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DOES SPECIFIC DESENSITIZATION AFFECT THE ADRENALS?

(Measuring of the potassium, sodium, chlorine, total protein and globulin contents of the blood, the eosinophil count and determination of 17-ketosteroids and glucosteroids in the urine under specific desensitization.)*

By

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INTRODUCTION

In recent years an increasing interest has been taken in the hormonal production of the adrenals. After various chemical substances had been isolated from the adrenal cortex (compounds E and F) an intensive research work was started in order to establish how these substances affect the normal organism. With the comprehensive work by Hench and collaborators (6) an extensive registration was begun of the pathological conditions that may be influenced by these hormonal agents. A great deal of attention has also been paid to allergic conditions, and today it may be stated with certainty that it is practicable—if only for a limited period of time—to influence bronchial asthma in a favourable manner.

It has therefore been of interest to find out whether the adrenals are affected during the specific desensitization of

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allergic conditions, as previous investigations indicate that the unspecific effect on allergic conditions is brought about by irritation of the adrenal cortex, with a resulting improvement in the condition of the patient (Schwartz (9)).

MATERIAL

In order to carry out this investigation, 6 persons were picked out, 4 of whom were suffering from hypersensitiveness to pollen while 2 showed a mixed hypersensitiveness (see Table 1).

TABLE 1
Results of the Usual Standard Tests on the Patient Material.
(Intracutaneous application of 1/20 ml. of 1/10 % of the extract.)

Journal No.	800/45	2128/45	423/50	1353/51	3792/50	4147/50
1. Milk	++	o	o	o	o	o
2. Horse and cow	++	o	(+)	o	+	+
3. Ascaris	o	o	o	+	o	o
4. Fish	++	o	o	o	o	o
5. Feathers	o	o	(+)	o	++	+
6. Shell-fish	o	o	o	o	o	o
7. "Vegetabil" ..	++	o	o	o	o	o
8. Mixed pollen .	+++	++	+++	+++	++	++
9. Fruit	o	o	o	o	o	+
10. Rice	o	o	o	o	o	o
11. Cosmetics	o	o	o	o	o	o
12. Cocoa	o	o	o	o	o	+
13. Fish meal	o	o	+	o	o	o
14. House dust ...	o	o	o	o	+	+
15. Cat, dog	o	o	o	o	+	+
16. Aspergillus ...	o	o	o	+	o	o
17. Wool, cotton .	o	o	o	o	+	+
18. Mixed flour ..	o	o	o	o	o	o
19. Rabbit, goat ..	++	o	o	o	o	+
20. Nuts	o	o	o	o	o	+
21. Meat	o	o	o	o	o	o
22. Eggs	o	o	o	o	o	o
23. Histamine	+++	++	++	+	++	++
24. Control	++	o	o	o	o	o

TABLE 2
Intracutaneous Application of 1/20 ml. Mixed Pollen.
 (The reactions were recorded 15 min. later.)

		Patient No. 800/45					
		1946	1947	1948	1949	1950	1951
Mixed pollen	1/10,000 ⁰ / ₀₀	—	++	++	(+)	+	+
	1/1,000 ⁰ / ₀₀	—	++++	++++	+	+	++
	1/100 ⁰ / ₀₀	+	+++++	+++++	++	++	++
	1/10 ⁰ / ₀₀	++	+++++++	+++++	+++	++	++++
	1/1 ⁰ / ₀₀	+++++		+++	+++++	++	++++
	1/2 ⁰ / ₀						
	1 ⁰ / ₀						
		Patient No. 2128/45					
		1946	1947	1948	1949	1951	
Mixed pollen	1/10,000 ⁰ / ₀₀	—	+	++	+	+	
	1/1,000 ⁰ / ₀₀	—	++	++	+	+	
	1/100 ⁰ / ₀₀	—	++++	++++	++	+	
	1/10 ⁰ / ₀₀	++	+++++	+++++	++	++	
	1/1 ⁰ / ₀₀	++	+++++	+++++++	++	++	
	1/2 ⁰ / ₀	+++++					
	1 ⁰ / ₀	+++++					
		Patient No. 423/50		1353/51	3792/50	4147/50	
		1950	1951	1951			
Mixed pollen	1/10,000 ⁰ / ₀₀	o	o	+++++++	+	+	
	1/1,000 ⁰ / ₀₀	o	o	+++++++	+	+	
	1/100 ⁰ / ₀₀	o	o	+++++++	++	+	
	1/10 ⁰ / ₀₀			+++++++	++	++	
	1/1 ⁰ / ₀₀			+++++++	+++	+++	
	1/2 ⁰ / ₀	1cm.		+++++++	+++	+++	
	1 ⁰ / ₀	Prick method					

