗] is applied to the living skin of the hay fever subject the following changes take place at the site of contact:-

- (i) preliminary dilatation of the minute blood vessels;
- (ii) increased permeability of the vessel walls leading to exudation of plasma; and
- (iii) reflex dilatation of the surrounding arterioles.

These changes have been shown by Lewis (1924-1927) to be the basis of the allergic skin reaction and incidentally the reaction of the skin to a variety of other forms of cellular damage. These changes are most conveniently demonstrated in the hay fever patient by placing a drop of pollen extract on the skin of the forearm and pricking the skin with a needle through the drop; the well-known urticarial wheal with surrounding erythema develops in 10 - 15 minutes. In comparison, the skin of normal individuals is insensitive to such treatment. The amount of pollen required to produce a well-marked reaction in the hay fever skin is exceedingly minute, a millionth of a gram or less of the dried pollen or its equivalent amount of extract.

[⊗] Unless otherwise stated, grass pollen or pollen extract means *Phleum pratense* (timothy) pollen. The specificity of the idiotoxins of the various grasses is discussed in Chapter IV, p.26.

The skin reaction to grass pollen occurs in practically 100.0 per cent of hay fever patients. Indeed, Freeman (1932) states that no case failing to give a skin reaction to grass pollen is true hay fever.

The reaction of the sensitive skin to the specific idiotoxin is similar to, if not identical with, the reaction of the skin to histamine (Lewis, 1924-1927). Lewis' researches indicate that a substance (H-substance) which is either histamine or a 'histamine-like' substance, is liberated from the sensitive cells by the action of idiotoxin on the latter, and this H-substance produces the actual changes in the blood vessels, etc., which constitute the allergic reaction. Dale (1929) believes that the reaction is due to the liberation of preformed histamine, present in the skin cells, the union of idiotoxin with idioceptor on or in the cells acting like other injurious stimuli. The liberation of histamine by the cells is the result of damage to them, and the allergic reaction is simply the expression of cellular damage produced by the special method of specific idiotoxin-idioceptor union on or in the cells.

That a substance identical in properties with histamine is liberated during anaphylactic reaction in vitro is shown by the experiments of Bartosch, Feldberg, & Nagel (1932):- the lungs of a sensitized guinea-pig were removed and perfused with a dilute solution of the antigen; the usual response occurred; the perfusing

fluid leaving the lungs was collected and was found to have the property of inducing contractions of the unsensitized guinea-pig uterus and behaved exactly like a dilute solution of histamine. That a similar mechanism operates in allergic man is indicated by an observation of Rackemann (1931):- he found that the serum of allergic patients taken during a general reaction (caused by injection of the specific idiotoxin) produced larger reactions in normal skins than did serum taken before the general reaction.

2. THE IDIOCEPTOR

When a small quantity of serum from a hay fever subject is injected into the skin of a normal person, the serum is rapidly absorbed and the skin resumes its normal appearance. Subsequently, on injecting pollen extract into the same area, there develops a wheal and erythema reaction identical with that seen on injecting the extract into the skin of the hay fever subject. If, instead of injecting the extract into the site of the serum injection, it is injected (in suitable quantity) subcutaneously or intravenously in a distant part of the body, the active principle is carried round in the blood and produces the same reaction at the site of the serum injection.

This passive transfer of hypersensitivity to the skin of normal persons was first described by Prausnitz and Küstner in 1921. Cases have been recorded of blood

transfusion from allergic individuals to non-sensitive persons leading to a condition of general hypersensitivity in the latter (Ramirez, 1919). The property of serum from the hypersensitive subject to sensitize the normal skin is considered to be due to the presence in that serum of a sensitizing antibody, the idioceptor, which is rapidly taken up by the skin cells. When idioceptor is attached to tissue cells the latter produce the allergic reaction on contact with the specific reaction-producing substance (the idiotoxin). The passively sensitized site retains its specific reactive properties for a considerable time, sometimes several weeks or months.

That the property of a hay fever patient's serum to sensitize the normal skin is not due directly to a lack of any substance or property in that serum, but rather to an additional substance or property (the idioceptor) is supported by the observation that the sensitizing power of such a serum is not in any way diminished by prolonged incubation at 37°C. when mixed with normal serum (Harley, 1935a).

The idioceptor content of hay fever serum is directly proportional to the degree of skin sensitivity (Levine & Coca, 1926; Harley, 1933a). Coca & Grove (1925) state that similar sensitizing property is present in the serum of all natural allergic individuals

where the skin reactions are positive and the idiotoxin is an antigen.

The hay fever idioceptor exhibits properties which are qualitatively different from those of anaphylactic and most other generally accepted antibodies, as indicated by the following points (modified from Coca, Walzer, & Thommen, 1931):-

(i) Thermolability. The idioceptor is partly destroyed by exposure to 56°C. for 30 minutes (Coca & Grove, 1925; Chant & Gay, 1927) and is completely destroyed by 60°C. for 30 minutes (Harley, 1933b; Loveless, 1940).

Anaphylactic and most other antibodies are but little affected by such treatment.

(ii) Precipitation. Hay fever serum does not produce any specific precipitation reaction when mixed with grass pollen extract or with any of the protein or carbohydrate fractions of pollen so far examined[⊗].

(iii) Complement-fixation. Hay fever serum - pollen extract mixtures do not develop complement-fixing properties in the usual quantitative relations. A few workers claimed to have demonstrated weak complement-fixation but the majority have failed to find any.

(iv) Affinity for cutaneous tissues. The idioceptor exhibits a strong affinity for the skin cells, as

[⊗] Certain carbohydrate and hydrolysed protein fractions of pollen have been found to give a slight precipitin reaction with hay fever serum. This was found to be non-specific as it was produced also by normal human and certain animal sera (goat, dog, and sheep).

evidenced by the duration of the specific reactivity of the passively sensitized skin site. Anaphylactic and bacterial antibodies, on the other hand, rapidly diffuse away from the site of their cutaneous injection (Freund, 1928).

(v) Transfer of sensitivity to the lower animals. With a few doubtful exceptions, all workers have reported their failure to transfer the specific sensitivity to the lower animals, either locally or generally, by the injection of human serum containing idioceptor. On the other hand, human serum containing precipitin, as found for example in certain stages of serum disease, is generally agreed to be capable of sensitizing the lower animals to the specific antigen (anaphylactic sensitization). However, immune animal and human sera containing precipitin are incapable of sensitizing the human skin (allergic sensitization).

(vi) Production of idioceptor in man and animals. The injection of pollen or pollen extract, even in enormous doses, does not result in the formation of idioceptor in normal man or animals. Occasional weak precipitin formation only has been reported by a few investigators to follow such treatment of animals, but as noted above such sera do not sensitize the human skin. Even those idiotoxins which are potent antigens, as for example egg albumin, do not engender idioceptor on injection in man or animals. However, idiotoxins such as that

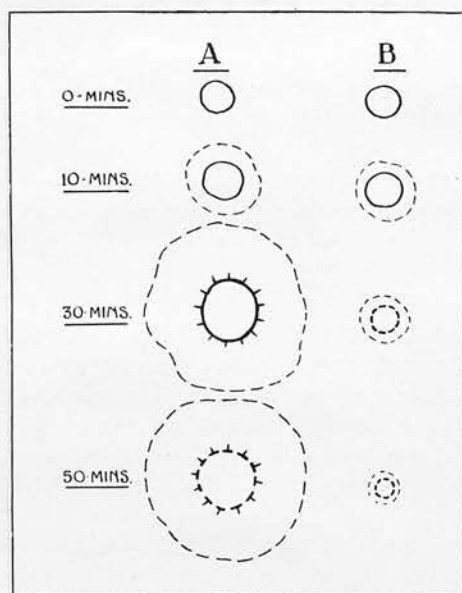
of pollen, which is a very poor antigen, may be very potent natural producers of allergic sensitization in humans with the allergic background or heredity, but it is very doubtful whether such idiotoxins could stimulate the production of idioceptor if injected into allergic individuals not naturally sensitive to pollen.

2. THE PROPERTIES OF IDIOTOXIN-IDIOCEPTOR MIXTURES

A. Reactions in Normal Skin Sites

Coca & Grove (1925) and Levine & Coca (1926) reported that mixtures of sensitive serum and specific idiotoxin failed to produce reactions on injection into normal skin sites. As the re-injection, after an interval, of the mixture sites with idiotoxin gave no reactions, these workers concluded that the idioceptor had been neutralized or inactivated by the idiotoxin in the original mixture in vitro. Clarke & Gallacher (1926) and Baldwin (1930) agreed with these conclusions though the latter worker noted some exceptions. Gay & Chant (1927) reported that there were differences between the reactions produced by idiotoxin-idioceptor mixtures and by control saline-idioceptor mixtures and concluded that the neutralization of idioceptor by idiotoxin is not complete until after injection into normal skin sites. Foran & Lichenstein (1931) found that idiotoxin-idioceptor mixtures produced reactions

Figure 2.



Reaction of Normal Skin to Idiotoxin-Idioceptor Mixture

(A represents the reaction to a hay fever serum - pollen mixture and B the reaction to a control serum - saline mixture.)

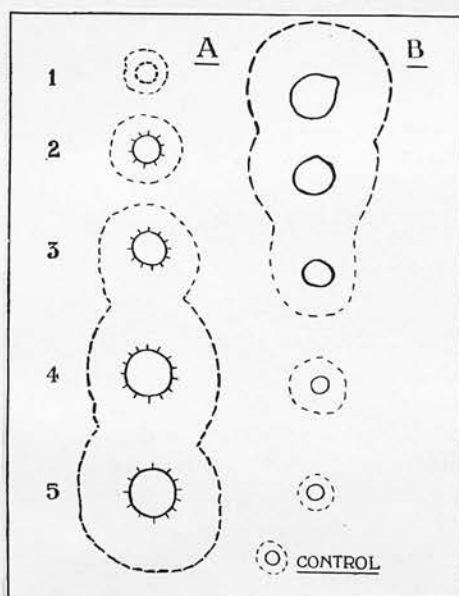
-from Harley, D.: (1933b) Brit. J. exp. Path., 14, 171.

on injection in normal skins and concluded that idioceptor is not neutralized in vitro.

In the writer's experiments (1933b, 1937a), idiotoxin-idioceptor mixtures on injection in normal skin sites produced reactions with regularity, though these differed somewhat from the reaction produced by idiotoxin in the passively sensitized or naturally sensitive skin. The chief difference was the time of development of the reaction after the injection of the mixture. This was about 45 - 60 minutes in contrast to the 10 - 15 minutes for the passively sensitized or naturally sensitive skin (Fig. 2).

The discrepancies in the earlier reports mentioned above may have been due to those workers who failed to find specific reactions not having observed the injection sites for a sufficient length of time, and also to the fact that sensitive and non-sensitive sera alike tend to develop non-specific irritative properties after storage at the usual ice-chest temperature, as first pointed out by Chant & Gay (1927). Such non-specific reactions, similar to the specific reactions of the previously sensitized site, are fully developed in 10 - 15 minutes and are usually fading in 30 minutes, while the slower specific reactions of the idiotoxin-idioceptor mixtures are not fully developed for 45 - 60 minutes, at which time the reactions should be observed.

Figure 3.



Reaction of Normal Skin to Idiotoxin-Idioceptor Mixtures (varying the quantity of idiotoxin) and the Reaction of the Mixture Sites to Idiotoxin Six Hours later

Mixtures were prepared as follows:-

Hay fever serum 4 parts plus pollen extract 1 part

Mixture	Pollen extract (units per c.c. of mixture)	Reaction shown in Fig. at site-
1	0.0 units	A1
2	0.4 "	A2
3	4.0 "	A3
4	40.0 "	A4
5	400.0 "	A5

Six hours later all sites, and a control untreated site, were injected with 0.02 c.c. of 2000 units per c.c. pollen extract. The reactions are shown in column B.

The explanation of the difference in reaction times of the skin to idiotoxin-idioceptor mixtures and of the sensitive skin to the idiotoxin, would appear to be that in the former the reaction takes place by degrees, the cells which are sensitized first being acted upon by the idiotoxin before the slightly more distal cells enter into combination with the remaining idioceptor.

The reactions produced by injecting the idioceptor mixed with idiotoxin were of the same magnitude as those in which the former was injected first and the site thus sensitized tested later with the idiotoxin. The re-injection of the mixture reaction sites with idiotoxin 24 hours later did not give rise to a further reaction provided there had been sufficient idiotoxin in the mixture to ensure the maximal reaction at the time of its injection. (Fig. 3) Neither did the presence of a large excess of idiotoxin in the mixture, or incubation at 37°C. for 24 hours, diminish its reactive power in normal skin sites.

It was concluded therefore that idiotoxin-idioceptor mixtures produce reactions in normal non-sensitive skin sites and that no inactivation or neutralization of idioceptor takes place *in vitro*. The neutralization of idioceptor by idiotoxin would appear to take place only *in vivo*, that is, by a reaction involving tissue cells. This conclusion has been supported by Cooke, Barnard, Hebal, & Stull (1935a).

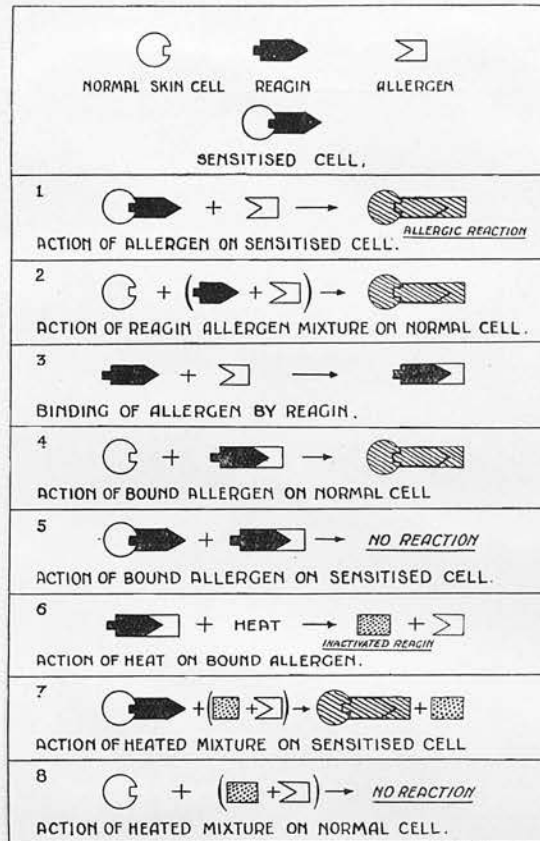
B. Effect of Blood Cells on Idiotoxin-Idioceptor Mixtures

Experiments were made on the effect of the addition of blood cells to idiotoxin-idioceptor mixtures (Harley, 1933b). After incubating and centrifuging the mixtures, the supernatant sera were injected into normal skin sites. Such preparations were found to produce reactions exactly similar to those of idiotoxin-idioceptor made up without blood cells, indicating that the idioceptor content of the serum was undiminished by the treatment and that no reaction had taken place in vitro between the blood cells, idiotoxin, and idioceptor. This is perhaps the result one would have expected *à priori*, since the cells which take part in an allergic reaction suffer some degree of damage in the process and there is no evidence to indicate that any damage to the red or white blood cells occurs when a hay fever patient is receiving large therapeutic doses of pollen extract. In vitro experiments were then made on the effect of pollen extract on the phagocytosis of staphylococci by the leucocytes of normal and hay fever bloods, and on leucocytic emigration. Observations were made with a wide range of pollen extract dilutions but no difference was detected between the behaviour of normal and hay fever bloods.

C. Action of Idioceptor on Idiotoxin in vitro

It was found that the incubation of idiotoxin-idioceptor mixtures containing an excess of idioceptor

Figure 4.



For 'reagin' read idioceptor
 " 'allergen' " idiotoxin

Skin Reactions to Idiotoxin-Idioceptor Mixtures

- from Harley, D.: (1933b) Brit. J. exp. Path., 14, 171.

rendered the mixture inactive on injection into the sensitive skin of the hay fever subject; that is the idiotoxin had been inactivated as far as its action on the sensitive skin was concerned. However, such mixtures were still capable of producing reactions in normal non-sensitive skins as described above. Heating such a mixture to 60°C. for 30 minutes so as to destroy the idioceptor, restored its property of reacting in the sensitive skin, that is, the idiotoxin had been reactivated. The heated mixture no longer reacted in normal skin sites as the idioceptor had been destroyed by the heating process.

It was concluded therefore that idioceptor was capable of binding or inactivating the idiotoxin in vitro provided that the former was present in excess. Several workers (Cooke et al., 1935; Loveless, 1940) have been unable to confirm the writer's results concerning the binding of idiotoxin.

The reactions of idiotoxin-idioceptor mixtures discussed in this section are represented in diagrammatic form in Fig. 4.

CHAPTER IV

THE GRASS POLLEN IDIOTOXIN

1. SKIN-REACTIVE SPECIFICITY

There has been considerable controversy concerning the specificity of the skin-reactive properties of the pollens of the different grasses. Noon & Freeman (1908) originally showed by skin tests that the idiotoxins of the various grass pollens were closely similar, if not identical, and recommended the use of timothy (*Phleum pratense*) pollen for skin testing and treatment in all cases of true hay fever (i.e. grass-pollen-hypersensitivity), as this pollen was one of the most potent of the series examined. Since that time several investigators, particularly in America, have disputed this view, but it would appear that their claims to have demonstrated an individual specificity of the members of the grass family were based on insufficient experimental evidence. Freeman (1933) has recently made a carefully controlled study of this question and his results strongly support the original view of Noon & Freeman that the grass pollens are immunologically closely similar. This worker made skin tests in a group of hay fever patients with the following pollens:- *Phleum pratense*, *Dactylis glomerata*, *Holcus lanatus*, *Lolium perenne*, *Anthroxanthum odoratum*, *Secale cereale*, *Aira flexuosa*, and *Hordeum sativum*, - and found "... that no hay fever patient who reacted to any one of these pollens failed to react to all eight of

them; and, within the limits of the experiment, the more powerful pollens reacted powerfully on all, the less powerful reacted less powerfully on all. . . . Furthermore it was observed that heavy (therapeutic) desensitization with extracts of Phleum, Dactylis, or Holcus, or with any combination of these three, when carried far enough, not only reduced and finally abolished the skin reactions to the particular pollen that was being used as an antigen, but abolished them to all the other pollens also." He concluded that extracts from the various grass pollens furnish one and the same idiotoxin for the purposes of therapeutic desensitization.

Additional evidence in favour of the identity of the grass pollen idiotoxins is afforded by the demonstration that the skin-reactive and desensitizing properties of such grasses as the sugar cane and bamboo in English hay fever cases fall into line with those of the common grasses (Freeman & Hughes, 1938).

2. CHEMICAL NATURE

It was thought originally that the pollen idiotoxins were of protein nature, a belief based perhaps on insufficient experimental evidence. In 1925 Coca & Grove reported their failure to inactivate timothy and ragweed extracts by digestion with proteolytic enzymes, and concluded that these idiotoxins were probably non-protein. Similar opinions were expressed by Black (1925) and

Black & Moore (1926). Black (1931, 1932) obtained from ragweed pollen a carbohydrate fraction (containing however about 6 per cent of nitrogen) which elicited specific skin reactions in sensitive individuals, and he concluded that this fraction was the active factor in ragweed. Meanwhile Loeb (1930) and Bouillene & Bouillene (1931) succeeded in inactivating ragweed and other pollen extracts by prolonged digestion with proteolytic enzymes, and they concluded that the idio-toxins were either protein or closely associated with protein. Then Stull and his co-workers (1930-1933) isolated albuminous proteins from ragweed, timothy, and certain other pollens, which produced specific skin reactions in dilutions of approximately 1-1000000. These proteins were found to completely desensitize active sera in passive transfer sites to whole pollen extract, and it was concluded that they were the only active hay fever constituents in their respective pollens. Stull et al. described also carbohydrate fractions (containing 5 - 6 per cent of nitrogen) which gave reactions in a number of sensitive patients, but he concluded that their activity was due probably to the presence of small amounts of the highly active albuminous proteins. Gough (1932) prepared a highly purified carbohydrate from timothy pollen, but Freeman and the writer (1932) failed to obtain skin reactions with this carbohydrate, and found that it had no desensitizing effect on active sera in passive transfer sites.

Experimental Investigations

More recently the writer has re-investigated this problem (1937b). From timothy pollen three fractions were obtained by chemical means -- fraction A, denatured protein of albumin type; fraction G, denatured protein of globulin type; and fraction C, carbohydrate. The following method was used.

Chemical Methods. 250 c.c. of stock 10 per cent (100000 units per c.c.) alkaline-saline extract prepared from acetone-defatted timothy pollen were employed. The slightly cloudy extract was cleared by the addition of N/10 NaOH sufficient to bring the reaction to approximately pH 8, left in the icechest overnight and then passed through a Seitz filter. The clear filtrate was made slightly acid with acetic acid and poured into 5 volumes of ethyl alcohol; a heavy precipitate was thrown down and the mixture was returned to the ice-chest. After 48 hours the major portion of the clear supernatant was poured off and discarded. The remainder was centrifuged and the dark brown sticky deposit washed with 90 per cent alcohol and this removed in vacuo. The deposit was dissolved in 50 c.c. of water by the addition of 0.1 c.c. of N/10 NaOH. A slight sediment was removed by filtration, and the clear filtrate acidified with a few drops of acetic acid and placed in a water-bath at 100°C. for 4 minutes. A heavy flocculent precipitate formed and was collected by centrifuge.

(1) The protein precipitate.— This was washed with water which had been slightly acidified with acetic acid, and then dissolved in saline by the addition of about 0.2 c.c. of N/10 NaOH. Solution took place rapidly at room temperature giving a slightly cloudy fluid. This was filtered clear and poured into 5 volumes of ethyl alcohol. The resulting precipitate was collected by centrifuge and redissolved in 5 c.c. of water by the aid of a little alkali. Dilute acetic acid was then added drop by drop until a precipitate appeared. More acid was cautiously added till no further precipitation occurred. The mixture was then centrifuged. (a) The precipitate ("G") was redissolved in 5 c.c. of water plus a little alkali. Acid precipitation and re-solution was carried out a second time. (b) The supernatant ("A") was filtered clear. Both G and A solutions were dialysed through cellophane 600 against distilled water for 48 hours. Solution A remained clear. G precipitated as the result of the dialysis and was cleared by the addition of a trace of alkali. Both solutions were then poured into 6 volumes of ethyl alcohol and the precipitates collected and dried in vacuo over calcium chloride. The yields of A and G were 16mg. and 4 mg. respectively.

(2) The carbohydrate-containing supernatant from the acid-heat precipitation of the proteins was poured into 6 volumes of ethyl alcohol and a heavy flocculent precipitate formed. After standing for a few hours in the ice-chest the supernatant was decanted and discarded.

The gummy precipitate was drained, and after the removal of the alcohol, dissolved in 10 c.c. of water plus a trace of alkali. Trichloroacetic acid was then added to remove any non-heat-precipitable proteins present and the mixture placed in the icechest. A flocculent precipitate settled out. The cloudy supernatant was filtered through paper, but as it remained cloudy it was returned to the icechest for a further 18 hours and was then passed through a small Seitz filter. The clear filtrate was poured into 10 volumes of dry redistilled acetone and the precipitate collected by centrifuge. The acid gummy precipitate was drained, dried and extracted with 5 c.c. of water, and sufficient alkali was added to bring the pH to about 5. The solution was then filtered clear and dialysed through cellophane 600 against distilled water for 48 hours. It was then poured into 10 volumes of acetone and the resulting precipitate collected by centrifuge. The precipitate ("C") was dried in vacuo over calcium chloride. The yield was 26 mg.

Chemical Properties of the Fractions A, G, and C

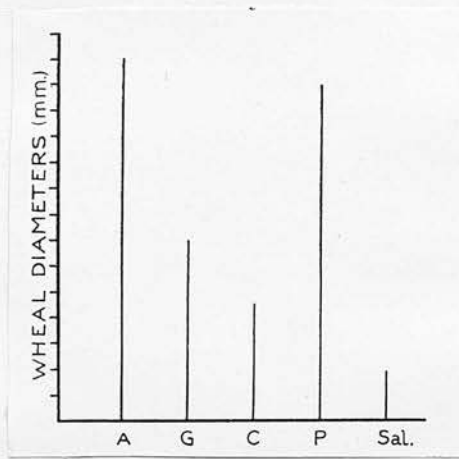
Fraction A (heat-precipitable, non-acid-precipitable). — This was readily soluble in saline and in water containing a trace of alkali. In 1 per cent solution it gave the following colour and precipitation tests characteristic of protein: biuret, ninhydrin, xanthoproteic, Millon, glyoxylic acid, lead acetate and salicylsulph-

onic acid. The Molisch reaction was a weak positive. Quantitative elementary micro-analysis gave the following figures: carbon, 54.5 per cent; hydrogen, 7.6 per cent; nitrogen, 12.5 per cent; and residue 3.1 per cent. These quantitative and qualitative data, together with the method of preparation, indicate that fraction A consisted chiefly of denatured protein of albumin type.

Fraction G (heat-precipitable, acid-precipitable).— This was soluble in saline containing a little alkali. A 1 per cent solution gave the above protein colour and precipitation tests and a slight Molisch reaction. There was insufficient material for micro-analysis, but this fraction was considered to be denatured protein of globulin type.

Fraction C.— This was readily soluble in water. The Molisch reaction was positive in high dilution. In 2 per cent solution it gave a faint biuret reaction and a weak ninhydrin reaction. Fehling's solution was not reduced. After hydrolysis with sulphuric acid Fehling's test showed the presence of considerable quantities of reducing sugars. The nitrogen content of this fraction was 3.45 per cent. It was concluded that fraction C consisted chiefly of carbohydrate, together with a small amount of protein.

Figure 5.



Skin-Reactive Potency of 1-1000 Solutions of
Fractions A, G, and C

Average wheal diameters (prick test) in a group of six hay fever patients. A = fraction A 1-1000; G = fraction G 1-1000; C = fraction C 1-1000; P = whole timothy pollen extract (20000 units per c.c.); Sal. = normal carbol-saline. The average wheal diameters were calculated from planimeter readings of enlarged wheal tracings.

- from Harley, D.: (1937b) Brit. J. exp. Path., 18, 469.

Skin-Reactive Properties of Fractions A, G, and C

All three fractions in dilutions of 1-1000, when tested by the prick method, elicited immediate skin reactions in grass-pollen-sensitive subjects exactly similar to those produced with whole timothy pollen extract, and failed to do so in normal non-sensitive individuals. The relative skin-reactive potencies of the fractions were examined by two methods. The first was the comparison of the size of the prick test reaction wheals to 1-1000 solutions of the three fractions, and the second was the determination of the highest dilution of each fraction capable of producing reactions by the intradermal test. Fig. 5 gives the average diameters of the prick test reaction wheals of a group of hay fever patients to 1-1000 solutions of A, G, and C, and to whole timothy extract. It was estimated from these data that the skin-reactive potency of fraction A was approximately 15 times that of fraction G and 20 times that of fraction C. This estimate of the relative potencies of the three fractions was confirmed by the results of their reaction titre determinations. Employing the intradermal technique with doses of 0.025 c.c. of test fluid, it was found that fraction A in a dilution of 1-5000000 regularly elicited reactions in patients sensitive to pollen, and occasionally did so in a dilution of 1-10000000. The titres of fractions G and C were about 250000.

The desensitizing effect of fraction A on pollen-sensitive sera was examined by the passive transfer method. Unit volumes of potent serum were mixed with unit volumes of (i) saline, (ii) whole timothy pollen extract (250 units per c.c.), and (iii) fraction A in 1-50000 dilution. The mixtures (0.15 c.c. quantities) were injected intradermally in normal non-sensitive individuals susceptible to passive transfer. After 48 hours 0.025 c.c. of timothy pollen extract (2000 units per c.c.) was injected into each mixture site through the original needle track and the ensuing reactions recorded 12 minutes later. It was found that the sites of the whole extract plus serum and fraction A plus serum mixtures did not react to the test injection of extract, while the control saline plus serum sites reacted in every case. It was concluded that fraction A was capable of desensitizing active serum to whole timothy extract, and that the skin-reactive property of this fraction was immunologically the same as that of the whole extract.

Discussion

The above results indicate that fraction A contained the timothy pollen idiotoxin in high concentration, the specific skin-reactive titre being as high as 1-5000000, which compares favourably with the potency of histamine as tested by the same technique. While it is not claimed that fraction A was necessarily a single

chemical entity, the data were strongly suggestive that it consisted practically entirely of protein of albumin type. From the immunological standpoint, therefore, it would seem reasonable to assume that this protein complex represents the idiotoxin of timothy pollen. The lower grade activity of fraction C (carbohydrate), together with the chemical evidence of the presence of small amounts of protein, and the previous failure to demonstrate skin activity with the purified carbohydrate prepared by Gough in 1932, suggest that this activity was due to the protein content of this fraction. Similarly, with fraction G (globulin) it is considered likely that its activity was due to small amounts of the highly active albumin. In these experiments there was insufficient yields of C and G to permit of further attempts at purification in order to settle this question concerning their skin activity.

These conclusions are in agreement with those of Stull and his collaborators (1930-1933), who worked with non-denatured albumin and globulin fractions prepared by salting-out methods. However, it is evident from the method of preparation that fraction A represented the idiotoxin protein complex in a state of considerable denaturation, and it is well known that the immunological properties of native proteins are usually considerably affected by even slight denaturation. Here we have this denatured albumin with a

skin-reactive potency of 1-5000000, which is at least as great as that of the non-denatured albumin isolated by Stull et al. (1930-1933), even when allowance is made for possible differences in skin test technique. The hypothesis which immediately presents itself is that the specificity of the idiotoxin is due to a comparatively stable group attached to or forming part of the protein complex, and that this group is activated by the remaining protein whether the latter is native or denatured. The study of synthetic antigens, prepared by linking simple chemical groups to proteins, has shown that the immunological specificity of the complex antigen is frequently determined more by the nature of the attached groups than by the proteins to which they are coupled, even though the in vitro action of the simple substance on the antibody to the complex antigen may be no more than an inhibition effect on the precipitation between complex antigen and antibody. The work of Benjamins, van Dishoeck, & German (1935) on the pressure filtration of pollen extracts through protein-tight celloidin membranes supports this hypothesis. These investigators reported that protein-free filtrates were capable of producing reactions in hay fever subjects, and further, that when such filtrates were diluted so that they failed to react in the hay fever skin, they could be rendered active by admixture with certain protein and other colloids such as serum or egg albumin. These results suggest that the specific activity of the

idiotoxin is due to a relatively small molecule, which needs a larger complex for its full activation.

3. ANTIGENIC PROPERTIES

Idioceptor

Most authorities are agreed that the allergic idioceptor has not been demonstrated in individuals who have not had direct or indirect contact with the specific idiotoxin, and therefore it is considered to be possibly an immune body (i.e. produced in human beings under antigenic stimulation). On the other hand, there is no direct experimental evidence to support the hypothesis that the idioceptor is a true antibody. Indeed, there has been a uniform failure on the part of numerous investigators, including the writer, to establish a state of allergic sensitization, mediated by idioceptor, in man, by the exhibition of pollen or pollen extracts by injection or otherwise.

Anaphylactin and Precipitin

Most idiotoxins, including those of pollen, are of protein nature, or at least are closely associated with protein, and may therefore be expected to function as antigens. Many of them, such as egg albumin for example, are potent antigens, and readily stimulate the formation of precipitin and anaphylactin in animals. Concerning the antigenic properties of the pollens

there have been contradictory reports. Coca (1920) originally considered the pollens to be non-antigenic but has recently modified his views (Coca, Walzer, & Thommen, 1931). Clock (1917) reported complement-fixing antibodies in the sera of animals treated with pollen extracts. Flood (1920) obtained negative results regarding the anaphylactogenic properties of pollen in animals. However, Dunbar (1911), Alexander (1923), and Parker (1924) demonstrated antigen in pollen extracts, and Walzer & Grove (1925) succeeded in showing its anaphylactogenic character in the guinea-pig. The workers claiming antigenic properties for pollens are agreed that these idiotoxins are only weakly antigenic, the antibodies being obtained with difficulty and only in low concentration. More recently Bernstein (1935) claims to have enhanced the antigenicity of pollens by mixing these with a potent antigen (horse serum). Employing non-sensitive and pollen-sensitive human sera mixed with timothy extract as antigens, the writer has failed to obtain any enhanced response to the pollen in rabbits, as tested by the precipitin reaction. Highly concentrated pollen extracts and pollen fractions treated in a variety of ways gave very feeble precipitin response in rabbits. It was concluded that while the timothy pollen idiotoxin is capable of acting as an antigen, very large doses must be given to evoke even the minimal antibody response.

4. ATTEMPTS TO MODIFY THE IDIOTOXIN FOR THERAPEUTIC PURPOSES

It must be admitted that however successful it may be, the heavy desensitization pollen therapy (to be described — Chapter VI, p.50) is often tedious or troublesome, or at any rate leaves room for further improvement in thses respects. The number of injections necessary for the desensitization of the average previously untreated case is about 50. This is due to the fact that the pollen idiotoxin is very quickly absorbed from the subcutaneous tissues into the blood stream. The routine procedure allows of an increase of 15 per cent on each dose if the comfort and peace of mind of the patient are considered. The problem of decreasing the number of injections by increasing the dosage increments has been studied. The use of agents such as calcium and adrenaline for the control of general reactions, while of assistance even if only in attaining the 15 per cent increase, is very limited. The problem has been approached in two ways. Firstly, attempts were made to render the idiotoxin less soluble in the hope that the pollen extract so treated would be less readily absorbed into the blood from the usual subcutaneous depot, and thus allow of greater dosage increments and fewer doses. The results so far have been disappointing, the only methods found to have an effective action on slowing down the absorption not being practicable for therapeutic purposes. The second

approach has been the employment of chemical means in an attempt to alter the idiotoxin in the hope of obtaining a product that would be relatively incapable of producing reactions but still able to exert a desensitizing effect. These attempts have been ineffective so far.

Physical methods. The absorption of the idiotoxin to colloidal precipitates, such as aluminium hydroxide, calcium phosphate, etc. has been uniformly unsuccessful both with preformed precipitates and those formed in situ. This is in sharp contrast to the effect of such precipitates on bacterial toxins. The only methods found to be effective were absorption to activated charcoal and to certain fine oil emulsions. The second was found to be therapeutically effective but the relative instability of the emulsions with consequent release of the idiotoxin was against its trial on an adequate scale. The charcoal method was of course therapeutically impracticable.

Chemical methods. As a preliminary, a large scale experiment for the recovery of workable quantities of the highly active fraction A of timothy pollen described in section 2 (p.29) was carried out. The methods so far employed have been acid and alkaline hydrolysis at different temperatures and for various times. The products isolated were tested for (i) skin-reactive

potency, (ii) desensitizing property for active sera in passive transfer sites, and (iii) ability to inhibit the reaction of normal skin sites to idiotoxin-idioceptor mixtures. This line of research has not yet been completed but so far the results have been negative, that is, all attempts to reduce the skin-reactive potency of the idiotoxin have resulted in a parallel reduction of its desensitizing power, and inhibiting substances have not been obtained.

CHAPTER V

THE NATURE AND ORIGIN OF THE ALLERGIC STATE

That the manifestations of pollen allergy are mediated by idioceptor cannot be held in doubt. Serum idioceptor is invariably present in all cases exhibiting clinical sensitization and positive skin reactions. The available evidence indicates that the serum idioceptor is quantitatively proportional to the skin sensitivity (fixed idioceptor) (Levine & Coca, 1926; Harley, 1933a). Serum containing idioceptor is capable of sensitizing the normal non-sensitive skin and the area thus treated reacts to the idiotoxin in a manner exactly similar to that of the naturally sensitive skin of the allergic individual. Furthermore, such serum is capable of sensitizing the normal upper respiratory tract mucosa so that the person thus treated exhibits the typical hay fever symptom-complex on contact with the idiotoxin (Freeman, 1925), and the classical report of Ramirez (1919) demonstrated the possibility of a transfer of general sensitivity to a normal non-allergic individual by a blood transfusion from a horse-sensitive asthmatic. One concludes that the cause of hay fever, and of similar allergic conditions in which an idiotoxin-idioceptor mechanism has been proved, is the presence of idioceptor in the tissue cells and serum. The problem of the causation of hay fever therefore is that of the origin and nature of the idioceptor.

With regard to the immunological nature of the idioceptor — while there has been much controversial speculation there is little positive information available. It is generally agreed that the idioceptor has not been demonstrated in persons who have not had direct or indirect contact with the corresponding idiotoxin (or with substances closely related biologically or chemically) and therefore that it is possibly an immune body, i.e., produced under antigenic stimulation. Some confirmation of this view is afforded by the observation that pollen therapy in hay fever is sometimes attended by an increase of serum idioceptor in the early stages of the treatment. Such findings have been reported by Cooke, 1922; Levine & Coca, 1924; Gay & Chant, 1927; and Sherman, Stull, & Cooke, 1940. However, as has been discussed in Chapter III (p. 16), the properties of idioceptor are qualitatively different from those of the anaphylactic and other antibodies, though in common with the latter it occurs in the pseudoglobulin fraction of the serum (Cooke, Barnard, Hebold, & Stull, 1935b). Furthermore, attempts to produce idioceptor by the inhalation of pollen or the injection of pollen extract in normal or allergic (non-pollen-sensitive) man have been uniformly unsuccessful with a few very doubtful exceptions in the latter group. Contact with the idiotoxin is not in itself sufficient to engender the formation of idioceptor. The determining factor without doubt is the hereditary element. Consideration of fact that individuals with allergic heredities

do not develop sensitizations to all the idiotoxins to which they are exposed, or even to those with which they come into close and repeated contact, suggests that the heredity factor must be more or less specific for the development of sensitization to a particular idiotoxin or group of idiotoxins. Evidence has been presented in support of this hypothesis, and to suggest also that heredity may determine the age of onset and clinical form of the sensitization (Cooke & Vander Veer, 1916; Coca, 1927; Balyeat, 1928).

An observation which may have a bearing on the nature of the hereditary factor in hay fever has been reported previously (Harley, 1933c) - the blood of normal persons is able to dissolve the intracellular granules of the pollen grain but the blood of hay fever patients is deficient in this property. One of the presumed normal individuals whose blood was tested gave the result characteristic of the hay fever bloods, though the skin reactions to pollen were negative and there was no history of personal or antecedent family history of hay fever or other allergic conditions. The patient stated that her daughter suffered from hay fever, though the husband's side of the family was negative for allergy. Unfortunately the daughter was not available for confirmatory skin testing. The possibility that the hereditary factor in hay fever is connected with the inability of the blood to dissolve or digest certain constituents of the pollen grain is in line with Oriel's

observations (1932) that the blood of asthmatics is deficient in its power to digest the peptone of the particular idiotoxin responsible for the symptoms. As the intracellular pollen granules used in the above experiments were believed to consist chiefly of carbohydrate, it was of moment to determine whether the deficiency of lytic power found in the hay fever bloods was related to a lack of diastase in the serum. Accordingly the diastatic indices of a number of hay fever bloods was measured; however, the results showed that there was no appreciable difference between the indices of normal and hay fever bloods.

The possibility that the heredity factor might be linked in some way with the blood group agglutinogens was examined by comparing the incidences of the A, B, M, and N agglutinogens in a group of allergics with those in normal controls (Harley, 1936, and unpublished). The results obtained showed no differences between the two groups, indicating that no relationship existed between the allergic inheritance and the blood groups.

The failure of the lower animals to develop allergic sensitization mediated by idioceptor, either naturally or experimentally, coupled with the failure of most workers to obtain any passive sensitization in animals with human sera containing idioceptor, suggested that the animals might possess some mechanism antagonistic to idioceptor, since human serum containing precipitin is

capable of inducing passive anaphylactic sensitization in animals. This hypothesis was examined by testing the effect of normal rabbit serum on the sensitizing power of hay fever serum for the normal human skin. It was found that the incubation of rabbit serum with hay fever serum resulted in the inactivation of the idioceptor as shown by the inability of the mixture to sensitize normal skin sites (Harley, 1935a). These experiments suggest that the lower animals possess some mechanism for inactivating idioceptor though it remains for future work to determine the precise nature of this mechanism.

CHAPTER VI

TREATMENT

PHYLACTIC TREATMENT

The most effective treatment of hay fever would be specific avoidance but unfortunately this is nearly always impracticable. It could be carried out in two ways, by removing the patient to a district free from grass pollen or by a system of air conditioning which would remove all pollen from the patient's immediate environment. The first method is not possible, in England at any rate, in view of the universal prevalence of pollen during the grass pollinating season. The second method, by the use of 'allergen-free chambers' (Van Leeuwen & Kremer, 1926) or masks containing air filters (Frankel & Levy, 1927) so restrict the activities of the patient as to be quite impracticable in the great majority of cases.

In the writer's experience the only two generally applicable methods are adrenaline locally and small doses of pollen extract with adrenaline subcutaneously. Drops containing adrenaline hydrochloride (1-1000 solution) 2 drachms and boric acid 20 grains to 1 ounce of rose water, applied to the nostrils and eyes several times a day, are occasionally very effective, usually give satisfactory relief in the majority of cases, but appear to have an irritating effect in some patients,

especially the more severe cases. The addition of cocaine to the drops is often helpful but should be employed cautiously in view of possible addiction. Specific treatment with small doses of pollen extract (10 - 40 units[⊗]) combined with 0.1 - 0.2 c.c. of adrenaline (1-1000) subcutaneously, at 2 - 3 day intervals during the hay fever season, often gives a surprising degree of relief and is perhaps the best line of treatment for the patient who presents himself after the hay fever season has started.

PROPHYLACTIC TREATMENT

Specific desensitization undoubtedly is the most effective practicable method of treatment at present available. In 1911 Noon reported the results he obtained with 'active immunization' using grass pollen extracts. After Noon's untimely death his method of treatment was developed by Freeman (1911, 1914, 1916) and the basic principles of the method have since met with almost universal acceptance and application.

The methods described below are those evolved by Freeman and employed in the Hay Fever Clinic at St. Mary's Hospital.

[⊗] The Noon pollen unit is employed. One unit is the amount of active principle extracted from one millionth (1/1000000) of a gram of pollen (Noon, 1911).

Heavy Desensitization and its Control by Skin Reactions

The rationale of this method is the use of massive dosage of pollen extract subcutaneously, sufficient to markedly diminish or preferably abolish the patient's skin reactions, as shown by a negative prick test reaction (Chapter XIV, p.139).

In the previously untreated case it is usually necessary to start with a dose of 20 - 40 units, increasing by 20 units each time to a dose of 200 units, after which a 15 per cent increase is usually made on each successive dose. The total number of injections necessary to reach the top dose of 100000 units on this system is about 50. The interval at which the 50 injections are given can be varied widely to suit individual requirements but generally the best results are obtained most conveniently by starting the treatment about three months before the hay fever season is due, i.e. the beginning of March. On the first visit the patient has his clinical history taken and his skin reactions are tested. If the former is typical and the latter positive treatment is commenced straight away with a suitable initial dose (usually 20 - 40 units) of pollen extract subcutaneously. The patient then attends the clinic on three days a week for one or two weeks, being given an increase of 20 units each time, and the degree of local reaction to the injections is observed. During this period he receives also instruction

in the rationale and conduct of the treatment and in the technique of self-inoculation. If the reactions to these preliminary injections have not been excessive and no special variation of the above mentioned scheme of dosage is indicated the patient receives three injections per week at the clinic or is supplied with a self-inoculation outfit and proceeds to inoculate himself at home. He gives himself 3 - 5 injections per week and reports his progress to the clinic or his own doctor at intervals. For routine purposes repeat skin tests are made after the 20000 unit dose and again after the 100000 unit dose. The interval between injections is timed so that the 100000 unit dose is reached just prior to the commencement of the hay fever season (third week in May in England). By this time the skin reactions are invariably found to be markedly diminished and in the great majority of patients they are abolished. With the commencement of the hay fever season the treatment may be stopped or the patient continues with a maintenance dose of 50000 units at weekly intervals during the remainder of the season. These maintenance doses are best given in the evening of a cool or rainy day when the pollen content of the air is at its lowest. Unless the patient is unduly adrenaline-sensitive, a small dose of 1-1000 adrenaline (0.1 - 0.2 c.c.) is usually given mixed with the pollen extract injections.



(i) Dosage and Frequency of Injections

The skin reactions are a rough guide to the size of the initial dose. This is usually 20 - 40 units in the previously untreated patient but when the reactions are very large it is safer to start with 10 units. In the average previously untreated patient the dosage scheme mentioned above, viz., a 15 per cent increase of each dose after the 200 unit level, has been shown by experience to be the most satisfactory rate, if the comfort and peace of mind of the patient are considered. Occasionally however a very sensitive patient may be unable to tolerate a 15 per cent increase and then a 10 per cent rise or even less may be necessary. One is sometimes tempted to increase more than 15 per cent, especially in patients with small skin reactions or whose hay fever is comparatively mild but it is the writer's experience that a 15 per cent increase is safer and often quicker in the long run.

The frequency of the injections can be varied within wide limits though the method outlined above is perhaps the most satisfactory. However, should it be considered necessary to carry out the treatment in 2 or 3 weeks as in the case of a patient who applies for treatment at the beginning of May, injections can be given at the rate of 2 or 3 a day so that the 100000 unit dose may be reached in 2 or 3 weeks. With the more intensive treatments however excessive reactions are

more likely to occur and one has often to be content with a final dose far short of 100000 units.