Explanation of signs: + = 0-5 mm.

++ = 6-10 "

+++ = 11-15 "

++++ = 16-20 "

+++++ = > 20 "

+++++++ = diffusion with oedema formation making exact measurement impossible.

By correlation of the anamnesis with the skin examinations it is safe to say that only the last two patients were suffering from mixed hypersensitiveness.

The material comprises 3 women and 3 men; 2 of these patients had been examined and treated since 1945, 2 had been under treatment one year previously (one in our clinic, the other had been treated elsewhere with helisen—a German pollen preparation), and the last 2 patients had not previously been submitted to any specific treatment. Table 2 shows the intracutaneous reactions to mixed grass pollen in various dilutions of the extract.

The mixed pollen extract employed consisted in a solution in physiological saline of equal parts of *phleum pratensis*, *avena elatior* and *dactylis glomerata*. It is freshly prepared year by year from the same dry substance and thus the strength of the extract may be reckoned as constant. The tests were made on the patients by means of intracutaneous application of 1/20 ml. of the extract and the results were read 15 minutes later. In a single case, however, the prick method was employed.

All the patients in this material have been treated with this extract, partly in previous years, partly in the spring of 1951 when this investigation was carried out. Tables 3 and 4 show how the patients reacted to the different tree and grass pollens.

The tests were made by means of the scratch method. After superficial scratching of the skin on the volar surface of the forearm, the pollen dust was rubbed in with a drop of 1/10 n sodium hydroxide and the results were read after 15 min.

The patients were kept under close observation during the desensitization treatment with extract of mixed pollen in spring 1951, and at suitable intervals the values for potassium, sodium, chlorine, albumin and globulin contents of the blood were measured and the number of eosinophil cells in the blood stream were counted. Further, the excretion in the urine of neutral 17-ketosteroids and glucosteroids was measured.

TABLE 3

Reaction of the Patients to the Scratch Test with Grass Pollen.
(See Table 2 for explanation of signs.)

	800/45		2128/45	423/50		1353/51	3792/50		4147/50
	1945	1951	1950	1950	1950		1950	1951	
<i>Phleum pratense</i>	+++++	+++++	+	+			++	o	
<i>Avena elatior</i>	+++++	+++++	o	++			+++	+	
<i>Poa pratensis</i>	+++	+++++	o	+			(+)	(+)	
<i>Agrostis alba</i>		o	(+)	++			o	o	
<i>Alopecurus pratensis</i>		+	o	(+)			(+)	o	
<i>Holcus lanatus</i>		+++	o	+++			o	o	
<i>Lolium perenne</i>	+++++	+++	o	+++			+	o	
<i>Festuca pratensis</i>	+++	+++	o	++			o	o	
<i>Secale cereale</i>		o	o	o			(+)	o	
<i>Bromus arvensis</i>	+++++	+	+	++			o	o	
<i>Dactylis glomerata</i>	+++++	++	o	+++			+	o	
<i>Rumex acetocella</i>		+		o			o		
<i>Plantago lanceolata</i>		+++		o			o		
<i>Zea mays</i>		o		o			o		

No test made

TABLE 4

Reaction of the Patients to the Scratch Test with Tree Pollen.

(For explanation of signs, see Table 2.)