Patients who have received previous courses of treatment may be given an initial dose of 60 - 200 units and will usually tolerate an increase of 50 per cent, slowing down to 25 per cent or so as the larger doses are reached.

(ii) Reactions During Treatment

Excessive local reactions are not common with the standard course of treatment detailed above. Local reactions form a very useful indication of the patient's degree of tolerance to the injections and should they tend to increase in severity with successive doses then the rate of increase had better be cut down, temporarily at any rate. It not infrequently happens that at some stage in the treatment the injections produce excessive reactions. In that case it is advisable to reduce the the dose and then increase at half the previous rate. After the 'sticking point' is passed it is usually possible to revert to the former rate without further trouble. This sticking point frequently coincides with some intercurrent ailment or infection or some psychological upset but it may occur occasionally, at about the same dosage level, in the same patient during two successive years of treatment, for reasons unknown. Excessive local reactions can often be reduced by taking

calcium lactate gr. 20 in water half an hour before the injection without recourse to reducing the dosage rate.

General reactions, except those caused by gross overdosage or accidental intravenous injection, are comparatively infrequent and usually mild, and can be relieved by the prompt use of adrenaline, preferably in small doses (0.1 - 0.2 c.c. of the 1-1000 solution) at 10 - 20 minute intervals. These reactions sometimes occur on beginning the treatment, especially in previously untreated patients, who may afterwards go through the complete course of treatment without further trouble. Once the treatment is well under way general reactions of any degree of severity with the standard scheme of doses, given truly subcutaneously, are rare in the absence of warning signals from increasing local reactions to the preceding injections.

(iii) Self-Inoculation

This technique was designed to overcome the difficulties attendant on the administration by the doctor of the rather lengthy series of injections necessitated by the heavy desensitization treatment. The candidate for self-inoculation is given a short instruction in the rationale and conduct of the treatment together with the following printed instructions for study at home. He is then given an informal examination by the supervising doctor and if his knowledge of the method

and his inoculation technique is deemed satisfactory he is supplied with an outfit (Plate 1) for use at home. The physician must use discretion in selecting a patient as suitable for self-inoculation and many patients are clearly unsuitable. As a rule the men are easier to teach than the women, particularly amongst the educated classes. The actual operation of self-inoculation involves practically no intellectual difficulty and is more a matter of temperment, concerning which the doctor must be the sole judge. The practicability of the self-inoculation method may be judged by the following figures from the St. Mary's Hospital Hay Fever Clinic (Table 2).

Table 2.

Year	Hay fever patients	
	Total No.	No. Self-inoculated
1937	443	256 (58%)
1938	514	402 (78%)
1939	611	461 (75%)
1940	583	443 (76%)

INSTRUCTIONS FOR THE USE OF THE INOCULATION SET FOR HEAVY DESENSITIZATION AGAINST HAY-FEVER.

1. **Contents.** This hay-fever desensitizing set is designed for self-inoculation by the patient. It therefore contains, besides the necessary dilutions of the pollen vaccine, a suitable syringe (sterile in a case), some alcohol for re-sterilization purposes, adrenalin for emergency injection for a slight overdose, a card showing what doses may be given in an average case and also blank spaces for entering the date and exact dose at every inoculation.

2. **The dilutions of pollen vaccine supplied** are ten in number, and range from the weakest strength, which contains only 100 units of pollen in every cubic centimetre of fluid in the bottle, to the strongest, which holds 100,000 units of pollen in each cubic centimetre. Each bottle contains about 8 cubic centimetres of the fluid, i.e. rather more than is needed of that particular strength before the gradually increasing dose makes it convenient to change to the next and stronger bottle in the series.

3. **The syringe** is provided already sterilized and ready for use. It should not be played with but used only for hay-fever treatment; preferably it should be kept and used for one patient in the bedroom. If it is not taken to pieces and used only as instructed it will be unnecessary to re-sterilize the **inside** of the syringe. Immediately before each inoculation the outside of the needle should be sterilized in alcohol: to do this, thrust the hypodermic needle (still on the end of the syringe, of course) through the centre of the rubber cap on the bottle containing the alcohol, hold this bottle inverted above the syringe, count ten, then withdraw the needle of the syringe from the rubber cap. It is unnecessary to draw any alcohol into the syringe during this manœuvre. Then proceed to measure into the syringe the correct dose of pollen vaccine.

4. **Calculating what each dose should be.** Each dose aims at being the maximum that can be given at the time without undue risk of uncomfortable symptoms. Each dose can only be given safely because of the preceding doses, and is itself a preparation for the dose to follow: they are ascending steps in a ladder reaching from, say, 40 units, to perhaps 100,000 units as is shown on the list. If a slight overdose has been given and an unpleasant reaction has resulted, the succeeding doses should not be given ruthlessly according to plan, but modified to suit the new circumstances; the reacting dose may even be repeated, or a still smaller dose resorted to, before increasing again. If necessary, the medical supervisor must be consulted.

5. **Correct measurement of the dose decided on.** Let us assume that the first dose is to be one of 40 units; this may conveniently be given by inoculating 0.4 of a cubic centimetre (i.e. up to the 4 mark on the syringe) from the weakest bottle, or 0.2 (i.e. up to the 2 mark) from the second bottle, which contains 200 units per cubic centimetre.

The mathematics for these calculations are elementary, but may be stated thus for those

List of suitable doses
40 units
60 "
80 "
100 "
120 "
140 "
160 "
180 "
200 "
230 "
265 "
300 "
345 "
400 "
460 "
530 "
610 "
700 "
800 "
920 "
1,060 "
1,220 "
1,400 "

(continued overleaf)

who need it: The first bottle contains 100 units of pollen in every c.c. of fluid, therefore if the syringe is drawn full to the 10 mark (i.e. if exactly 1 c.c. is drawn into it) it would then contain 100 units of pollen; if it is drawn only to the 1 mark (i.e. if exactly 0.1 of a c.c. is drawn into it) it would then contain 100 divided by 10, i.e. 10 units of pollen—10 being one-tenth of 100. It follows that if four times this, i.e. 0.4 of a c.c. (up to the 4 mark) is drawn in, then the desired dose of 40 units will have been attained.

By a similar argument the second bottle contains 200 units of pollen extract in each c.c. of its fluid (the label says so), therefore if the syringe is drawn full to the mark 10 (i.e. if exactly 1 c.c. is drawn into it) it would then contain 200 units; if it is drawn only up to the 1 mark (i.e. if exactly one-tenth of a cubic centimetre is drawn into it) it would then contain 20 units of pollen—20 being one-tenth of 200; it follows that if twice this, i.e. two-tenths of a cubic centimetre, is drawn in, then once more the desired dose of 40 units will have been taken. The same mental process may be carried out to obtain any dose in the series. Taking at random a dose later in the series—3,500 units are conveniently obtained from the 5,000 unit per c.c. bottle, thus: a full syringe = 5,000 units; one-tenth of a syringe = 500 units; therefore 7×500 (i.e. 3,500 units) are contained in 0.7 of a c.c. (i.e. up to the 7 mark). These calculations are all either elementary and obvious to the self-inoculator, or he would be well advised to work at it with pencil and paper privately and then come back to the supervising doctor for a short examination before embarking on self-inoculation.

List of suitable doses

(continued)

1,600	units
1,840	„
2,100	„
2,400	„
2,750	„
3,150	„
3,600	„
4,100	„
4,700	„
5,400	„
6,200	„
7,100	„
8,100	„
9,300	„
10,700	„
12,300	„
14,200	„
16,300	„
18,800	„
21,600	„
24,800	„
28,500	„
32,800	„
37,800	„
43,500	„
50,000	„
57,000	„
66,000	„
76,000	„
87,000	„
100,000	„

6. Technique of drawing vaccine into a syringe.

Immediately after sterilizing the needle of the syringe (see Section 3) place the plunger at the point it should be at when the syringe contains the required dose (i.e. draw into the syringe as much air as you propose to draw in of fluid subsequently); pierce the centre of the rubber cap of the correct bottle (weakest bottle to start with, probably) and expel the air from the syringe into the bottle, then with the cap still impaled by the needle, hold the bottle and syringe vertically with the bottle on top so that the point of the needle is in the vaccine fluid. Withdraw the plunger, thus sucking the fluid into the syringe to the required amount—bubbles may be got rid of by blowing them back into the bottle; withdraw needle from the bottle, see that the amount of fluid in the syringe is quite correct, and place the syringe with its measured dose conveniently on a table without allowing the needle to touch anything.

7. **Sterilizing the skin** before the inoculation should not be attempted because it is unnecessary to do it. If anything special is done, then a wash with soap and water is perhaps the best thing. If an antiseptic is insisted on, then see that it is harmless.

8. **The Injection.** Any area of the body will serve, but it is better to choose a spot which is not usually seen in public and where there is fairly loose skin over the muscles. If the inoculator is also the inoculatee, the front of the thigh is

convenient because it leaves both hands free for the operation and the area is in plain view in the bedroom.

9. **Record at once** the number of units of pollen inoculated, with the date and time on the form provided. If any local or general reaction occurs this may also be noted, if desired, in the margin, thus: "L.R." or "G.R.," or even "G.R. + + +!" If adrenalin is given, then "A" will serve to indicate this. (But for the most part the remarks column had better be kept for recording the skin reactions, which will be progressively diminishing as the desensitization treatment proceeds.)

Probably nothing worth calling a reaction will occur: any anyway, recording them is not necessary. But unless the record of doses given is kept punctiliously, it is impossible for the doctor in charge to assure himself that the course of treatment is being properly given or to correct any past errors of judgment.

10. **Reactions may be local or general.** If **local** (i.e. at or around the site of the injection of pollen), they should be disregarded unless unpleasantly severe, in which case the rate of increase may perhaps be modified till there is less pain, redness and swelling and local reactions can often be stopped by taking lactate or calcium grains xx in water half an hour before the dose.

If the reactions are **general**, they will show themselves as an ichiness of the skin with perhaps nettle rash in patches in an hour or so. If the reaction is strong, it may cause nettle rash over large areas (the so-called giant urticarias), migraine headaches, signs of asthma, etc.; in such cases it is better to give an inoculation of the adrenalin subcutaneously (just like a dose of vaccine)— $\frac{1}{4}$, $\frac{1}{3}$ or $\frac{1}{2}$ a cubic centimetre out of the bottle supplied is about the right amount, and if no more than $\frac{1}{3}$ of a cubic centimetre (i.e. half-way between the 3 and 4 marks), it may be repeated every fifteen minutes for three or four times. Nine self-inoculators out of ten do not find it necessary to use this adrenalin at all.

11. **Frequency of inoculation.** We have here a wide range to choose from. The outside limits of the intervals between doses are perhaps from a week (on the long side) down to four hours (on the short side). If time serves, it is convenient to re-inoculate every two or three days till the technique is thoroughly mastered and then to settle down to a steady dose once a day. If time presses, this can be quickened up to morning and evening doses, or even to a dose morning, noon and night. It is desirable that the skin reaction should be abolished (i.e. the hay-fever person should be completely protected) just at the beginning of June, when symptoms would have been severe; if this stage is reached too soon, it may be necessary to give maintaining doses to keep the immunity up to the desired pitch. Therefore, when the larger doses are reached (say, when using the 20,000 or 50,000 units per c.c. bottle), it is a good thing to calculate how much time is still left for the treatment, and space the doses out accordingly.

12. **Skin reactions as a guide to treatment** are primarily the concern not of the patient but of the doctor in charge of the case; and, of course, this treatment should never be commenced till he has assured himself that the case is one of genuine and uncomplicated hay-fever. It is suggested that the patient should also present him or herself for re-testing at, say, the end of the 2,000 unit and of the 20,000 unit bottle. When there is no reaction then the patient is completely desensitized; if there is still some reaction on the skin then the desensitization is not complete, but there will certainly be marked diminution of symptoms and possibly complete relief.

Recapitulation.

These instructions are lengthy, but the actual things to be done are few and simple:—

1. Take syringe with needle attached from its case and sterilize the outside of the needle. Time, 10 seconds.
2. Draw into the syringe the exact dose to be inoculated. After the first half-dozen doses, time probably 10 seconds at most.
3. Pick up a fold of the skin over the upper surface of either thigh, puncture the skin almost at right angles to the surface and squirt the contents of the syringe well into the centre of the fold. Time, 2 seconds upwards. This will probably be the longest operation for the beginner. The pain is in proportion to the diffidence displayed and the time taken.
4. Wipe the needle with a clean rag (but do not attempt to re-sterilize it) and place the syringe carefully in the case provided. Time, 20 seconds.
5. Record the dose on the form provided, and put away the box. Time, 30 seconds.

After the emotional interest in self-inoculation has subsided, i.e. after the first few doses, the whole business can be done carefully and without hurry in a minute to a minute and a half.

It is again emphasised that, if failure or disappointment is to be avoided, this self-inoculation should only be carried out with the approval of a medical man, and after careful instruction by him. Every year many people, calling themselves typical hay-fever cases, present themselves for treatment when they have not got hay-fever at all, and can derive no benefit.

Great care is taken that this Self-Inoculation Set does not get into the hands of the lay public save under medical supervision.

Plate I
Self-Inoculation Outfit.

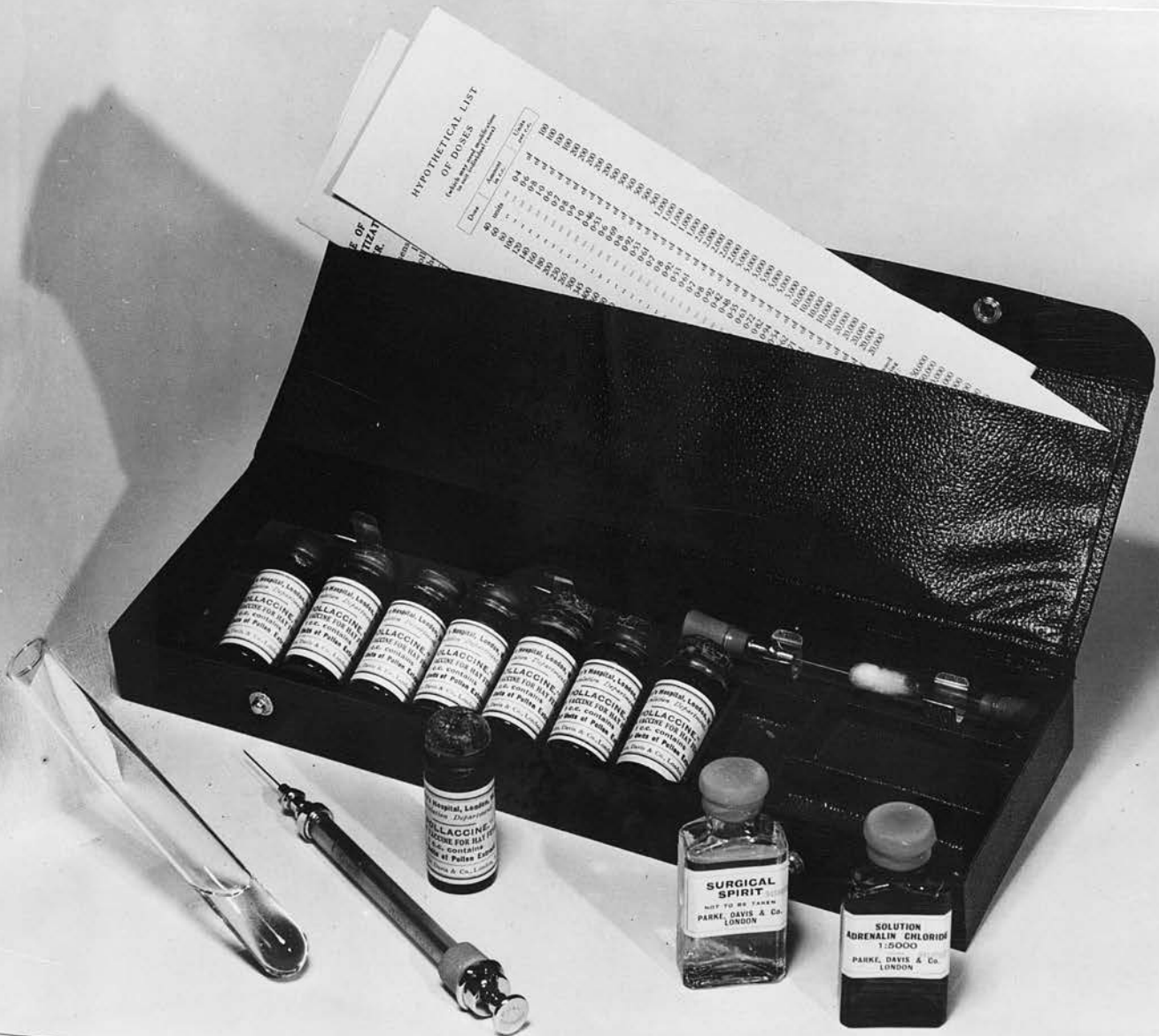


Photo by courtesy of Messrs. Parke Davis & Co.

(iv) Clinical Results of Heavy Desensitization Treatment

The heavy desensitization treatment aims at abolishing the patient's skin sensitivity prior to the commencement of the hay fever season. The abolition of skin sensitivity appears to go hand in hand with abolition of the sensitivity of the mucous membranes so that the patient who no longer reacts to the test dose of pollen extract in the skin no longer reacts to the atmospheric pollen in the nose and eyes. Complete relief from uncomplicated hay fever can be practically guaranteed if the treatment is carried to the length of abolishing the skin sensitivity. I am in agreement with Brown (1932) who describes his results with massive dose pollen therapy as 'almost monotonously perfect'. Occasional unsatisfactory therapeutic results are almost invariably due to the failure to recognize and treat other clinical sensitivities complicating the primary pollen sensitization.

As has already been mentioned above, satisfactory relief from hay fever can often be obtained by a course of prophylactic injections much less than that necessary for the abolition of the skin sensitivity, but here the results are less certain and it is usually impossible to decide before hand whether a particular patient whose skin sensitivity is only partly reduced is likely to have satisfactory relief during the approaching season

or not. Nor is the intensity of the patient's past attacks of much aid in assessing the minimum dosage necessary for complete relief, except that it is the writer's experience that patients whose hay fever is comparatively mild often require a longer course of treatment to gain complete relief than do the more sensitive cases. In view of the lengthy course of treatment necessary to abolish the skin sensitivity and to ensure complete freedom from hay fever, it has to be admitted that the thorough prophylactic treatment of a mild case of hay fever is often not worthwhile, and then one has to fall back on the less certain co-seasonal treatment with small doses of pollen extract and on palliative adrenaline subcutaneously or locally.

(v) The Possibility of Permanant Cure

It has to be admitted that while the standard desensitization course gives excellent results for the season immediately following the treatment, the symptoms will almost certainly return the next year, though not so intensely as before, in the absence of further treatment. Such partial return of symptoms are found to coincide with a partial return of skin sensitivity, but it usually happens that further treatments can be given with much less trouble, that is, the initial dose and the rate of dosage increase can be considerably and progressively increased during successive years, so that the

maximum dose can be reached with fewer and fewer injections. The number of years during which treatment is necessary before the patient can hope to remain permanently free from hay fever, is very variable, and the question awaits the result of further investigation. The writer has had patients who have remained free from hay fever after two consecutive courses of treatment, but on the other hand there have been instances of patients who had received five and six years treatment and then missed a year only to find that the symptoms returned. The chance of permanent cure would appear to be roughly proportional to the number of treatments received but it is not clear why one patient will remain free after one or two years of treatment, while another patient, whose hay fever and skin sensitivity are of the same degree as the first, will relapse after a greater number of treatments. The results obtained by Brown (1932, 1934a) suggest that permanent cure is more likely to be obtained by repeating the maximum dose of pollen extract, after the hay fever season is over, at increasing intervals for another year or longer (perennial treatment) instead of stopping the treatment and allowing the skin sensitivity to return in part before embarking on a second and third course of preseasonal treatment. The writer's experience with perennial treatment is not extensive but so far the results have been highly satisfactory.

CHAPTER VII

THE MECHANISM OF SPECIFIC DESENSITIZATION

Though the value of specific pollen therapy in hay fever is acknowledged now almost universally, there has been considerable doubt expressed regarding the mechanism of the clinical protection obtained thereby:-

Levine & Coca (1926) stated "The results ... provide no basis for a satisfactory explanation of the alleviating effect of the specific treatment of atopic conditions (hay fever, asthma, & c.) ... allows no grounds for the assumption that the relieving effect of the specific treatment of atopic conditions is due to a 'desensitization' (neutralization of sensitizing antibodies)." Cooke (1922) expressed a similar view. Rackemann (1931) summarized as follows:-

"Whether its effect is to reduce the quantity of cellular antibodies and thus desensitize the patient in a literal sense, or whether its effect is to induce the development of circulating antibodies and thus to provide immunity, is doubtful."

These views would appear to have been based on the following observations:-

(i) The skin sensitivity is not reduced by treatment (Cooke, 1922; Levine & Coca, 1926; Rackemann, 1931).

(ii) The serum idioceptor is not reduced by treatment (Levine & Coca, 1926; Gay & Chant, 1927).

(iii) The results of specific treatment are not satisfactory (reviewed by Rackemann, 1931).

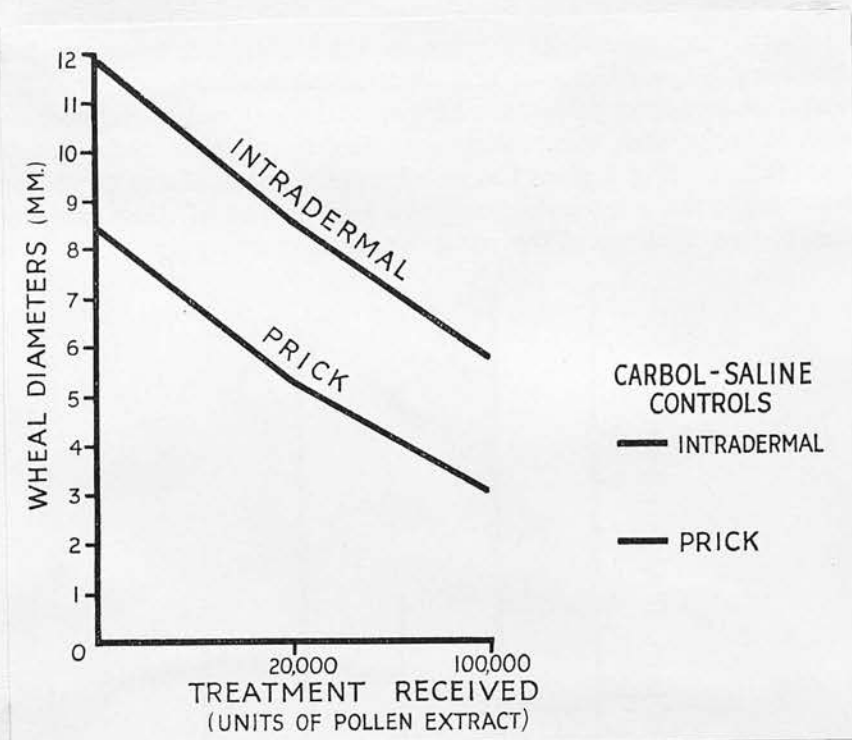
The writer's observations are at variance with all three statements and they allow of a rational explanation of the mechanism of specific therapeutic desensitization.

1. THE EFFECT OF POLLEN THERAPY ON THE SKIN SENSITIVITY

Some observers have reported no reduction of cutaneous sensitivity following treatment (Cooke, 1922; Levine & Coca, 1926; Rackemann, 1931; Cooke, Barnard, Hebdal, & Stull, 1935a) while others, including the writer, have reported reduction and even abolition of sensitivity (Freeman, 1930; Markin, 1931; Brown, 1932; Harley, 1933a, 1935a). Cooke et al. (1935a) have suggested that this discrepancy may be due in part to variations in skin test technique and point out that the workers claiming reduction of skin sensitivity employed the scratch or prick methods while those reporting no reduction used the intradermal technique. The writer has recently re-investigated this question (Harley, 1937a):- A group of 40 hay fever patients were treated with grass pollen extract to a top dose of 100000 units and prick and intradermal tests were made before, during and after treatment. The reaction wheals were accurately measured by planimeter readings of the enlarged wheal tracings.

Methods. The technique of the prick method is described in Chapter XIV (p. 139). The intradermal tests were made by injecting a volume of fluid sufficient to raise a wheal approximately 2 mm. in diameter. All tests were made on the flexor surface of the forearms. Pollen extract dilutions of 100 and 20000 units per c.c. were employed for the prick and intradermal tests respectively. Carbol-saline was used for control tests in both methods. The skin reactions were examined 12 minutes after making the tests and the wheal outlines were traced in ink on albumin-coated glass slides. The tracings were then copied on paper and the areas of the wheals measured by an 'Allbrit' planimeter. It was found convenient to employ a fixed-focus photographic enlarger for copying the tracings on to paper and to enlarge each wheal outline to x3 or x5 diameters. The enlarged tracings were then measured and the necessary reduction made. To avoid making separate readings of the area of each wheal the following device was used. The planimeter was mounted on a sheet of semi-transparent paper pinned to the drawing board, and an ink mark was made on the paper underneath the tracer point. Paper strips, each bearing the series of tracings of corresponding reactions of the whole group of patients, were inserted under the transparent paper and the sum of the areas of each series of tracings obtained by adjusting each tracing under the tracer point mark in turn. The average wheal area and the average wheal diameter were then calculated.

Figure 6



Effect of Pollen Therapy on the Prick and Intradermal Reactions. Average Wheal Diameters in a Series of 40 Hay Fever Patients.

- from Harley, D.: (1937a) J. Path. Bact., 44, 589.

Treatment: This was preseasonal, commencing in March or April with an initial dose of 40 - 100 units subcutaneously and increasing by 15 - 25 per cent each time to a final dose of 100000 units at the end of May, when treatment was stopped. All patients were self-inoculated (Chapter VI, p. 54) after a preliminary period of clinic treatment. Skin tests were made before starting treatment, after the 20000 unit dose, and on completion of treatment.

Discussion

The results of the skin tests are set out in composite form in Fig. 6. They demonstrate the marked reduction of the skin reactions, both prick and intradermal tests, following treatment. This reduction was quite definite in each individual case. Comparison of the reactions at the 20000 unit dose stage of treatment with those before treatment shows a 37 per cent reduction of the average wheal diameter for the prick test and a 27 per cent reduction for the intradermal test. In all patients at this stage the prick reactions were definitely reduced, but a number of the intradermal reactions were not appreciably diminished. It had been established previously that the average patient does not exhibit any significant reduction of the prick test reactions until treatment to a dose of the order of 5000 units has been given. The present results indicate that a higher dose than this is necessary before the intradermal reactions

show a significant reduction in size.

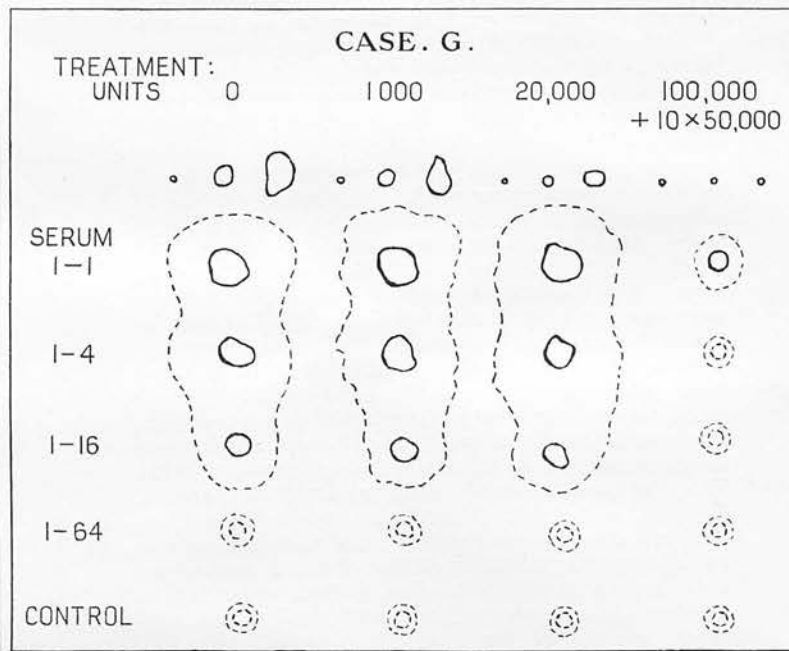
These findings are in agreement with the writer's previous conclusions that a reduction in size of the specific skin reactions is regularly induced by specific pollen therapy provided that sufficient dosage of potent pollen extract is administered (Harley, 1933a). The matter of dosage would appear to be of major importance if the intradermal test reactions are to show a significant reduction, and this may explain in part the failure of many investigators to detect a diminution of the intradermal reactions in patients who have received only moderate doses of pollen extract, e.g. 10000 units or less (Cooke, 1922; Levine & Coca, 1926; Rackemann, 1931; Cooke et al., 1935a), whereas other workers have reported a reduction of the scratch and prick reactions in patients given similar treatment. Allowance must be made also for possible variations in the potency of the extracts used by different workers, especially when we consider that at present there is no established chemical test for the potency of pollen extracts.

This question of potency was first brought to the writer's notice in 1934 by the following incident. A hay fever patient presented himself for investigation with the history that he had been treated with a certain brand of mixed grass pollen extract during the previous spring and had reached a dose of 100000 units but had not obtained satisfactory relief from his hay fever that year, and in spite of having a dose of 100000 units

repeated at monthly intervals after the season, the skin reactions were not appreciably diminished. When tested with the writer's pollen extract he gave large reactions. He had with him a sample of the pollen extract with which he had been treated. This was labelled as 50000 units of mixed grass pollen extract per c.c. This extract was then found to have a skin-reactive potency equivalent to that of the writer's 3000 units per c.c. extract (by comparative skin tests). According to the writer's standard of potency the patient had been having a dose of only 6000 units. The patient was treated by the writer and finally reached a dose of 100000 units, with abolition of the skin reactions (prick test) and complete relief from hay fever.

In view of this, a number of grass pollen extracts were obtained from various commercial houses and their skin-reactive potencies were tested on a group of hay fever patients, taking care to select comparable skin sites for each test. Very considerable variations of potency were found. Fig. 7 gives the reactions of a group of 5 hay fever patients to the most potent and the least potent of these extracts and to two dilutions of the writer's extract. Sample C (mixed grass pollen extract, 60000 units per c.c.) the most potent of the series, is seen to be practically as good as the writer's 50000 unit strength, while sample D (mixed grass pollen extract, 50000 units per c.c.) is rather weaker than the writer's

Figure 8



The Effect of Pollen Therapy on the Skin Sensitivity and Serum Idiocyte of Case G

The top part of the diagram represents the patient's skin reactions (wheals only) to saline, to 5000 unit pollen extract, and to 50000 unit extract, by the prick method. The reactions of normal skin sites, sensitized with the three sets of serum dilutions, to intradermal injection of pollen extract are shown underneath (dotted line represents erythema).

The hay fever serum was diluted 1-1, 1-4, 1-16, 1-64, and 1-256; 0.1 c.c. of each was injected intracutaneously in a normal receptive individual; 24 hours later 0.02 c.c. of pollen extract (2000 units per c.c.) was injected into the sensitized sites and into a control site. The intradermal technique was used here in preference to the prick method in order to obtain the maximum reactions. The same normal subject was used throughout for the passive sensitizations to ensure comparable results.

-- from Harley, D.: (1933a) Lancet, 2, 1469.

5000 unit strength extract.

It was concluded therefore that pollen therapy results in a reduction of the skin sensitivity provided that a sufficient dosage of potent pollen extract is administered. This is in agreement with previous reports from St. Mary's and other clinics that the skin sensitivity is reduced and can be abolished entirely if suitable dosage is given (Freeman, 1930, 1933; Markin, 1931; Brown, 1932; Harley, 1933a, 1935a). It is of interest that several workers who formerly denied that pollen therapy had any appreciable effect on the skin sensitivity have now changed their opinion (Sherman, Stull, & Cooke, 1940).

2. THE EFFECT OF POLLEN THERAPY ON THE SERUM IDIOCEPTOR

In a detailed investigation of 10 cases it was found that the serum idioceptor was markedly reduced by pollen therapy (Harley, 1933a). Figure 8 shows the results in one of the cases, which was quite typical of the series. It was found that the reduction of serum idioceptor only occurred with very large doses and only by continuing with large doses after the skin sensitivity (as tested by the prick test) had been abolished. This conclusion was in agreement with that of Markin (1931). Reports by Levine & Coca, 1926; Gay & Chant, 1927; Cooke et al., 1935a; had stated that no such reduction of serum idioceptor took place. It is of interest that

Cooke and his collaborators who previously denied any reduction of serum idioceptor, have now observed a decrease or loss of serum idioceptor in about 50 per cent of a series of cases treated over a period of years (Sherman, Stull, & Cooke, 1940).

3. CLINICAL RESULTS OF POLLEN THERAPY

Heavy dosage pollen therapy aims at abolishing the patient's skin sensitivity prior to the commencement of the hay fever season. The abolition of skin sensitivity appears to go hand in hand with the abolition ^{of mucous membrane sensitivity} so that the patient who no longer reacts to the test dose of pollen extract in the skin no longer reacts to the atmospheric pollen coming in contact with the nose and eyes. It is the experience of the St. Mary's Hospital Hay Fever Clinic that complete relief from hay fever can be practically guaranteed if treatment is carried to the length of abolishing the specific skin reactions (Freeman, 1930, 1933; Harley, 1933a, 1935a). The writer is in agreement with Brown (1932) who describes his results as 'almost monotonously perfect'. The results of treatment by earlier workers were reviewed by Rackemann (1931) and Coca, Walzer, & Thommen (1931); they give the percentage of cases obtaining complete relief as 10 - 30. The dosage in most of the cases rarely exceeded 10000 units. Rackemann, Graham, & Scully (1926) were of the opinion that there is an optimum dose for each patient

and that poor results are obtained by exceeding this; I am in agreement with Brown (1932) who thinks their error lay in continuing to increase the doses, during the hay fever season, of patients who were not well desensitized. Inadequate dosage appears to be the reason for the poor results of the earlier reports and it is interesting to note in the literature of the past few years that many clinics are now employing larger dosage and are obtaining much better results than previously.









4. IMMUNE BODIES ENGENDERED BY POLLEN THERAPY

In 1935 Cooke, Barnard, Hebal, & Stull obtained clinical improvement in a series of previously untreated ragweed fever patients by the transfusion of blood from other ragweed cases that had received a course of ragweed pollen extract injections with consequent relief from symptoms, indicating the presence of some transferable protective property in the blood of the donors. These workers then made passive transfer experiments with the serum of ragweed cases taken before (serum A) and after (serum P) a course of treatment with ragweed extract. They found that serum A - pollen extract mixtures, on injection in the skin of normal non-allergic test individuals, gave rise to immediate reactions, and provided that the mixtures contained sufficient pollen extract, the skin sites failed to react to ragweed 48 hours later. Similar mixtures made

with serum P, however, produced no reactions on injection on non-allergic persons, but when the mixture sites were injected with ragweed 48 hours later marked reactions were obtained. The serum P - pollen mixtures required for their neutralization ten times the amount of pollen extract necessary for serum A - pollen mixtures, though titration of the serum P failed to show any increase of idioceptor compared with serum A. Cooke et al. concluded that the serum of treated ragweed-sensitive patients contained a special type of specific immune antibody which did not appear to be an anti-pollen antibody (since it did not precipitate or inactivate ragweed extract) but which inhibited the reaction of the sensitive cells to ragweed. This effect appeared to be specific. Evidence that a similar reaction-inhibiting-substance occurs in grass-pollen-sensitive patients under treatment with grass pollen extract is afforded by the following experiments (Harley, 1937a):—

Methods. A group of twelve hay fever (grass-pollen-sensitive) patients was investigated. These received treatment to 100000 units when treatment was stopped. All patients showed a marked reduction of skin sensitivity and complete relief from hay fever following the treatment. Serum was obtained from each patient before (serum A) and after (serum P) treatment. In general, the passive transfer methods used by Cooke et al. (1935a) were employed, viz., the intradermal injection of mixtures

Figure 9.

MIXTURES	REACTIONS TO	
	(A) MIXTURES	(B) POLLEN EXT. 24 HRS. LATER
1 { SERUM A. + POLLEN EXT.		
2 { SERUM A. + SALINE		
3 { SERUM P. + POLLEN EXT.		
4 { SERUM P. + SALINE		
CM. 5- 4- 3- 2- 1-		
SERUM OF PATIENT N°1. TEST SUBJECT B.		

Reactions of Normal Skin Sites to (A) Serum-Pollen Mixtures and (B) Pollen Extract 24 hours Later

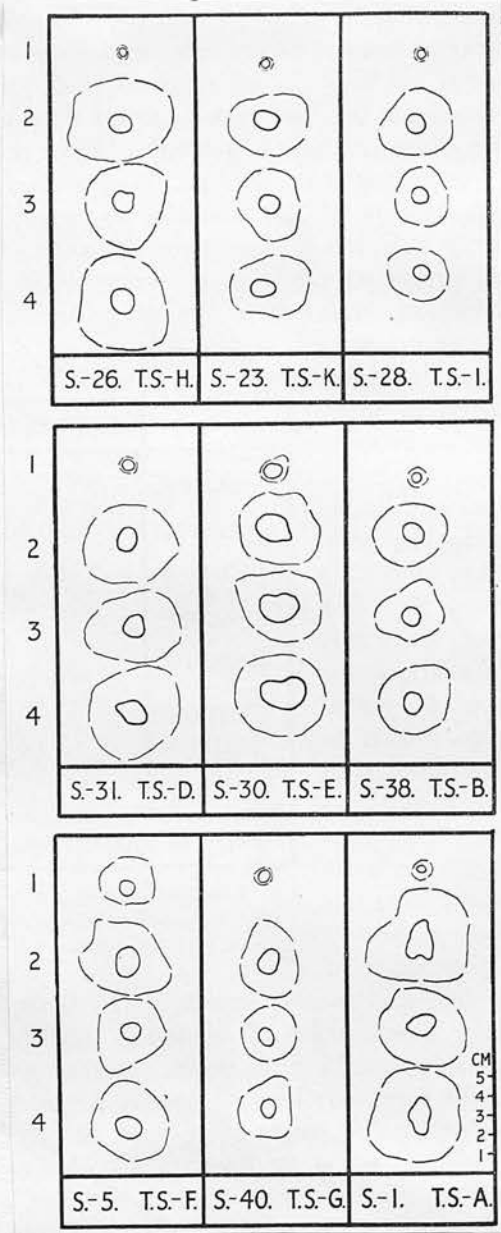
Technique: Each of the test mixtures was made up as follows-

No.	Equal volumes
1	Serum A + pollen extract (200 units per c.c.)
2	" + saline
3	Serum P + pollen extract (200 units per c.c.)
4	" +saline

The mixtures were placed in the ice-chest. The following morning 0.1 c.c. of each mixture was injected intradermally in a non-allergic test subject; mixture 1 proximally, mixture 2 distally, in one forearm, and mixtures 3 and 4 likewise in the other arm. After an interval of 45 minutes the reactions were recorded. Next day the mixture sites were reinjected with 0.025 c.c. of pollen extract (2000 units per c.c.) and the reactions recorded in 12 minutes.

- from Harley, D.: (1937a) J. Path. Bact., 44, 589.

Figure 10.



Reactions of Serum-Pollen Mixture Sites to Pollen Extract 24 Hours After the Mixtures Were Injected

- 1 Serum A + pollen extract
- 2 " +saline
- 3 Serum P +pollen extract
- 4 " +saline

S = Serum of patient No. - T.S. = Normal test subject

of serum A and P with pollen extract and with saline in normal non-allergic test subjects susceptible to passive transfer, observation of the ensuing reactions, and the reinjection of each mixture site with pollen extract 24 hours later.

A. The Reactions of Serum - Pollen Mixtures in Non-
'Allergic Test Subjects

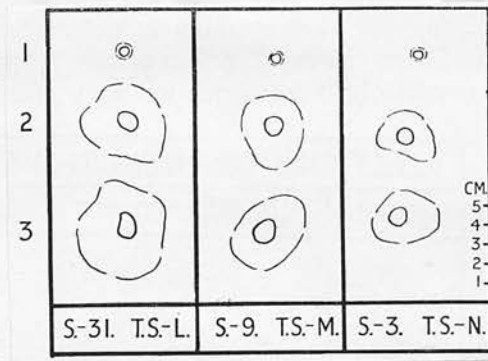
Comparison of the reactions of serum A - and serum P - saline mixture sites to pollen extract showed that no marked reduction of sensitizing power of the serum had occurred as the result of treatment (Figs. 9 and 10). It had been reported previously that a reduction of sensitizing power is obtained only if massive dose treatment is continued after the skin sensitivity is abolished. In the present series of cases the skin sensitivity was markedly reduced but not abolished. All serum A - pollen mixtures gave rise to reactions which reached their maximum in 45 - 60 minutes. This is in agreement with the findings of Chant & Gay (1927), Gay & Chant (1927), Foran & Lichtenstein (1931), Cooke et al. (1935a), and those of the writer recorded previously (Harley, 1933b). The reinjection of these sites with pollen extract 24 hours later produced no reactions, with the exception of the site of mixture S.-5; patient No. 5 however had received treatment the previous year so that the serum A was not strictly ante-treatment serum. This indicated that the idioceptor had been inactivated or

neutralized as the result of the reaction occurring at the time the mixtures were injected. The serum P - pollen mixtures, on the other hand, produced negative or very feeble reactions at the time of injection, but when the sites were tested with pollen extract 24 hours later marked reactions resulted, practically as large as those of the serum P - saline mixture sites.

These results are interpreted as indicating the presence of a reaction-inhibiting substance in serum P. This substance did not inactivate or destroy the idioceptor since the serum P - pollen mixture sites were shown to be fully reactive to pollen 24 hours later, which suggests also that the reaction-inhibiting-substance was itself rendered inactive or removed from the skin site by that time. It was found that the failure of these serum P - pollen mixtures to produce reactions was not due to a destruction or inactivation of idiotoxin since, on injection in hay fever patients, they induced skin reactions as large as those of serum A - pollen mixtures[⊗]. Also there was no anti-pollen precipitin found in any of the sera. It was then shown that a

⊗ It has been reported previously (Harley, 1933b; and Chapter III, p. 23) that serum A on incubation with small quantities of pollen extract renders the latter inactive in the hay fever skin. This effect was found to be without influence on the capacity of the mixtures to react in normal skins, and is therefore unrelated to the inhibiting action present in serum P described above.

Figure 11.



Reaction of Serum-Pollen Mixture Sites to Pollen Extract
24 Hours After Mixtures Were Injected. Serum P mixtures
 prepared (A) immediately before injection and (B) 24 hours
 before injection.

1	Serum A + pollen extract	Prepared 24 hours before injection.
2	" P + " "	" "
3	" P + " "	Prepared immediately before injection.

- from Harley, D.: (1937a) J. Path. Bact., 44, 589.

reacting serum A - pollen mixture could be converted into a non-reacting mixture exactly similar to a serum P - pollen mixture by the addition of an equal volume of a serum P at the time the mixtures were made up. It was found that the addition of serum from normal individuals was without such inhibiting effect. The above results are in close agreement with those obtained by Cooke et al. (1935a) in ragweed-sensitive cases and they demonstrate the presence of a reaction-inhibiting substance in the serum P of grass-pollen sensitive patients.

B. The Reaction-Inhibiting Substance

Though the above experiments had indicated that the R.I.S. (reaction-inhibiting substance) did not produce its effect by inactivation of either idioceptor or idiotoxin it was thought possible that the inhibition effect induced in serum A mixtures by the addition of serum P was due to some action in vitro of the R.I.S. on (i) idioceptor, (ii) idiotoxin, or (iii) both. The following experiments were made to test this hypothesis.

(i) Action of the R.I.S. on Idiotoxin. Test subjects were injected with serum P - pollen mixtures prepared (a) 24 hours before, and (b) immediately before, injection. No reactions were obtained at the time the mixtures were injected and the reinjection of the sites with pollen extract 24 hours later gave rise to similar reactions at both sites (Fig. 11).

Figure 12.

	REACTIONS TO		REACTIONS TO		REACTIONS TO	
	MIXTURES.	POLLEN EXT. 24 HRS. LATER	MIXTURES.	POLLEN EXT. 24 HRS. LATER	MIXTURES.	POLLEN EXT. 24 HRS. LATER
1						
2						
3						
4						
5						
	SERUM A.-24. SERUM P.-25.	T.S.-A.	SERUM A.-23. SERUM P.-2	T.S.-D.	SERUM A.-33. SERUM P.-5.	T.S.-O.

CM
5
4
3
2
1

Reactions of Normal Skin Sites to (A) Serum A - Pollen - Serum P Mixtures and (B) Pollen Extract 24 Hours Later

- | | | |
|---|-------------------|--------------------------------------|
| 1 | Serum A +saline | } Prepared 24 hours before injection |
| 2 | " +pollen extract | |
| 3 | " + " " +serum P | |
| 4 | " + " " + " | |
| 5 | Serum P +saline | Prepared immediately before |
| | | Prepared 24 hours before |

— from Harley, D.: (1937a) J. Path.,Bact., 44, 589.

This experiment indicated that the inhibiting effect was not dependent on any lengthy interaction between the R.I.S. and the idiotoxin in vitro.

(ii) Action of the R.I.S. on the Idioceptor. Mixtures were prepared as follows:-

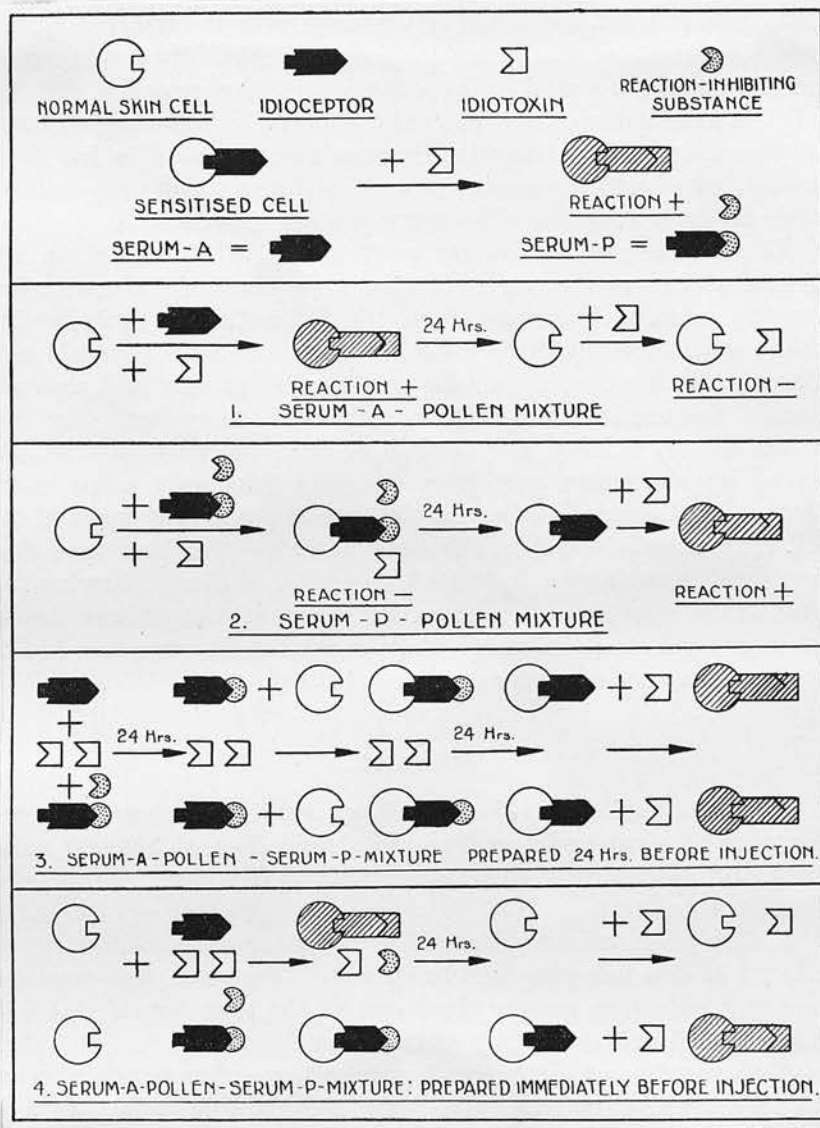
	2 vols.	1 vol.	1 vol.	
1	Serum A + saline	+ saline		Mixed 24 hours
2	" + pollen ext.	+ "		before
3	" + "	+ serum P		injection
4	" + "	+ "		Mixed immed. before
5	Saline + saline	+ "		Mixed 24 hrs. before

Pollen extract: 400 units per c.c.

One tenth of a c.c. of each mixture was injected in a test subject, the reactions recorded in 45 minutes and the sites reinjected with pollen extract 24 hours later.

The results (Fig. 12) demonstrated that the reaction-inhibiting effect produced in serum A - pollen mixtures by the addition of serum P was dependent on the addition being made some time before the mixtures were injected, in which case they behaved as serum P - pollen mixtures, producing no reaction on injection but leaving the sites reactive to pollen 24 hours later. On the other hand, the serum A - pollen - serum P mixtures which were put up immediately before injection gave rise to reactions similar to those of serum A - pollen mixtures and the reinjection of the sites with pollen produced reactions similar to those of serum P - pollen mixtures, the latter

Figure 13.



Diagrammatic Representation of the Reactions Produced by Serum-Pollen Mixtures

- from Harley, D.: (1937a) J. Path. Bact., 44, 589.

due presumably to the idioceptor of serum P that had escaped inactivation at the time of injection of the mixtures.

These experiments have suggested that the reaction-inhibiting effect was the result of an action of the R.I.S. on the idioceptor which prevented the latter from uniting with idiotoxin but which did not prevent its attachment to the skin cells.

Fig. 13 gives a diagrammatic representation of the reactions discussed above.

C. Discussion

The first problem which presents itself concerns the nature and origin of this R.I.S. Cooke et al. (1935a) have suggested that it may be a special type of immune body but admit that it is not an anti-pollen antibody in the usual sense of the term since it neither precipitates nor inactivates pollen extract. The production of a similar immune body by the injection of large doses of pollen extract in normal non-allergic subjects has been reported by Cooke, Loveless, & Stull (1937). The writer's experiments above indicate that the grass pollen R.I.S. is not an anti-pollen antibody but acts by attaching itself to the idioceptor and so prevents the idiotoxin from uniting with the latter. The other possibility is that the R.I.S. may be a direct derivative of the idiotoxin, a kind of inactivated idiotoxin which retains some

measure of specific immunological activity but is no longer capable of inducing the allergic reaction in sensitized cells. However, it remains for future work to determine its immunological nature. (The part played by the R.I.S. in the clinical desensitization process is discussed in Chapter VIII, p. 94).

CHAPTER VIII

THE MECHANISM OF SPECIFIC DESENSITIZATION (CONTD.):
DISCUSSION

That the clinical immunity induced in hay fever patients by pollen therapy is the result of inactivation of idioceptor is shown by the reduction or abolition of the skin sensitivity and, provided the pollen dosage is sufficiently high, by the loss of serum idioceptor. Such desensitization therefore would appear to be the result of a series of mild extensive allergic reactions. As has been already discussed (Chapter III, p. 13) the allergic reaction is believed to be the expression of cellular damage produced by the special method of specific idiotoxin-idioceptor union on or in the cells, and in common with other forms of cellular damage, is attended by the liberation of histamine (or a 'histamine-like' substance:- H-substance) from the cells participating in the reaction. What happens to the histamine substances formed as the result of this massive desensitization? Dale (1929) has shown that histamine in the circulation calls forth the secretion of adrenaline which neutralizes its action. Best & McHenry (1930) have demonstrated the presence of a histamine-inactivating enzyme in the tissues of the dog and other animals, especially in the kidneys and intestine. They showed that histamine, added to the perfusing fluid of organs in vitro, was removed and inactivated. The desensitization process in hay fever patients might therefore be expected to bring about an

increased tolerance of the body to histamine. In view of these considerations the histamine skin reactions of a series of 24 hay fever patients were measured before, during, and after treatment with pollen extract. It was found that the reactions to histamine were not in any way diminished by the treatment, though the reactions to pollen progressively diminished. At first sight this result may seem to discredit the histamine-tolerance theory, but when one considers that histamine is believed to be necessary for the physiological adjustment of the tone of blood vessels, it could not be expected that such a profound change of the blood vessels of the skin as would have been entailed by a reduced skin reaction to histamine could result from pollen therapy. The above result, therefore, does not in any way invalidate the histamine theory or lessen the probability that the histamine tolerance of the body as a whole may be increased.

The occurrence of general reactions during desensitization treatment is of interest in this connection. These reactions are produced by the injection of a larger dose than the patient can tolerate, or by the rapid dissemination of a smaller dose — e.g. injection into a vein. The action of histamine in the general circulation is neutralized by adrenaline (Dale, 1929); the general reactions are promptly relieved by adrenaline. It is a common occurrence during treatment to

find a point at which the patient has a general reaction; often, on decreasing the next dose and then working up more slowly, one can get the patient over the sticking point without further reactions. This would indicate that if the desensitization process is an allergic reaction accompanied by the liberation of histamine, as suggested, the tolerance of the body as a whole to histamine might be raised. Ramirez and St. George (1924) reported that the histamine tolerance of two allergic patients had been definitely raised as the result of successful specific treatment.

One very interesting observation which sheds some light on the problem from another angle was first reported by Freeman (1930) and has been confirmed frequently at the St. Mary's Clinic, namely, a hay fever patient who exhibits skin sensitivity also to say egg and horse idiotoxin, on being thoroughly desensitized to pollen, has the skin sensitivity to egg and horse definitely reduced, though this regains its former intensity in a few weeks. Now, if a normal skin site is sensitized with serum containing idioceptors for both pollen and horse, and is desensitized to pollen by one injection of extract, the site retains its full sensitivity to horse; also, the injection of pollen into a site sensitized to horse alone does not diminish its subsequent reaction to horse extract, nor does pollen extract have any desensitizing effect on the patient sensitive only to horse. The actual desensitization

process therefore is strictly specific, yet, as stated above, the repeated injection of pollen extract in a patient showing sensitivity to both pollen and horse leads to diminution of the skin sensitivity to horse in addition to the loss of sensitivity to pollen. The only feasible explanation that presents itself to account for the non-specific action of a process which is apparently strictly specific, in view of the absence of any decrease of the reaction of the skin to histamine, is that the sensitized cells as the result of repeated trauma by one specific idiotoxin-idioreceptor union in the cells, develop a temporary increase of resistance to trauma of the same type produced by other idiotoxin-idioreceptor unions. Thus, when the horse-pollen-sensitive patient is thoroughly desensitized to pollen and is then skin tested with a quantity of horse extract equal to that used before the desensitization course, the skin cells, though still containing their full complement of horse idioreceptor, suffer less damage by the horse idiotoxin-idioreceptor union and liberate less histamine, causing the blood vessels to give a diminished skin reaction. This mechanism might account also for the clinical improvement frequently reported to follow peptone and other forms of non-specific treatment of allergic diseases.

It has been shown previously (Harley, 1933a) that 1.0 c.c. of serum from an average case of hay fever requires over 40 and less than 400 units of pollen

extract for its complete neutralization in the normal skin site. The observations of Cooke et al., (1935a); Harley, (1937a); and Loveless, (1940) indicate 200 units for the average serum. On this basis calculation shows that the amount of idioceptor, allowing for fixed idioceptor, in a hay fever patient, would probably require pollen extract of the order of 2500000 units for its complete neutralization. This is in agreement with the amount of pollen required in practice to abolish skin sensitivity and serum idioceptor, and to give 'permanent' cure of hay fever, according to Brown (1934). The hay fever patient treated with moderate dosage leading to diminution of skin sensitivity, but insufficient to ensure complete neutralization of idioceptor, may have satisfactory relief from symptoms for that season, but after an interval there will be a redistribution of idioceptor from the serum to the skin with the return of a varying degree of skin sensitivity. The patient who has been completely desensitized, both as regards fixed and circulating idioceptor, is apparently a normal person as regards his reaction to pollen, and in order to become a hay fever subject again will have to manufacture a fresh supply of idioceptor. Whether such cases are permanently cured, as suggested by the results of Brown (1934) or not, remains to be seen, but the chances appear hopeful at least.

The part played by the R.I.S. in the process of therapeutic desensitization is rather debatable at the moment. The blood transfusion experiments reported by Cooke et al., (1935a) indicate that the R.I.S. can give a definite degree of clinical protection in the absence of any apparent change in the skin sensitivity or serum idioceptor. It is not clear however how the R.I.S. can produce a lowering of the sensitivity of the respiratory mucosa to atmospheric pollen, as shown by the clinical improvement, without producing a similar change in the sensitivity of the skin as shown by a diminished skin reaction to pollen extract. It is possible that the relatively inaccurate intradermal test, used by Cooke et al. failed to detect a partial reduction of skin sensitivity as the result of the action of the transfused idioceptor. A crucial point in support of the R.I.S. hypothesis would be the demonstration of a reduction of local skin sensitivity in the untreated hay fever patient following the intradermal injection of a serum P. The experiment was carried out in one case and the reaction of the treated site was found to be smaller than that of control untreated sites. In relation to general reactions occurring during treatment, it is probable that the R.I.S. plays a part, by slowing down the action of the injected pollen extract; the occurrence of reactions being due to dosage that overrides the R.I.S. blocking action.

CHAPTER IX

ALLERGIC RHINITIS (NON-POLLEN)

The symptom-complex typical of true hay fever can be produced in other sensitive individuals by a variety of specific irritants other than pollen. The inhalant or air-borne group of idiotoxins (animal epidermals, occupational dusts, orris root face powder, etc.) are the chief offenders, the ingestants etc. being only rarely responsible in uncomplicated cases. This type of allergic rhinitis is sometimes referred to as 'non-seasonal' hay fever in view of the non-seasonal nature of most of the idiotoxins involved, and its symptomatology, pathology, and immunological mechanism are precisely similar to those of seasonal hay fever.

The diagnosis is made from the symptomatology, clinical history, and the skin reactions; these methods are similar to those employed in bronchial asthma which are described in Chapter XIV, p. 138.

In allergic rhinitis the inhalant group of idiotoxins are more frequently responsible than are the ingestants. In the latter case other allergic manifestations such as urticaria or asthma usually accompany the rhinitis or precede it. With the inhalant cases in which asthma also occurs, the asthma

usually comes on after the nasal symptoms have developed. Irritation or itching of the eyes is always strongly suggestive of an inhalant cause.

The treatment consists of (i) specific avoidance, or (ii) specific desensitization (see Chapter XV, p.153).

Illustrative Case No. 1. Female aet. 19 years.

Occupation:- typist. Attacks of sneezing with a watery nasal discharge accompanied by itching of the nose and eyes. Duration 2 years. Father asthmatic. Patient suffered from eczema as a baby. The attacks usually came on after the morning toilet and occasionally at other times of the day. No marked seasonal variation. Skin tests: orris root - positive; other idiotoxins - negative. It was suggested to the patient that the attacks were associated with the use of face powder and she agreed. The patient was advised to change over to a brand of cosmetics free from orris root and this resulted in marked improvement of the rhinitis.

Illustrative Case No. 2. Male aet. 24 years. Complaining of violent sneezing with copious clear nasal discharge together with irritation of the eyes. The attacks occurred during the months April to October. Father suffered from hay fever. The patient had been seen previously by a specialist who reported positive skin reactions to grass pollens and diagnosed hay fever. A course of grass pollen therapy had not produced any clinical improvement.

Skin tests gave the following results: grass pollen - positive; horse hair - moderate positive; stock dust - slight positive; other idiotoxins - negative. The duration of the complaint (April to October) was too long for typical hay fever. It was elicited that the attacks occurred only at the weekends and during visits to a country cottage where the patient regularly spent his weekends from April to October. The symptoms were almost invariably present on awaking in the morning but they usually quickly cleared up after the patient went out of doors, and this in spite of the fact that he spent most of his time on the golf course, and he remained symptom-free until the following morning. The complaint seemed to be connected with his presence in the cottage. Extracts were prepared from dust taken from the bedroom and living rooms; to these the patient gave marked and moderate reactions respectively. The bedding included an old wool mattress (skin tests to wool were negative). In an attempt to determine the location of the causal idiotoxin, which appeared to be connected with the bedroom, the following clinical test was made:- First night: slept in neighbour's cottage on bed supplied by neighbour; result, no symptoms next morning. Second night: slept in neighbour's cottage on own bed moved in for the occasion; result, marked rhinitis next morning. Third night: slept in own cottage on bed borrowed from neighbour; result, very slight rhinitis only next morning. Forth night; slept

in own cottage on own bed; result, severe rhinitis next morning. The bed therefore appeared to be the culprit. Accordingly the patient was instructed to discard the bed in question and install a rubber mattress after a thorough cleaning of the cottage by vacuum cleaner. Since then he has remained quite free from the rhinitis.

The nature of the specific idiotoxin remained undetermined in this case, but it was possibly a mold in the mattress, especially as the bedding was stored in the cottage during the winter months when the retreat was unoccupied. The skin sensitizations to grass pollen and horse hair did not appear to have any causal significance in the rhinitis at the time the investigation was carried out.

Illustrative Case No. 3. Female aet. 26. Occupation:- housewife. Patient complained of attacks of sneezing with clear nasal discharge during the day time. Duration:- 5 years. Since childhood she had avoided eggs and foods containing eggs as thier consumption was immediately followed by oedema of the lips and mouth. Recently she had noticed that eating fish produced mild bouts of urticaria. The sneezing attacks occurred at frequent intervals practically every day and showed no seasonal variation, nor were they affected by change of environment. There had never been any eye symptoms with the rhinitis. Nose and

throat examination revealed no gross abnormalities. Skin tests showed a marked sensitivity to egg, moderate to wheat, and slight to fish. Reactions to other foods and to inhalants were negative. The patient was instructed to avoid wheat bread and cereals etc. and to substitute rye bread. This resulted in definite improvement of the rhinitis. A course of desensitization with a mixed extract of wheat, egg, and fish, was then given, the patient being on an egg-, wheat-, and fish-free diet. The rhinitis cleared up completely. Wheat and fish were then returned to the diet and did not produce any return of the rhinitis or the urticaria. The addition of egg however produced some irritation of the mouth and gastric discomfort and had to be discontinued. The patient remains symptom-free on a maintenance injection of the mixed extract every four weeks.

Bacterial Sensitizations

One frequently encounters patients with paroxysmal rhinitis in whom the clinical history gives no clue to a possible inhalant or ingestant causal idiotoxin and in whom the skin reactions are negative. Most of these cases are found to be due to bacterial sensitizations resulting from some infection of the upper respiratory tract. In these patients bacteriological examination shows the presence of quantitative or qualitative abnormalities (bacteriological methods are described in Chapter XIV, p. 147). A family history of allergy and

and the presence of, or history of, other allergic manifestations in the patient may be negative. Also, the nasal symptoms are not referable to contact with any extrinsic idiotoxin and the attacks are often worse in cold damp weather (though in certain cases dry dusty weather aggravates the sneezing - see illustrative case No. 4) and the nasal discharge is commonly thicker and less copious than in the hay fever type of sensitization. Signs of sinus infection may be present and the nasal mucosa is injected in most cases in contrast to the pale oedematous mucosa of the hay fever type. It should be noted however that a bacterial sensitization may occur in the absence of signs of acute or chronic infection. Eye irritation is very rare in the bacterial cases, and itching of the nose, throat etc., common in the inhalant idiotoxin type, is seldom present.

Illustrative Case No. 4. Male aet. 54. Complained of attacks of sneezing, accompanied by a nasal discharge, chiefly in the summer months and aggravated by dry dusty weather but occurring at intervals at all times of the year, together with a general feeling of stuffiness in the nose between attacks. There was also a certain amount of nervous irritability and inability to concentrate. On questioning the patient it was found that the attacks had no clear-cut onset or termination and that the discharge was slightly muco-purulent. There had never been any itching of the eyes. The family history was negative for allergy, as was the patient's previous

history. Skin tests with pollens and other idiotoxins were negative. The naso-pharyngeal mucosa was injected. There was no indication of sinus infection. Culture of the post-nasal secretion yielded a heavy growth of a Gram-negative coccus of the micrococcus catarrhalis group. The condition was diagnosed as a bacterial sensitization and complete relief was subsequently obtained by a course of autogenous vaccine therapy.

Reflex Nasal Type

A condition simulating allergic rhinitis may be produced by structural nasal abnormalities such as a badly deflected septum. In cases of this type the patient often awakes in the morning free from symptoms but immediately on arising the attack starts, before any exposure to a possible idiotoxin, such as orris root in tooth paste etc. In these nasal reflex cases the precipitating factors appear to be the change of position and slight chilling of the body. Changing from a warm stuffy room to the cool outside air, or the reverse, may act in the same manner. Allergic history and skin reactions are usually negative, and itching of the nose is absent. In uncomplicated cases there is no evidence of nasal infection. Treatment is surgical.

Illustrative Case No. 5. Female aet. 23 years. Attacks of paroxysmal sneezing with some watery discharge. The attacks occurred almost exclusively in the morning

immediately on arising and were worse in winter. There were no eye symptoms. The family history and the patient's previous history were negative for allergy. Skin tests were negative. Bacteriological examination showed no obvious infection. Nasal examination revealed a badly deflected septum. The condition was diagnosed as reflex rhinitis and complete relief resulted from resection of the septum.

Mixed Types

Though the various types of paroxysmal rhinitis have been discussed separately, it often happens, as in asthma, that more than one type of causal mechanism is involved in the same patient - infection being *super-*imposed on a true allergic rhinitis or mild degrees of sensitivity to inhalants developed as the result of the bacterial trauma to the nasal mucosa in patients with an allergic hereditary factor.

The presence of gross nasal abnormalities such as a deflected septum or polypi in cases with an allergic basis (bacterial or non-bacterial) is fairly common, but the writer is strongly of the opinion that the correction of these by surgical methods should be deferred until after a course of specific treatment has been given and not as the first step in the treatment. Surgical interference as the primary treatment sometimes does afford relief of symptoms but frequently leads to an extension of the sensitization with the

development of asthma, which renders the specific treatment less satisfactory.

Illustrative Case No. 5. Female aet. 20 years. Occupation:- office worker. Attacks of sneezing with nasal discharge, occasionally accompanied by mild asthma. Duration:- 2 years. Nasal polypi had been removed 9 months previously with slight temporary relief only. The family history was positive for allergy but the patient did not give a history of previous allergic trouble. The attacks occurred chiefly during the day time and were worse in winter. There were no eye symptoms with the rhinitis. The nasal mucosa was injected. Skin tests showed a slight sensitivity to horse hair, feathers, orris root, and pollen (grass). Culture of the post-nasal secretion yielded a pure growth of pneumococcus. The bacteriological evidence, together with the clinical history, suggested a bacterial sensitization. There was no correlation between the symptoms and exposure to horse hair, feathers, orris root, or grass pollen. The condition was diagnosed as a bacterial sensitization primarily. Autogenous vaccine treatment was carried out and complete relief from the rhinitis was obtained.

S E C T I O N I I A S T H M A

CHAPTER X

INTRODUCTORY

The evolution of the asthmatic state can be divided into three parts:-

(i) The predisposition of the individual to become hypersensitive, which is commonly inherited but may also be acquired. The exact nature of the underlying biochemical or immunological kink is unknown, as has already been mentioned in connection with hay fever.

(ii) The development of hypersensitivity to one or more of a wide variety of foreign substances. Contact with the offending substances then results in the violent reactions characteristic of the hypersensitive state — the basis of which is spasm of smooth muscle and increased permeability of blood capillaries. Though the hypersensitivity is developed commonly to substances with which the individual came into close and repeated contact before the commencement of the asthma, this is by no means constant and the capriciousness of the selection of sensitizing substances is well known. When the sensitive state is first established the specificity of the reactions is usually very definite, the horse-sensitive asthmatic reacting to the hair and dandruff of horses but not to that of dogs or cattle. More commonly the sensitivity is multiple but specificity is still a

prominent feature. After a time the asthmatic tends to have his attacks precipitated by one or more of a wide variety of non-specific factors unrelated to the primary specific cause:—

(iii) Secondary non-specific factors. These include nearly all possible forms of minor trauma - toxic and psychic, direct and reflex, dietetic indiscretions, etc. It has been suggested that these act by lowering the 'tolerance' of the asthmatic to the primary specific irritants, thus enabling the latter to provoke an attack in even more minute doses than is usually necessary.

Hypersensitivity to Non-Bacterial Products

These include the inhalants (animal epidermals, pollens, occupational dusts, etc.) acting directly on the lungs, and ingested and injected substances (foods, drugs, sera, etc.) which reach the sensitive lung tissue via the blood stream. The immunological mechanism is precisely similar to that of pollen allergy which has already been discussed in detail (Chapter III, p. 12).

Hypersensitivity to Bacteria and Their Products

One is impressed by the large number of asthmatics presenting themselves for investigation and treatment in whom the asthma first appeared after, or in association with, some infective process - often comparatively mild infections of the respiratory tract. Most of these cases give negative or only very feeble skin

reactions to inhalant and ingestant idiotoxins but bacteriological examination almost constantly reveals the presence of marked quantitative or qualitative abnormalities. The satisfactory results of vaccine therapy in the majority of these cases support the hypothesis that the relationship between the bacteria and the asthma is one of cause and effect. However it must be admitted that the precise nature of the mechanism by which the infectious process produces the asthma is by no means clear. Such hypersensitivity to bacteria is of quite a different immunological character to that of hypersensitivity to non-bacterial idiotoxins. In the latter the skin reactions are of the immediate type, consisting of urticarial wheal with surrounding erythema, fully developed in 10 - 15 minutes, and passive transfer of the sensitivity to the skin of a normal non-allergic individual by the injection of serum from the sensitive person can be accomplished with regularity. Though immediate skin reactions to bacterial vaccines have been reported occasionally, the common type of reaction is a delayed one, similar to the tuberculin reaction. which takes 24 hours or more for its development, and passive transfer of sensitivity by the injection of serum from the sensitive person is not obtained.

Bacterial skin tests in the diagnosis and treatment of bacterial-sensitization asthma have been widely used in recent years, especially in America. The usual method

is to prepare vaccines or extracts of the bacteria of the sputum etc., and to test the patient's skin reaction to these (Thomas, 1930; Touart, 1930; Thomas & Touart, 1933; Brown, 1934). Those preparations which produce reactions (immediate or delayed) are employed for therapeutic purposes. Unfortunately these vaccine skin tests have proved unsatisfactory as it has been found that non-asthmatics often give similar reactions to the vaccines, and also that vaccines of the normal intestinal Gram-negative bacilli often cause bigger reactions in the skin of the asthmatic patient than do the actual infecting organisms from the sputum (Rackemann, & Graham, 1933; Benson, 1933).

The state of bacterial allergy is regularly induced in man and animals by natural infections; for example, the tuberculin reaction and the reaction of the convalescent pneumonia patient to pneumococcus nucleoprotein and type carbohydrate. The majority of 'normal' individuals give a skin reaction to *B. coli* vaccine, presumably because their tissues have been in contact since infancy with the coliform bacillus and its products, so this may be regarded as an 'allergy' normal to man.

The presence of such bacterial allergy in asthmatic patients therefore is not in itself proof that the particular organism producing any, or the biggest, skin reaction, is the one responsible for the asthma. At present we have to rely chiefly on the clinical history, the absence of skin reactions to non-bacterial idiotoxins

and the bacteriological examination, to guide us in the diagnosis and treatment of bacterial-sensitization asthma.

CHAPTER XI

BACTERIAL ALLERGY. SPECIFICITY OF VACCINE SKIN REACTIONS

It is a well established belief that certain diseases of man, such as bacterial asthma, rheumatoid arthritis, etc. are expressions of allergy to bacteria and their products, presumably combined with a lack of immunity. Accordingly, attempts have been made to identify the organisms responsible for the particular condition by preparing vaccines of all the available organisms from the patient and injecting these into the patient's skin; the organism producing the biggest reaction is assumed to be the culprit. Though our knowledge of the mechanism of bacterial allergy is far from complete, many clinicians use the above method as a guide to vaccine therapy. Opinions on the theory and rationale of the method vary widely. There is at present little or no experimental evidence concerning the specificity or otherwise of skin reactions to bacterial vaccines, most of the evidence in favour of this method of vaccine selection being either clinical or presumptive, i.e. by analogy with the pollen reaction in hay fever, the tuberculin reaction, or the toxin reactions in individuals susceptible to scarlet fever and diphtheria.

EXPERIMENTAL INVESTIGATIONS (Harley, 1935b)

It was planned to study the mode of development and the specificity of the skin reactions of rabbits to

pneumococcal vaccines and other preparations. In brief, rabbits were injected with vaccines of virulent and avirulent pneumococci by the intravenous and intracutaneous routes, and their skin reactions, serum agglutinins, protective and anaphylactic antibodies were measured before and after treatment.

Experimental Methods

Cultures. Pneumococcus types 1 and 2, both of high virulence; an intraperitoneal injection of 2×10^{-8} c.c. of a 17 hour culture (approximately 10 cocci) regularly kills mice in less than three days. Avirulent (R) pneumococcus, obtained from the type 1 virulent strain by cultivation in homologous immune serum. Mice survived 0.5 c.c. undiluted culture (250000000cocci) intraperitoneally. Strains of staphylococcus albus, streptococcus viridans, and B. coli were employed also.

Vaccines. Pneumococci were grown in 2 per cent rabbit serum broth for 17 hours; the cultures were then enriched by the addition of half their volume of glucose broth and were incubated for a further $2\frac{1}{2}$ hours. The organisms were collected by centrifuge, resuspended in saline, and immediately heated to 60°C. for 50 minutes. The object was to obtain young organisms killed with the minimum of autolytic change. The streptococci were grown in serum broth, the B. coli and the staphylococcus in plain broth; all were collected and killed as above.

Immunization and Sensitization of Rabbits. Each animal received 4 doses of 1.0 c.c. of pneumococcal vaccine (each equivalent to 10 c.c. of the original culture) at 2 week intervals by the intravenous or intracutaneous route. The intracutaneous doses were given in 5 injections of 0.2 c.c. into a depilated strip of skin on the back close to the spine, and consecutive sets of injections were given on alternate sides.

Skin Sensitivity Tests (Kahn's method, 1933). Intracutaneous injections of 0.1 c.c. of the following dilutions were made into the depilated skin of the flanks, viz. undiluted (representing an equal volume of original culture in the case of the pneumococcal vaccines; the other vaccines were diluted to corresponding strength) and diluted 1-10, 1-100, 1-1000, 1-10000, and 1-100000, in saline. Skin tests with specific carbohydrates were made by injecting 0.1 c.c. of solutions containing 2.5 mg. per c.c.. The reactions were measured by tracing on to glass slides when they were at their maximum.

Agglutinins and Anaphylactic and Protective Antibodies.

Technique described previously (Harley, 1934).

Table 3.

A. Agglutinins for virulent (S) and avirulent (R) pneumococci.

Rabbit no.	Injected with vaccine of	Route.	Type 1.					Type 2.		Avirulent.				
			1/2·5	1/5	1/12·5	1/25	1/50	1/2·5	1/5	1/25	1/50	1/125	1/250	1/500
1	Type I virulent	IV	++	++	++	+	±	0	0	++	++	+	±	0
2	„ „	IC	+	±	0	0	0	0	0	++	++	+	±	0
3	Avirulent .	IV	0	0	0	0	0	0	0	++	++	++	+	±
4	„ .	IC	0	0	0	0	0	0	0	++	++	++	+	±

++, +, ± and 0 represent respectively complete, partial, trace and absence of agglutination.

IV = intravenous. IC = intracutaneous. Controls (not shown) negative. Sera obtained before treatment did not agglutinate in above dilutions.

B. Protective action of sera for mice. Animals received 0·5 c.c. of serum intraperitoneally and were tested against the living organisms the following day.

Test dose of pneumococci.		Mice receiving serum of rabbit no.				Control mice (untreated).
		1	2	3	4	
Type 1	10 organisms	—	—	—	—	D 2
	10 ² „	—	—	—	—	D 2
	10 ³ „	—	—	—	—	D 2
	10 ⁴ „	S	S	D 2	D 1	—
	10 ⁵ „	S	D 2	D 1	D 2	—
	10 ⁶ „	S	S	D 1	D 1	—
	10 ⁷ „	S	D 2	D 1	D 1	—
Type 2	10 „	—	—	—	—	D 2
	10 ² „	D 2	D 3	D 2	D 1	D 2
	10 ³ „	D 2	D 2	D 2	D 2	D 2
	10 ⁴ „	D 2	D 2	D 2	D 2	—

S=survival. D=death. Number following=survival time in days. —=not done. Sera obtained before treatment did not protect mice.

C. Anaphylactic antibodies. Animals received 2·0 c.c. of serum intraperitoneally and were injected with 0·25 mg. SSS (in 0·1 c.c. saline) intracardially the following day.

Intracardial injection of	Guinea-pig receiving serum of rabbit no.			
	1	2	3	4
SSS1	++	±	0	0
SSS2	0	0	0	0

++ = acute anaphylactic shock with death in 2½ minutes.

± = mild shock : animal survived. 0 = no symptoms observed.

The development of antibodies in the sera of rabbits injected with vaccines of virulent (S) and avirulent (R) pneumococci by the intravenous and intracutaneous routes.

(Sera were obtained before treatment and 8 days after the last injection.)

Results

These are detailed in Table 3 and in Fig. 14. The vaccine skin reactions were tested 4 weeks after the last intravenous or intracutaneous injection. These reactions were of the inflammatory type, commencing 12 - 24 hours after the test injections and reaching their maximum size in about 48 hours; they subsided slowly, the larger taking several weeks to disappear completely. The specific carbohydrate ('SSS') tests were made 7 days after the last injection and the reactions were of a different character, starting earlier (3 - 6 hours), reaching their maximum size in 24 hours, being more haemorrhagic than inflammatory in nature, and clearing up more quickly than the vaccine reactions. Two months after these vaccine tests (three months after the last immunizing injection) the animals were retested; the vaccine reactions were found to be undiminished but no reactions were produced by the SSS. At this time the serum antibodies (type-specific agglutinins, protective and anaphylactic antibodies and R agglutinins) were no longer present. Two weeks later a fifth injection of the original vaccine preparation was given to each animal by the route previously employed. This resulted in the return of serum antibodies of slightly higher titre than before and the skin reactions to the SSS reappeared in rabbits Nos. 1 and 2.

Discussion

It is well known that the type of immunity which is associated with the presence of type-specific agglutinins and protective antibodies is induced in animals by the injection of vaccines of virulent encapsulated (S) pneumococci, while the avirulent unencapsulated (R) forms yield neither agglutinins nor protective antibodies for the virulent strains from which they were derived[⊗]. This is due to the presence of type-specific antigens in the S types. The 'specific soluble substances' (SSS) of the various types of S pneumococci are closely related to virulence and to type-specificity. The R organisms contain no SSS, and R forms derived from the various S types are serologically indistinguishable. The 'nucleo-protein' fractions of S pneumococci produce antibodies which are closely similar to those engendered by the R organisms.

We will now examine the relationship of the type-specific immunizing antigen and its antibody to anaphylaxis and allergy as exemplified by the above results.

[⊗] It has been reported by several workers that a low-grade non-specific immunity against virulent pneumococci is sometimes produced in animals by injection of the avirulent (R) organisms, without demonstrable serum antibodies for the former. The evidence on this point is rather conflicting and the matter awaits further study. Also, it has been shown that a high-grade heterologous immunity can be obtained with certain preparations of virulent pneumococci containing little or no type-specific antigen (Day, 1933; Harley, 1935c)

It is well established that the route of injection has a considerable influence on the antibody response of animals to vaccines (Julianelle, 1930; Kahn, 1933). The above results demonstrate that the intravenous route leads to excellent type-specific antibody formation, while the intracutaneous route is inferior in this respect (rabbits Nos. 1 and 2). The route of injection has no effect however on the R agglutinin response to either S or R vaccines. It would appear that the type-specific antigen is largely destroyed or inactivated in the skin and only a fraction escapes and reaches the site of antibody formation, while the somatic nucleoprotein, etc., is unaffected and produces R agglutinins in full amount. This is similar to the change in antigenicity of S pneumococci when they undergo complete autolysis at alkaline reaction in vitro, the type-specific antigen being destroyed and the nucleoprotein remaining. Parallel with the development of type-specific agglutinins and protective antibodies is the skin reaction to the SSS of homologous type and the capacity of the serum to render guinea-pigs anaphylactic to the homologous SSS. These three phenomena come and go in company. There seems little reason to doubt that these three types of reaction are expressions of the same immunological mechanism viz. the union of type-specific antigen (or its haptens the SSS) with the homologous antibody, and that the apparent differences are only quantitative variations of the common mechanism - 'immunity' when the antibodies react

in vivo with small quantities of antigen in the test dose of living organisms and render the latter vulnerable by the host; 'anaphylaxis' when the reaction takes place on a greater scale between the same antibodies and the antigen hapten in the tissue cells; and 'allergy' when it occurs in the skin.

In contradistinction to the type-specific antibody response, R agglutinins are engendered by the S and R vaccines equally and are quantitatively the same when the latter are given intravenously and intracutaneously. These R antibodies (nucleoprotein antibodies) are known to be responsible for the production of anaphylaxis to nucleoprotein.

The rabbits injected with S and with R vaccines intravenously show little or no increase of skin reactions to whole vaccines while the animals treated by the intracutaneous route develop a high degree of skin sensitivity to vaccines. The quantity of SSS necessary to elicit the type-specific skin reaction in the immune animal represents a very much larger volume of culture than that required for the production of the vaccine reaction in the sensitized animal. As shown above the immune rabbit (type 1 vaccine intravenously) reacted specifically to 0.25 mg. of SSS1 but the reactions to vaccines of types 1 and 2, in the strengths used, were negligible; though the type 1 vaccine contains some SSS1 the amount of the latter is insufficient to evoke the

specific reaction.

This condition of skin allergy to whole vaccines is induced by intracutaneous injections of S and R vaccines equally and is therefore independent of the type-specific antibody response and of allergy to the SSS; furthermore, this skin sensitivity does not seem to depend on the presence of R agglutinins, as the latter are present in the non-sensitive (intravenously injected) and in the sensitive (intracutaneously injected) animals to the same extent, and the skin sensitivity remains after the R agglutinins have disappeared from the circulating blood. The development of this type of allergy seems to depend on the production of repeated reactions between the skin cells and the sensitizing injections.

As the sensitizing injections resulted in general and not local sensitivity only, it would appear that some substance is produced by the interaction of the vaccine and the skin cells which leads to the sensitization of the skin as a whole. This is in agreement with the conclusions reached by Zinsser in his work on the tuberculin reaction.

In contrast to the strictly type-specific nature of the skin reaction to the SSS in the 'immune' animal, these vaccine reactions are not type-specific or even species-specific, the rabbits sensitized with type 1

and with R vaccines reacting equally to to types 1 and 2, to R, and to Streptococcus Viridans vaccines, though not to B. coli. or staphylococcus. The reaction-exciting substance common to the various types of pneumococci and the viridans streptococci is probably the somatic nucleoprotein; the nucleoproteins of the two species are immunologically similar, and Julianelle (1930) has demonstrated that rabbits sensitized by nucleoprotein and by vaccines react equally to the nucleoprotein in the skin. The immunological function of skin sensitivity of the delayed type reaction to whole vaccines is by no means clear and the matter awaits further study.

Summary

The state of skin allergy to pneumococcal vaccines is induced by intracutaneous injections of vaccines of virulent (S) and avirulent (R) pneumococci alike, and is independent of both type-specific and nucleoprotein (R) antibodies. It is non-type- and non-species-specific, the animal sensitized with one type of S pneumococcus reacting equally well to the other types, to R vaccine, and to Streptococcus Viridans vaccines. This type of allergy appears to be of the nature of an increased tissue reaction to the somatic nucleoprotein in contrast to an antigen-antibody reaction. It is independent of type and species circulating antibodies. Its immunological function is doubtful.

CHAPTER XII

BACTERIAL ALLERGY (CONTD.). RELATIONSHIP TO IMMUNITY

There has been considerable controversy regarding the place of bacterial allergy in the immunization process (see reviews by Tytler, 1930; Rackemann, 1931; Zinsser, 1931). Many workers regard the allergic state as an essential part of the immunological mechanism accompanying recovery from infection. Others oppose this view on the ground that allergy and immunity may exist independently and believe that their association in many natural infections is fortuitous. An examination of the literature suggests that much of the conflict of opinion is due to a failure to realize that there may be more than one form of bacterial allergy and that any given relationship between one form of bacterial allergy and say type-specific immunity does not necessarily hold for the other forms. The following experiments were carried out in rabbits in an attempt to analyse further the relationship of antipneumococcal immunity to cutaneous allergy to pneumococci and their products (Harley, 1937c).

Experimental Methods

Groups of albino rabbits were given 4 injections of type 1 S (virulent) or R (avirulent) pneumococcus vaccine by the intravenous or intracutaneous routes at 2 week intervals. The animals were bled 8 days after the last

injection and the sera were tested for type and species agglutinins. The following day all animals were skin tested with pneumococcus NP (nucleoprotein) and with vaccine. Three days later the animals were given an immunity test by injecting living cultures of pneumococci intracutaneously according to the method of Goodner & Stillman (1933).

Cultures, Vaccines, Immunization of Rabbits, etc. as described in Chapter XI, p. 110.

Skin Sensitivity Tests. (i) R vaccine: 0.1 c.c. of dilutions 1-10 and 1-100 injected intracutaneously in the depilated flanks; reactions recorded 48 hours later. (ii) NP: 0.25 mg. nucleoprotein in 0.1 c.c. of saline injected intracutaneously; reactions recorded 24 hours later.

Immunity Tests (Goodner & Stillman, 1933). Each animal received 0.2 c.c. of an 18 hour culture (serum broth) of type 1 pneumococcus intracutaneously in the flank. Rectal temperatures and extent and character of the local lesion were noted daily. Immunity was graded from - 1 (extensive local lesion; temperature above 105.5°F. persisting till death within 4 days) to - 7 (slight local lesion; no elevation of temperature; survival).

Table 5.

Rabbit no.	Skin reactions to			Grade of active immunity to pneumococcus type I.
	R vaccine.		nucleoprotein.	
	1:10.	1:100.		
1	0	0	++	+7
2	0	0	++	+7
3	0	0	++	+7
4	0	0	++	+7
5	±	0	++	+3
6	0	0	++	+4
7	0	0	++	+3
8	0	0	++	+3
9	+	±	++	+3
10	++	+	++	+3
11	++	+	++	+4
12	++	+	++	+3
13	0	0	±	+1
14	0	0	0	+1
15	0	0	0	+1
16	0	0	0	+1

Size of reactions : 0 = $< \frac{1}{2}$ cm. diameter.
 ± = $\frac{1}{2}$ -1 cm. „
 + = 1-2 cm. „
 ++ = > 2 cm. „

The development of skin sensitivity in
 rabbits Nos. 1 - 16.

— from Harley, D.: (1937c) J. Path. Bact., 45, 257.

Table 4.

Rabbit no.	Injected with vaccine of	Route.	Pneumococcus type 1.					R pneumococcus.				
			1:2.5.	1:5.	1:12.5.	1:25.	1:50.	1:25.	1:50.	1:125.	1:250.	1:500.
1	type 1 pneumococci	IV	++	++	++	±	0	++	+	+	±	0
2			++	++	++	+	0	++	+	+	±	0
3			++	++	+	±	0	++	+	+	+	+
4			++	++	++	±	0	++	++	+	+	±
5	avirulent (R) pneumococci	IV	0	0	0	0	0	++	++	+	+	±
6			0	0	0	0	0	++	++	++	±	+
7			0	0	0	0	0	++	++	+	±	0
8			0	0	0	0	0	++	++	+	+	±
9	avirulent (R) pneumococci	IC	0	0	0	0	0	++	++	+	+	0
10			0	0	0	0	0	++	++	+	++	0
11			0	0	0	0	0	++	+	+	+	0
12			0	0	0	0	0	++	++	+	+	±
13	Controls (untreated)	...	0	0	0	0	0	±	0	0	0	0
14			0	0	0	0	0	0	0	0	0	0
15			0	0	0	0	0	0	0	0	0	0
16			0	0	0	0	0	0	0	0	0	0

++, +, ± and 0 = complete, partial, trace of and absence of agglutination respectively.
 IV = intravenous. IC = intracutaneous.

The development of agglutinins in the sera of rabbits injected with vaccines of type 1 and avirulent (R) pneumococci by the intravenous and intracutaneous routes.

- from Harley, D.: (1937c) J. Path. Bact., 45, 257.

Table 4.

Rabbit no.	Injected with vaccine of	Route.	Pneumococcus type 1.					R pneumococcus.				
			1:2.5.	1:5.	1:12.5.	1:25.	1:50.	1:25.	1:50.	1:125.	1:250.	1:500.
1	type 1 pneumococci	IV	++	++	++	±	0	++	+	+	±	0
2			++	++	++	+	0	++	+	+	±	0
3			++	++	+	±	0	++	+	+	+	+
4			++	++	++	±	0	++	++	+	+	±
5	avirulent (R) pneumococci	IV	0	0	0	0	0	++	++	+	+	±
6			0	0	0	0	0	++	++	++	±	+
7			0	0	0	0	0	++	++	+	±	0
8			0	0	0	0	0	++	++	+	+	±
9	avirulent (R) pneumococci	IC	0	0	0	0	0	++	++	+	+	0
10			0	0	0	0	0	++	++	+	++	0
11			0	0	0	0	0	++	+	+	+	0
12			0	0	0	0	0	++	++	+	+	±
13	Controls (untreated)	...	0	0	0	0	0	±	0	0	0	0
14			0	0	0	0	0	0	0	0	0	0
15			0	0	0	0	0	0	0	0	0	0
16			0	0	0	0	0	0	0	0	0	0

++, +, ± and 0 = complete, partial, trace of and absence of agglutination respectively.
IV = intravenous. IC = intracutaneous.

The development of agglutinins in the sera of rabbits injected with vaccines of type 1 and avirulent (R) pneumococci by the intravenous and intracutaneous routes.

- from Harley, D.: (1937c) J. Path. Bact., 45, 257.

Results

These are detailed in Tables 4 and 5. The NP (nucleoprotein solution) reactions started within a few hours of the test injection, reached their maximum in 24 hours, when they consisted of an area of erythema 2 - 3 cm. in diameter, with slight oedema, and disappeared in 3 - 4 days. The NP reactions developed and regressed in a manner similar to that of the SSS (specific soluble carbohydrate) described previously (Chapter XI, p. 114) though they did not show any of ecchymosis common in the latter. The vaccine reactions did not reach their maximum size for 48 hours or more and subsided much more slowly than the NP reactions; necrosis of the skin with discharge of purulent matter occurred in the centre of the larger reactions.

Discussion

The above results show that the state of cutaneous allergy to the NP (nucleoprotein fraction) of pneumococcus is induced by treatment with S and R vaccine independently of whether the vaccine is given intravenously or intracutaneously. There is a close relationship between the presence of circulating R agglutinin (NP antibody) and the capacity to react to the NP. It is of interest that the control rabbit No. 13, which gave a slight reaction to NP, was the only control in which R agglutinin was found. This conclusion is in agreement with the

work of Julianelle (1930), who showed further that the state of allergy to NP was induced by treatment with NP as well as with vaccines and that the sensitive state was readily transferred to normal individuals by the injection of serum from the sensitive animal. It would appear probable that the skin reaction to NP is essentially an antigen-antibody reaction between the NP and its antibody.

There is clearly no relationship between the NP allergy and type-specific antibodies and type-specific immunity. It has been established by several workers that both S and R vaccines are capable of inducing a low-grade immunity to pneumococci generally. The above results with R vaccine are in agreement. Though this form of species immunity is associated usually with the presence of circulating NP antibodies, these are not interdependent, as it has been shown that the treatment of animals with NP does not induce any appreciable immunity though it engenders NP antibodies.

The state of allergy to whole vaccine also appears to be independent of this species immunity, since the former is induced by vaccine given by the intracutaneous route but not by the intravenous, while the latter results from vaccine by either route. It has been shown (Chapter XI, p. 118) that allergy to vaccine is independent of NP antibodies and that the animal sensitive to one type of pneumococcus is sensitive to the other types

Figure 15

RABBIT INJECTED WITH	ROUTE	SKIN ALLERGY TO			SERUM ANTIBODIES		ACTIVE IMMUNITY	
		SSS	NP	VACCINE	ANTI-S	ANTI-R	TYPE	SPECIES
S [VACCINE]	IV	++	++	-	++	++	++	⊥
S [VACCINE]	△IC	+	++	△++	+	++	+	⊥
R [VACCINE]	IV	-	++	-	-	++	-	⊥
R [VACCINE]	△IC	-	++	△++	-	++	-	⊥
NUCLEO- -PROTEIN	IV OR IC	-	++	-	-	++	-	-
PASSIVE TRANSFER BY INJECTION OF SERUM		+	+	-	+	+	+	?-
IMMUNOLOGICAL MECHANISM		A-A	A-A	CELLULAR REACTION ? NATURE			A-A	? CELLULAR REACTION ? NATURE

IV = INTRAVENOUS · IC = INTRACUTANEOUS ·
A-A = ANTIGEN-ANTIBODY REACTION

Diagrammatic representation of relationship of the different types of pneumococcal allergy and immunity.

- from Harley, D.: (1937c) J. Path. Bact., 45, 257.

and to Streptococcus Viridans. These limits of reactive-specificity correspond to immunological similarity of the NP fractions of the reacting organisms, so presumably the nucleoprotein is concerned in the reaction. The two types of reaction to nucleoprotein, namely to NP (nucleoprotein fraction obtained by chemical means and in solution) and to nucleoprotein contained in the bodies of the organisms of the heat-killed vaccine, are clearly different mechanisms. The former is closely associated with circulating NP antibodies and is transferable to normal animals by the injection of serum from the sensitive individual; the latter is independent of such antibodies and is not capable of passive transfer. The vaccine reaction would appear to be of the nature of an increased reactivity of the tissue cells as distinguished from an antigen-antibody reaction.

Summary

Figure 15 is an attempt to summarize and correlate the main points established up to the present concerning the immunological relationships of cutaneous allergy to pneumococcus NP, SSS, and vaccine.

These three types of allergy are immunologically independent. Allergy to the SSS is closely related to type-specific immunity. It seems likely that the manifestations of SSS allergy and of type-specific immunity depend on a common mechanism, namely an

antigen-antibody reaction between the type-specific antigen (or haptén) and its antibody.

Allergy to NP is dependent on the presence of circulating NP antibodies, is unrelated to type or species immunity and is essentially an antigen-antibody reaction between the NP and its antibody.

Allergy to vaccine is independent of circulating antibodies and of type and species immunity. It appears to depend on an increased reactivity of the tissue cells as opposed to an antigen-antibody reaction.

In conclusion, it is clear that no broad generalization on the relationship of 'allergy' to 'immunity' is possible, with reference to the pneumococcus at any rate, in view of the complexity of the phenomena of bacterial allergy and of their immunological relationships.

CHAPTER XIII
TYPES OF ASTHMA

Clinically, the two main types of asthma discussed above (bacterial and non-bacterial sensitizations) may occur separately or together, with varying predominance of one or other. The following classification is not claimed to be a complete one, but it serves as a guide to the treatment of asthma from the immunological standpoint.

- (a) Hypersensitivity to non-bacterial idiotoxins.
- (b) Ditto, plus secondary infections or toxaemias.
- (c) Bacterial-sensitization asthma.
- (d) Ditto, plus secondary non-bacterial sensitizations.

Type (a). The sensitivities may be single or multiple. Single sensitizations are rather uncommon, if one excludes the seasonal pollen cases, and the diagnosis is usually readily established from the history and the skin reactions. Multiple sensitivity is the general rule, though one sensitivity may predominate clinically. As this type of case becomes more chronic the sensitivities tend to become more multiple and less distinct, and the constant trauma to the mucous membrane of the respiratory tract encourages the entry of infections to complicate the picture (Type (b)). Alternatively, an infection may convert a sub-clinical sensitization

into an active one, by lowering the tolerance of the mucous membrane to the specific irritants. The same effect may take place indirectly e.g. toxins from a distant focus of infection reaching the lungs via the blood stream. It may be mentioned in this connection that many cases of so called food-sensitization, in which the asthma is definitely referable to the consumption of a particular food and is improved when that food is withheld, but skin reactions to that food are negative, are believed to be due to the effect of that food on an established intestinal infection, encouraging toxin production and absorption. In these cases the asthma does not usually develop till 12 or 24 hours after the consumption of the suspected food, in contrast to the short period between consumption and onset of symptoms in the case of a true food-sensitization (see Illustrative Case No. 12, p. 136).

Type (c). The asthma results from an infection of the respiratory tract. In the case of naso-pharyngeal infections, the asthma is often reflex. The history, bacteriological findings, and the absence of skin reactions to non-bacterial idiotoxins, establish the diagnosis. The lowering of the vitality of the mucous membrane by the infection may encourage the development of sensitivity to non-bacterial substances, particularly of the inhalant group, in individuals with a positive

family history of allergic disease (Type (d)). Bacteriological examination reveals the primary cause. Actually, in practice, it is usually difficult to differentiate between the (b) and (d) Types, that is, to decide whether the infection or the inhalant sensitivity is the primary cause, though it does not matter much as far as the treatment is concerned.

Taking the general run of cases, but excluding the seasonal pollen cases and the frankly asthmatic bronchitis group, it is the writer's experience that only in one case in every four or five is the diagnosis of specific hypersensitivity to non-bacterial idiotoxins (either to a single idiotoxin or a small number of idiotoxins) sufficiently clear-cut to allow of its classification as a Type (a) case and admit of its successful treatment by methods based on these findings alone. The remaining 75 - 80 per cent of cases consist of bacterial sensitizations (Type (c)) and mixed types (b and d) in about equal proportions.

The modern tendency to consider the asthmatic patient in terms of skin reactions to non-bacterial idiotoxins alone, and to institute treatment accordingly, though it may produce excellent results in the Type (a) patient, leads to disappointing results where the primary cause is bacterial. The writer is of the opinion that this is due partly to the intradermal

method of skin testing (Chapter XIV, p. 142) which frequently produces false positive reactions that are liable to be misinterpreted by the enthusiast in the absence of evidence of the presence of the corresponding clinical sensitivity, and partly to the failure to make a bacteriological examination of every patient in whom the skin reactions are multiple and indistinct.

Illustrative Case No. 7. Female aet. 7 years. Asthma for 4 years. Family history strongly positive for allergy. Eczema as a baby. The attacks were worse in the summer but the patient was never quite free from asthma at other times of the year. The attacks usually started after going to bed in the evening and often got worse in the early morning. No obvious food or locality factors. Skin tests: horse hair, feathers, and wool - strong positives. Other idiotoxins tested gave negative results. The symptoms occurred on exposure to the bedding materials and the skin reactions confirmed the diagnosis of sensitivity to horse hair, feathers, and wool.

Illustrative Case No. 8. Male aet. 24 years. Occupation: clerk. Asthma and eczema since the age of 3 years. Family history positive for allergy. The asthma came on between 2 and 3 a.m. and was rather worse in summer. The eczema showed no seasonal variation. Skin tests: horse hair and grass pollen - positive, egg - slight positive, other tests - negative. It was concluded that the horse hair

sensitivity was the chief causal factor in the asthma and that the pollen sensitivity was only of secondary importance. The eczema was diagnosed as probably due to the egg sensitization.

Illustrative Case No. 9. Female aet. 28 years. Asthma for 9 years, slight eczema for 2 years, summer rhinitis for 'many years'. Patient had suffered from mild asthma and eczema during early childhood. Family history: father asthmatic. The present complaint had started gradually, the first attack following a winter cold. Turbinectomy and (?) sinus drainage had been performed for obstructive symptoms. This was followed by a septic bronchopneumonia after which the asthma became much worse. Subsequent X-ray examination of the chest and sinuses had given apparently satisfactory results. The asthma attacks were occurring at frequent intervals, chiefly during the night, but with almost constant wheeziness at other times. The attacks were most severe during the winter months, usually following colds, to which the patient was prone, and sometimes during the hay fever season. There was no clinical evidence of a food factor in the asthma, other than the usual effects of late meals, etc. Change of locality had no effect on the asthma. The eczema showed no seasonal variation. Skin tests gave the following results: grass pollen and cat hair - positive, heather pollen, potatoes, pork and herring - slight

positives. Bacteriological investigation resulted as follows: pathogen-selective culture of the post-nasal secretion - pure culture of a haemolytic streptococcus (not present in direct blood-agar cultures); faeces - (tellurite media and pathogen-selective culture) haemolytic streptococcus of a different type to that found in the post-nasal space.

The clinical history and laboratory findings suggested that the case was of the mixed bacterial and non-bacterial sensitization type, the inhalant idiotoxins and the respiratory infection being responsible for the asthma, and a possible food sensitization and intestinal infection for the eczema. This was borne out by subsequent clinical trial - general measures and the banishment of the family cat resulted in a moderate but definite improvement of the asthma, as did the eczema when potatoes, pork, and fish were removed from the diet. It was not until a course of autogenous vaccine therapy had been given however, that satisfactory clinical improvement was obtained.

Illustrative Case No. 10. Female aet. 44. Occupation: housewife. Attacks of asthma for 2 years. Family history negative for allergy but the patient had suffered from asthma as a child. The patient was prone to head colds during the winter and these usually 'went on the chest', and were followed by asthma in a few days.

The asthma did not occur in the absence of a preceding cold. The patient did not take aspirin. There was a certain amount of cough and some muco-purulent sputum between attacks. There was no evidence of any locality or food factors. Physical examination showed a mild bronchitis and the throat was inflamed. Skin tests were negative with the exception of a slight positive to horse hair. The sputum and post-nasal secretion gave a heavy growth of streptococcus viridans on culture. Pathogen-selective culture gave a pure culture of the same streptococcus. The condition was diagnosed as a bacterial sensitization. The slight sensitivity to horse hair was considered to be a relic of the childhood asthma as it did not appear to have any causal relationship to the present complaint.

Illustrative Case No. 11. Male aet. 42 years. Occupation: carpenter. Asthma for 7 years. Family history and patient's previous history negative for allergy. The attacks came on during the late winter months and he was usually fairly free at other seasons. There had been a winter cough for many years, and the asthma followed exacerbations of the cough. On being questioned as to when the asthma was worse, the patient, whose mental condition seemed rather retarded, stated that it was worse in the evening when he was on his way upstairs to bed, and volunteered the information that he was afraid of the dark stairway. He was unmarried and lived in the country with his sister in

a house in which oil lamps were the sole illumination. On questioning the patient's sister it was discovered that the asthma attacks were worse after any emotional upset and that his three worst attacks of asthma had occurred (i) after a road accident in which he was involved but not hurt, (ii) following his mother's death, and (iii) following an accident to his brother. There was some chronic bronchitis present and examination of the sputum indicated a non-haemolytic streptococcus as the infection. The sputum was negative for T.B. Skin tests were negative. It was concluded that the asthma was due primarily to a bacterial sensitization and complicated by a strong psychological factor.

Illustrative Case No. 12. Female aet. 33 years.

Occupation: nil. Asthma for 6 years, chiefly in winter, following exacerbations of a chronic nasal catarrh. Polypi had been removed on several occasions with little or no relief of the asthma. There was no indication of any food or locality factor. Skin tests were negative. Bacteriological examination showed haemolytic streptococci in the tonsils and viridans streptococci in the post-nasal secretion, both present in large numbers. The diagnosis of bacterial sensitization was made. On a later visit the patient stated that she had forgotten to mention that the consumption of carrots sometimes lead to an increase of the asthma. Skin tests to carrot were

negative by both prick and intradermal methods. The patient was instructed to keep a careful note of the dietary particularly with respect to carrots. Later questioning elicited the information that the carrots had to be consumed in fair quantity before they brought about an attack of asthma, and that the interval between consumption and onset of symptoms was 12 hours or longer. This was attended by slight looseness of the bowels (the patient was usually rather constipated). It was considered that the effect of the carrots was due to their aggravating effect on an established intestinal toxæmia and subsequent examination of the faeces showed the presence of large numbers of a non-lactose-fermenting coliform.

CHAPTER XIV
DIAGNOSTIC METHODS

CLINICAL HISTORY AND GENERAL EXAMINATION

The importance of a careful and thorough examination of the clinical history as the first step in the investigation of the asthma patient can hardly be over emphasised. It is difficult to give a full account of all the factors to be considered in taking the clinical history, and the recognition of the most pertinent line of enquiry for any given patient depends chiefly on the clinical experience of the investigator. The following is an outline of the main points to be considered.

After noting the sex, age, and occupation, the nature and duration of the complaint are enquired into. It is then convenient to ascertain the presence or absence of allergic diseases in the patient's family and the presence or history of allergic diseases, other than the present complaint, in the patient himself. Then the manner, season, and time of onset of the present condition, whether the attacks are remittant or intermittant, the length of the periods of freedom from symptoms, the presence of respiratory or other infections, and the relationship of the attacks to environment, occupation, climate, change of residence, etc., to other ailments or infections complained of, to foods and drugs, to exercise and emotional upsets, (to menstruation and pregnancy), the presence of pets and other animals in the

patient's environment, the type of bedding used, and the effects of drugs such as adrenaline or ephedrine in alleviating the symptoms.

The chief objects of this part of the examination are:-

(i) To establish that the symptoms complained of are probably of allergic nature and not due primarily to non-allergic causes (cardio-vascular, renal, etc., or to gross lung lesions).

(ii) To ascertain whether the primary cause of the asthma is likely to be bacterial or non-bacterial in nature, and in the latter case to decide on the group or groups of idiotoxins likely to be involved.

It is desirable that a general medical examination should have been made prior to the allergic investigation, with special reference to the respiratory system, to the presence of septic foci, and including any special examinations (X-ray, test meals, blood counts, Wassermann, etc.) as may be indicated.

2. SKIN TESTS. THE PRICK METHOD

Technique

The prick method was introduced by Lewis (1924) in his studies of the reaction of the skin to histamine, and has been applied by Freeman (1930) to the routine diagnostic skin testing of allergic patients. A 1 c.c.

all-glass or tuberculin syringe fitted with a sharp No. 15 standard hypodermic needle is employed. A small quantity of the extract to be tested is drawn into the syringe and a small drop is ejected on to the area of skin to be tested (the fore-arm, arm, or front of the thigh, are usually the most convenient). Holding the syringe pen-fashion the skin is lightly pricked once with the needle, through the drop, at right angles to the surface. The drop of extract is then wiped off gently with a pledget of cotton-wool. A control test with normal carbol-saline is made on a neighbouring skin site. The optimum depth of the puncture is about $\frac{1}{2}$ - 1 mm. i.e., just sufficient to be felt as a definite prick; the process is not painful and blood need not be drawn. Comparative tests have shown that increasing the depth of the puncture so as to produce an unpleasantly sharp sensation and draw blood is without much effect on the size of the ensuing reaction.

Apart from an occasional gentle wash with soap and lukewarm water in the case of certain types of out-patients, no attempt is made to sterilize or prepare the skin to be tested. The method, frequently advocated, of washing the skin with soap and warm water followed by the application of spirit, has been found to be not only unnecessary but definitely disadvantageous, especially when dealing with dermographic or other delicate skins. The syringe is sterilized by filling and emptying a few times with hot oil from a small bath which is maintained at 125' - 130'C. The excess of oil is removed

by drawing sterile carbol-saline into the syringe, shaking, and emptying. When performing a number of tests on one patient it is unnecessary to re-sterilize the syringe between each test; it is sufficient to wash out twice with carbol-saline between the individual tests.

A positive reaction consists of the usual urticarial wheal with surrounding erythema about the site of the skin puncture, with absence of reaction at the control carbol-saline site. The wheal of the positive reaction is fully developed in 10 - 12 minutes from the time of making the test; the reaction therefore is examined at this time; after 12 minutes the edges of the wheal tend to get less distinct. Records of reactions are made as follows:- An albumin-coated glass slide (microscopic or lantern) is placed in contact with the skin, coated side uppermost, and is gently pressed against the skin reaction. This outlines the wheal clearly and the latter is traced in ink on the slide. The slide is then placed on an illuminated opal glass plate, the patient's record card is superimposed, and a permanent record is made by copying the tracing on to the card. For routine purposes a record of the reaction wheal without particulars of the erythema, is sufficient.

The advantages of the prick method over the scratch and intradermal methods of testing are the simplicity, accuracy, almost complete absence of discomfort to the patient, and the rapidity of performance, the latter a

very important point when dealing with children and with large numbers of patients in the clinic. As the amount of trauma inflicted on the skin by the prick method is much less, and more constant in degree, than with the scratch and intradermal methods, doubtful and pseudo-reactions are much less frequent. The danger of general reactions, by no means negligible with the intradermal method, is reduced to a minimum by the prick method. The writer has only once seen a general reaction following a prick test, and that a very mild reaction in a patient exceedingly sensitive to grass pollen.

The chief essential for the satisfactory performance of the prick test is the use of potent concentrated fluid extracts. It is not proposed to deal here with the details of the manufacture of extracts for skin testing, except to say that the extracts used in the St. Mary's Clinics are manufactured in our own laboratories and the majority are not less than 10 per cent strength, i.e. one gram of substance treated with 10 c.c. of extracting fluid, or 100000 units per c.c. on the Noon unit system. The keeping properties of these extracts vary somewhat, but the average loss of potency after one year is not usually more than 25 per cent with the majority of the extracts, as judged by comparative skin tests. It is advisable however to renew the stock supplies at least once per year.

The Interpretation and Significance of Skin Reactions

There is usually no difficulty in deciding on the degree of reaction of the skin to any idiotoxin compared with that to the control carbol-saline, as tested by the prick method. With the standard technique described above the size of the reactions to a particular idiotoxin are remarkably constant as shown by the results of making the tests in duplicate or triplicate on comparable areas of skin. The results of the prick method therefore are very readily assessed as 'strong positive', 'positive', 'weak positive', etc. By any technique there is never any doubt about a strong positive, but with regard to slighter degrees of reaction the prick method gives more uniform results than does the scratch and intradermal methods. The accuracy of assessment of the degree of reaction, especially when dealing with weak reactions, depends on the absence of appreciable non-specific irritant effect of the extract used, and all extracts should be tested in normal non-allergic skins before being employed as specific test reagents. Except in dermographic skins, non-specific reactions are rare with the prick method, in view of the very slight and constant trauma inflicted on the skin and on the very minute amount of test fluid deposited in the cutis vera.

The assessment of the clinical significance of the skin reaction is a much more difficult matter.

A positive reaction may mean that the patient (i) is clinically sensitive to the particular substance when met with in the natural matter, or (ii) is not clinically sensitive, though he may have been sensitive at some time in the past or may be about to develop such sensitivity. Occasionally a reaction may occur to a substance which could not be responsible for present or past sensitizations, or even to a substance with which the patient has never been in contact e.g. the reaction of English hay fever patients to the pollen of the bamboo and sugar cane (Freeman & Hughes, 1938). Most of these reactions are due probably to biological relationships between the idiotoxins in question, but occasionally may be due to chemical similarities in biologically unrelated substances akin to the precipitin reaction between type 2 anti-pneumococcus serum and certain hydrolysed gums which is caused by similarities of the carbohydrate groups of the hydrolysed gums and the type 2 pneumococcus. In this connection also, it is well known that practically every person who has received animal serum for therapeutic purposes exhibits a positive skin reaction to that serum (Harley, 1933d), but if a person thus sensitized to say rabbit serum does not develop allergic symptoms on natural contact with rabbit fur or rabbit meat.

A negative skin reaction may mean that the patient (i) is not clinically sensitive to the substance, (ii) is clinically sensitive in the absence of skin reactions,

or (iii) that the extract used is not potent.

As a general rule, however, it is to be emphasised that the importance of any idiotoxin as a specific causal factor in an allergic disease should not be adduced from a positive skin reaction alone. A positive reaction is rarely of much help as a clue to the specific diagnosis and treatment in the absence of evidence of a corresponding clinical sensitivity obtained from a study of the clinical history. It is the correlation of skin reactions with clinical sensitivity that is the basis of accurate specific diagnosis and successful treatment. Instances are not uncommon of the skin test enthusiast who concludes from the skin test examination that a particular child of very tender years should avoid 'lobsters, venison, and strawberries' but may eat with impunity 'mackerel, duck, and pineapple'. The writer frequently sees patients who state that positive results had been obtained from previous skin tests (invariably intradermal or scratch), in whom the clinical history clearly shows that the particular substances incriminated could not possibly have been responsible for the symptoms, and subsequent skin tests by the prick method give negative results. The skin reactions are very valuable as confirmatory evidence of a suspected clinical sensitivity, and in some cases the specific causal idiotoxin may be recognised from the clinical history alone e.g. the patient who complains of asthma and rhinitis between May 20th and July 15th but is symptom-free at other times

of the year, is almost certainly a case of grass pollen allergy; the diagnosis is then clinched by obtaining a positive skin reaction with grass pollen. The clinical history will usually afford indications of possible sensitizations and will aid in selecting particular groups of idiotoxins for skin tests. The indiscriminate testing of a patient with a large number of idiotoxins as the first (or only) step in the routine investigation is always laborious and often futile. If a patient has symptoms with little or no seasonal variation it is not likely to be of much avail to test him with uncommon seasonal foods, or, should his trouble come on during the day time when he is out of doors, to test with a large variety of bedding materials.

Though the majority of asthma and rhinitis patients who give a clear history of a specific clinical sensitization to some food or inhalant will give a well-marked reaction to that substance in the skin, it sometimes happens that the reaction may be negative (especially in the case of a food) even though the avoidance of that food is attended by excellent clinical results. Many of these cases are certainly due to the effect of the food on bacterial growth in the alimentary tract, as has been pointed out above (p. 130). It has been suggested by some writers that the skin may not necessarily share in a sensitivity established in other

organs. On the other hand, as has already been stated, a positive reaction does not necessarily establish the causal relationship of the idiotoxin to the allergic disease, so that the idiotoxin which gives the largest reaction in the skin of a particular patient may not be the most important one for that patient. Generally speaking, the pollen reactions are the strongest, the foods weakest, the inhalants intermediate, and the younger the patient (after infancy) the larger the reactions. Skin reactions to drugs vary - aspirin sensitive patients usually give negative reactions to solutions of the drug, while those sensitive to atropine or iodine often give an immediate reaction followed by a contact dermatitis type of reaction.

In this connection it is worthy of note that a considerable percentage of 'positive' reactions has been obtained in presumably normal individuals with no family or personal history of allergy, by the intradermal injection of concentrated idiotoxins (Grow & Herman, 1936; Pearson, 1937).

3. BACTERIOLOGICAL EXAMINATION

This includes (i) routine blood-agar plate cultures of swabs of tonsils, naso-pharynx, and sputum; and (ii) special examination of faeces, urine, cervix, teeth, and other possible sources of infection if there is any suggestion of an underlying toxæmia, as in the case with

feeble skin reactions and normal respiratory tract flora. Tellurite blood media and anaerobic culture of the faeces are frequently valuable for the isolation of pathogenic streptococci. In the absence of any obvious pathogens, auto-haemo-cultures (pathogen-selective cultures) which utilize the in vitro bactericidal power of the patient's own whole blood on organisms to which he is 'immune' and allow the growth of 'pathogens', often indicate possible infections. It is the writer's practice to make auto-haemo-cultures in addition to ordinary cultures when ever possible. Subcultures are made of the predominating or frankly pathogenic organisms for vaccine construction. In the absence of any reliable guide in the way of a specific skin or other test for determining the importance of any one particular infecting organism as a causal factor of the asthma, the selection of the particular vaccine or mixture of vaccines for use in treatment of a given case depends at present chiefly on the experience of the worker investigating the patient.

CHAPTER XV

TREATMENT

1. TREATMENT OF THE ASTHMATIC ATTACK

Adrenaline

Adrenaline is undoubtedly the most effective agent at present available for the treatment of the natural or artificially induced allergic reaction. Its prompt therapeutic action would appear to be due to physiological neutralization of the histamine substances mediating the allergic attack. The rapid absorption of adrenaline from the subcutaneous tissue allows of its convenient and effective administration by the subcutaneous route. The preparation commonly employed is a 1-1000 solution in saline of the hydrochloride of the base. The minimal effective dosage in asthma depends on the severity and duration of the attack. In the writer's experience the best results are obtained with comparatively small doses (0.1 - 0.2 c.c.) repeated at 10 - 30 minute intervals. Given early in the attack a few doses will alleviate rapidly the paroxysm in the great majority of cases, but when the attack is fully developed more prolonged treatment is usually necessary. For this reason the self-inoculation of adrenaline at the commencement of an attack is valuable for those patients in whom milder abortive treatments are ineffective, particularly when the attacks occur at night, as they often do, and when the administration of the drug

by the patient's doctor would be attended by considerable delay. For self-inoculation it is more satisfactory to employ a 1-5000 solution in doses of 0.5 - 1.0 c.c. repeated at 20 to 30 minute intervals, which most patients find facilitates the measurement of the dose.

A small percentage of patients exhibit an intolerance to adrenaline, even in the moderate dosage recommended above, as evidenced by giddiness, palpitations, headache, tremors, etc. Cutting down the minimum dose by 50 per cent will usually overcome this difficulty without much sacrifice of therapeutic effect.

Intravenous or intracardial administration of adrenaline is practically never necessary, except perhaps in the occasional patient reaching hospital in an almost moribund condition.

The inhalation of adrenaline is frequently effective, particularly for cutting short the attack, but is less reliable than the subcutaneous route for the fully developed attack. A 1 per cent solution is advisable, administered by hand atomizer to the back of the throat, though mechanically produced sprays applied through a face mask are less troublesome for the patient and are effective with weaker adrenaline solutions. The use of 1 per cent solution is often attended by considerable dryness of the mouth and throat though this may be mitigated somewhat by the use of a

mouth wash immediately after the inhalation.

The use of proprietary adrenaline mixtures containing pituitrin etc. has not, in the writer's opinion, been shown to have results superior to those of adrenaline by itself.

Ephedrine

Ephedrine in doses of $\frac{1}{2}$ - 1 gr. is valuable as a preventive measure in a proportion of cases though it has little alleviating effect in other than mild attacks when fully developed. Intolerance to ephedrine is common and usually precludes its use.

Narcotics and Anaesthetics

These have been recommended occasionally in the past for very severe attacks but the writer has never had occasion to employ them, with the occasional exception of small doses of morphia.

Aspirin

Aspirin is sometimes taken by asthmatic patients at the beginning of an attack with apparently good results, but in view of the non infrequent occurrence of sensitivity to the drug its use is seldom advised.

General Measures

These include strict avoidance of food and alcohol,

rest in the sitting position, warmth and fresh air - measures which most asthmatics instinctively adopt. Catharsis or emesis, the latter particularly in children, are sometimes helpful early in the management of the attack. When the attack is prolonged ample fluids by mouth or rectum are essential. The addition of glucose is beneficial (for oral administration 'Lucozade' diluted with water is a most palatable and acceptable preparation).

Hospitalization

In the writer's experience hospitalization is an almost unailing remedy for the severer grades of asthmatic attack. While this is usually accompanied by the routine exhibition of adrenaline and the general measures detailed above, most patients improve rapidly even when these accessory treatments are withheld. The same treatment may have been applied previously in the patient's home surroundings with singular lack of success. It is difficult to analyse fully the modus operandi of hospitalization in these cases. The psychological effect produced by admission to the ward - and the improvement is usually more marked in the general ward than in the private room - is probably the chief factor. The quiet efficiency of the nursing staff, the absence of fussing or over-anxious relations, and the belief that 'all the resources of medical science' are about to be applied, apparently suffice to induce a rapid improvement even before the latter are instituted.

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Doubtless the physical change of surroundings, with absence of the home atmosphere idiotoxins, plays a part in a proportion of cases.

2. TREATMENT OF THE ASTHMATIC STATE

While the foregoing palliative treatments for the asthmatic attacks are effective in all etiological types of true bronchial asthma, the successful treatment of the asthmatic state depends on the accurate assessment of the specific causal factors in the individual patient.

A. Immunological Methods

(i) Specific Avoidance

In Type (a) cases - non-bacterial sensitizations - when the clinical sensitivity is to a single substance or to a small number of substances which can be removed readily from the patient's environment, specific avoidance gives excellent results. This measure is generally applicable to all substances which are relatively localized in their distribution and which can be completely eliminated from the patient's environment without serious inconvenience or economic loss.

Illustrative Case No. 13. Female aet. 30 years.


Occupation:- nil. Asthma for 3 years. Family history:- father asthmatic. Attacks during the night only. No clear seasonal variation. Intervals of complete freedom from attacks up to several weeks, usually coinciding

with change of residence. Patient had lived in India for a number of years and returned to England a few weeks prior to the onset of the asthma. There was a slight dry cough. No apparent relation to diet. The patient's bedding included a horse hair mattress and feather pillows, since returning to this country. The patient had owned a dog for some years but did not come in contact with other animals. Skin tests:- horse hair, marked positive; feathers, moderate positive; dog hair and milk, slight positives. The clinical sensitivity was clearly to horse hair and feathers only. Treatment consisted of the substitution of a rubber mattress and rubber pillows for the hair and feather articles, following which the asthma stopped completely.

For how long?
SD

Illustrative Case No. 14. Male aet. 32 years. Asthma for 5 years. Family history:- migraine and (?) food allergy. Patient complained also of headaches (non-migranous type) and indefinite gastric symptoms, duration about 10 years. Previous gastric test meal and alimentary tract X-rays were reported to be negative. Patient had been on a milk diet originally and had continued on a light diet of the lacto-vegetarian type. As this failed to relieve the dyspepsia appendectomy had been performed: result - slight temporary relief only. Some months later the asthma started, mildly at first but gradually increasing in severity. The asthma occurred mainly during the day and appeared to be rather worse after meals. There was no seasonal

variation. Fasting was attended by relief from the asthma but the latter promptly reappeared on return to light diet. Skin tests (prick method) were negative with the exception of a slight but definite reaction to milk. Repeat tests gave the same result and an intradermal test gave a marked positive. A tentative diagnosis of milk sensitization was made. The patient was instructed to fast for 24 hours (ample fluids and fruit juices) and then return to a light diet but avoiding milk and milk foods. After one month the asthma was much improved. As a milk substitute 'Allergillac' was added to the diet. The asthma continued to improve. In three months the asthma was completely relieved and the dyspepsia was improved (the headaches also were less frequent and less severe). Owing to the patient's departure for abroad a follow-up history was not obtained.



(ii) Specific Desensitization

When specific avoidance is impossible or impracticable, specific desensitization is indicated. The results in selected cases are highly satisfactory. The technique employed is similar to that for the prophylactic treatment of hay fever (Chapter VI, p. 49). In order to minimize the risk of reactions it is sometimes advisable to carry out the early stages of the treatment during a preliminary period of specific avoidance.

Illustrative Case No. 15. Female aet. 40 years. Occup-

-ation:- housewife. Severe asthma for 7 years.

General condition:- poor. The attacks occurred during the daytime chiefly, particularly when the patient was engaged in household duties of a dusty nature. The attacks never developed when she was away from home.

There was no indication of any food, seasonal, or animal factors. Routine skin tests were negative.

A quantity of dust of ~~dust~~ was obtained from the patient's house (collected by vacuum cleaner) and an extract of this was prepared. Skin tests with this extract gave strong reactions. The diagnosis of dust sensitization was made. The patient was given a course of desensitizing injections which resulted in marked improvement of the asthma.

This does not improve we a by large volume of extract. Skin tests to dust. Fresh and to injects AH-20.

Illustrative Case No. 16. Male aet. 31 years. Occupation:- baker. Attacks of asthma, preceded by sneezing with copious clear nasal discharge and sometimes irritation of the eyes. Duration:- asthma, 5 years; rhinitis, 7 years. No family history of allergy.

Two years after the onset of the rhinitis the patient had his nasal septum removed but this apparently aggravated the condition as he subsequently developed the asthma. For the past two years he had noticed some irritation of the skin of the hands and fore-arms accompanying the respiratory symptoms. There was no seasonal variation. The attacks always started when he was at work. The patient had noted that the attacks

were most severe when he was working with flour, particularly rye flour. Skin tests to rye and wheat flour were positive, confirming the diagnosis of sensitivity to flour. Specific avoidance being impracticable for economic reasons, the patient was desensitized with rye and wheat extracts and this resulted in complete freedom from symptoms. (It was interesting to note that the ingestion of wheat and rye foods was not followed by any allergic symptoms in this patient.)

Why not?

Type (b) cases, with single or multiple sensitizations plus microbic infections or toxaemias, usually respond best to vaccine therapy (p. 158) with or without the above measures, depending on the relative importance of bacterial and non-bacterial causal factors.

Illustrative Case N. 17. Male aet. 8 years. Asthma for 2 years. Family history positive for asthma. The attacks came on during the winter months, following bouts of bronchitis, to which the child had been prone for the previous five years. The attacks developed during the night chiefly. The bedding included a horse hair mattress. There was no indication of a food or locality factor. Skin tests:- horse hair, feathers, and grass pollen - moderate positives; other idiotoxins tested - negative.

The history suggested that the chief causal factor was the respiratory infection. The horse hair and feather sensitivities appeared to be of secondary importance only, while the reaction to grass pollen had no clinical

significance at the time. Treatment consisted of a course of stock anti-catarrah vaccine combined with horse hair and feather extracts (substitution of rubber or kapok mattress etc. was impossible for economic reasons). The asthma stopped and the bronchitis improved. The treatment will be repeated for several successive years, starting in the early autumn.

(iii) Vaccine Therapy

Where the microbic element appears to be the only or the chief causal factor - Types (c) and (d) - vaccine therapy is the treatment of choice. Whether a stock, or preferably an autogenous vaccine, is employed, it is the writer's practice to start with not more than $\frac{1}{2}$ - 1 million heat-killed organisms subcutaneously. The dose is repeated at 5 - 7 day intervals and is cautiously increased by 25 - 50 per cent each time until satisfactory clinical results are obtained. The increase of dosage is based on the absence of focal, general, or marked local reactions, to the preceding injections. The interval between injections, after a few months of weekly injections, is then gradually increased to 2, 3, or 4 weeks. The optimum dosage and the duration of treatment required varies greatly but it is usually necessary to repeat the maximum dose at 2 - 4 week intervals for a least 6 - 12 months. When there is evidence of bronchitis or frequent winter colds, etc., a shorter course of vaccine treatment

each autumn is recommended. In the writer's experience the best results are generally obtained by the use of the minimal effective doses - rarely in excess of 10 million organisms and frequently less.

Illustrative Case No. 18. Female aet. 28 years.

Occupation:- nil. Attacks of asthma and rhinitis for 6 years. Family history negative for allergy. Patient stated she had some mild asthma as a child. Tonsils and adenoids had been removed 3 years previously with no relief of the rhinitis or the asthma. The patient had been examined by a specialist who made skin tests (intradermal) and reported positive reactions to a number of pollens and foods. A course of therapy based on these findings had not relieved the condition.

On going into the clinical history in detail it was ascertained that the symptoms showed no seasonal variations and that they occurred during the day time chiefly, particularly in the mornings. The rhinitis was accompanied by a nasal discharge which was not quite clear, and there had always been rather an excessive amount of nasal secretion between attacks. The asthma followed exacerbations of the rhinitis. There were no accompanying eye symptoms. The more severe bouts were followed by gastric discomfort and some distension. The patient found that ephedrine helped the digestive symptoms. There was no apparent food or locality factor. Skin tests (prick method)

with a variety of foods and inhalants were negative. Nose and throat examination showed an inflamed mucous membrane but no gross abnormalities. There was no signs of bronchitis. Bacteriological examination of the post-nasal secretion showed the presence of large numbers of a partly haemolytic streptococcus; pathogen-selective culture gave a pure culture of this organism; blood-agar and bile-salt-agar plate cultures of the faeces showed no abnormal organisms but tellurite broth culture yielded a streptococcus whose morphological and colony characteristics were identical with those of the streptococcus from the post-nasal space.

These findings suggested a bacterial sensitization. The patient was given a course of autogenous vaccine injections, starting with $\frac{1}{2}$ million organisms subcutaneously, injections being given at weekly intervals, and the dose gradually increased to 5 million. The condition improved and in 4 months the patient was symptom-free. She has remained well up to the present, 2 years since starting the treatment, on one injection per month, except for a bout of mild asthma following a cold last winter.

The association of gastric symptoms with the asthma, together with the presence of the same streptococcus in the post-nasal space and in the faeces, was considered to have been due to the action on the stomach of the

infecting organisms contained in swallowed nasopharyngeal secretion, a condition not infrequently encountered in these respiratory bacterial sensitization cases.

B. Accessory Measures

The methods of treatment outlined above aim at correcting the primary specific causal factors. In a considerable number of cases, particularly where the causal factors are clear-cut and few in number - as is frequent in patients whose asthma is of relatively short duration - these measures suffice to yield satisfactory results. When the specific factors are multiple and indistinct, and when the secondary non-specific factors discussed in Chapter X, (p. 105) assume increasing importance - as is common in cases of long duration - the foregoing methods of treatment become more difficult of application and less effective in their action. Recourse must then be made to more general lines of treatment with the object of correcting these secondary factors.

(i) General Hygiene

The dietary is perhaps the most important consideration, apart from actual food sensitizations. Simple meals of easily digested foods are best, avoiding highly seasoned, recooked and made-up dishes, pastry,

foods cooked in oil, etc. Salads, vegetables and fruit when ever acceptable. Milk in moderation. The main meal should be taken at lunch time. A substantial tea should be followed by abstinence from food until the following morning. Milk and milk foods before retiring are particularly poisonous for the majority of asthmatics. The fluid intake should be ample with at least $\frac{1}{2}$ pint of warm water or its equivalent first thing in the morning and if possible last thing at night.

Regulation of the bowels, with the relief 'of the toxiy load' of the colon, is also of prime importance. In this connection lactic milk preparations and acidophilus oil emulsions are of value. Light exercises in the open air when applicable. Breathing exercises, with the emphasis on the expiratory phase, are often helpful.

(ii) General Medical Measures

These consist mainly in the medicinal treatment of chronic bronchitis and dyspeptic symptoms. Potassium iodide with ammonium carbonate and tincture of stramonium is excellent when there are signs of bronchitis present.

(iii) Surgery

Surgical treatment of toxic foci, particularly when

the upper respiratory tract is involved, should be as conservative as possible. In these cases, surgical methods, even when the indications appear to be clear, are best postponed if possible until after a thorough trial has been made of treatment directed at correcting the primary specific factors, and are best carried out during a period of relative freedom from the asthmatic attacks.

(iv) The Psychological Factor

While it is rather difficult to accept the claims of some psychologists that psychological trauma plays a prime part as a constitutional predisposing factor in the etiology of the asthmatic state, there is little doubt that the psychological factor is often of importance as a secondary non-specific factor (p. 105) in the course of the disease. Instances are not infrequent in which the precipitating effect of psychological trauma seems to exceed the that of the primary specific causes. It should be borne in mind however that many of the so-called psychological effects may have a neuro-biochemical basis of a normal physiological kind. For example, the effects of sudden fright and of prolonged worry in an asthmatic patient are more probably due to the increase and exhaustion respectively of the secretion of the adrenals than to a purely psychological effect.

When a psychological element assumes major proportions

it calls for treatment. Apart from psychological treatment, of which the writer has no experience, much can be accomplished in these patients by the application of commonsense principles - the removal of an over pampered child to boarding school, the institution of active hobbies and interests for the unduly introspective, the correction, when possible, of domestic or emotional stress and strains, etc.

Illustrative Case No. 19. Female aet. 6 years. The child was highly strung, nervous and irritable, and was not amenable to examination on the first two visits. Winter colds and mild bronchitis for $3\frac{1}{2}$ years. Slight asthma followed the respiratory infections for the first two years. Since then the asthma attacks were much worse and more erratic in their appearance and duration. Family history: father migraine, otherwise nil. Skin tests: horse hair and sheeps wool - slight positives; other idiotoxins tested - negative. Diagnosis: bacterial sensitization (examination indicated a non-haemolytic streptococcus as the infection) with secondary non-bacterial sensitizations. Treatment instituted: substitution of rubber mattress, use of well-washed blankets only, and autogenous vaccine. Two months treatment produced a definite improvement, the customary night wheeziness clearing up completely; the child was however still having sharpish attacks of relatively short duration at other times, particularly marked after any emotional stress. On closer enquiry being made into

the patient's home life the following facts were elicited. The patient, a first child, had been unduly pampered by both nurse and parents. (This was in evidence during the consultations - the parents continually charging the child to behave and promising rewards.) The increase of the asthma had coincided with the arrival of a baby brother, and the nurse admitted that the patient had not been amicably disposed to the new infant. To compensate for the displacement from the limelight of the patient, the parents had apparently increased their over-fussing behaviour towards her, though presumably this was rather intermittent in view of the claims of the new-born upon them. The child was attending a kindergarten school, which she appeared to like, but she had no playmates for her out-of-school hours.

Without presuming to attempt an analysis or labelling of the particular brands of psychological stress active in this case it was obvious that the child was in a state of revolt against her home environment. It was suggested that the child be sent to a boarding school - perhaps too drastic measure in view of her age and upbringing - but the parents refused to consider the suggestion. Finally the parents reluctantly agreed to send the child to live for a time with friends who had a family of four, including a girl of the same age as the patient. After taking a few weeks to settle into her new surroundings,

the patient improved very satisfactorily, with regard to both her asthma and general condition. Whether her re-habilitation later will be accomplished without mishap will depend chiefly on the parents; probably a boarding school would be the best.

C. Miscellaneous Treatments

It is notoriously difficult to evaluate the results of new therapeutic procedures in asthmatic patients with any degree of accuracy. The psychological factor, in addition to its effect on the course of the disease, plays a very definite part in the response of many patients to treatment, and for this reason allergy has been an exceedingly happy hunting ground for the experimental therapist. That the enthusiasm of the originator of a new treatment is often the chief or only factor active in that therapy, is suggested by the excellent results obtained by the originators of numerous new treatments in recent years and by the progressively poor results reported by later and perhaps more skeptical workers. One may cite in this connection the auto-haemo, proteose, potassium, and more recently, the histaminase treatments.

It is also to be noted that a therapy, based on more or less empirical grounds, is sometimes abandoned only to be resuscitated after an interval when a more rational basis for its supposed efficacy is elaborated. The present trends in the treatment of hay fever hold

promise of being a good example of this:- In 1903 Dunbar, believing that the pollen idiotoxin was a true toxin, immunized horses with pollen and the resulting anti-toxin achieved great vogue as a cure for hay fever. As far as one can judge from the early reports of the originator and of independent workers it was at least moderately successful. Later the anti-toxic serum (called Pollantin) was supplanted by Graminol - the serum of normal oxen grazing in summer pastures, supposedly containing a similar anti-toxin. Both treatments fell into disrepute after the introduction of 'active immunization' by Noon in 1911. Then Stull and his co-workers reported good results in hay fever by the transfusion of blood from other hay fever patients who had received pollen therapy, and demonstrated that this protection was produced through the mediation of special immune or blocking antibodies. Later work suggested that the same immune body could be produced in normal non-allergic individuals by the injection of pollen extracts, and the most recent claim is its production in sheep by the same treatment. Whether or not the cycle will be completed with the introduction of a new therapeutic animal serum remains to be determined.

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