	800/45	2128/45	423/50	1353/51	3792/50	4147/50
<i>Ulmus glabra</i>	o	o	o	o	o	o
<i>Quercus</i>	o	o	o	o	o	o
<i>Alnus vulgaris</i>	o	++	o	o	+++	o
<i>Fagus sylvatica</i>	o	o	o	o	(+)	o
<i>Betula pendula</i>	o	+	o	o	+	o
<i>Populus alba</i>	o	o	o	o	o	o
<i>Coryllus avellana</i>	o	o	o	o	o	o
<i>Sorbus</i>	o	o	o	o	o	o
<i>Sambucus niger</i>	o	o	o	o	o	o
<i>Acer</i>	o	o	o	o	o	o
<i>Pinus silvestris</i>	o	o	o	o	o	o
<i>Pinus montana</i>	o	o	o	o	o	o
<i>Larix</i>	o	+	o	o	o	o
<i>Juglans</i>	o	o	o	o	o	o
<i>Tilia europea</i>	o	++	o	o	o	o
<i>Taxus baccata</i>	o	o	o	o	o	o
<i>Salix alba</i>	o	o	o	o	o	o
<i>Prunus avium</i>	o	o	o	o	o	o
<i>Pyrus communis</i>	o	o	o	o	o	o
<i>Pyrus malus</i>	o	o	o	o	o	o

The potassium determinations were made by means of spectrography with a Biering & Nielsen flame photometer with internal standard (8).

The sodium determinations were made by zinc amyl acetate precipitation (7).

The chlorine was measured a.m. Eisenmann (3).

The albumin and globulin values were determined a.m. Henriques & Klausen (5).

The eosinophil cells were counted according to van Dungen's technique modified by H. C. Andersen (1), as follows: 25 cmm. of blood was mixed with 475 cmm. eosin solution consisting of 10 g. of aqueous eosin, 15 g. acetone, 10 g. of 3 % sodium citrate and 65 g. distilled water. After standing for some hours all the cells were counted in a Fuchs Rosenthal

chamber and the result was multiplied by 6.25, which gives the cell count per cc. The upper limit for the normal count after H. C. Andersen is 350; counts exceeding 450 indicate the presence of eosinophilia. This upper limit is probably too high; the lower limit is perhaps 80-100.

The neutral 17-ketosteroids were determined a.m. Hamburger, with combined acid hydrolysis and benzene extraction and measuring on a Coleman spectrophotometer with correction for unspecific chromogenic substances by means of a nomogram (4).

The glucosteroids were determined a.m. Sprechler (10).

Finally, the blood pressure was controlled during the treatment and at suitable intervals the urine was examined for the presence of sugar. At no time whatever were any changes observed in the blood pressure—nor did glycosuria appear.

CASE HISTORIES AND LABORATORY FINDINGS

In the following a brief review will be given of the case histories as well as of the objective, laboratory and roentgenological findings. The numbering of the patients is the same as previously employed for the demonstration of the cutaneous reactions. Lastly a short description is given of the patients' reactions to a direct exposure test (with inhalation of Timothy pollen) to which they were submitted after the desensitization treatment. Each case history is followed by a graph which illustrates the course of the measured values obtained.

Case 1 (Rec. No. 800/1945).

Man, aged 29, veterinary surgeon.

The patient's father was suffering from asthma of unspecific origin. His mother had asthma from hypersensitiveness to horse.

On his first admission in 1945 he had been troubled with itching and smarting of the eyes, and rhinitis which began in June and diminished during the summer.

Examination of urine: No abnormality.—Hb.%: 95.—B.P.: 140/90.—S.R.: 3 mm./1 hour.—Roentgenography of the lungs and sinuses was not performed.

The patient was treated with mixed pollen in 1945, 1946, 1947, 1948, 1949 and 1950.

No local or general reactions appeared during the desensitization treatment in 1951.

There was no reaction to the exposure test with Timothy pollen after the desensitization treatment.

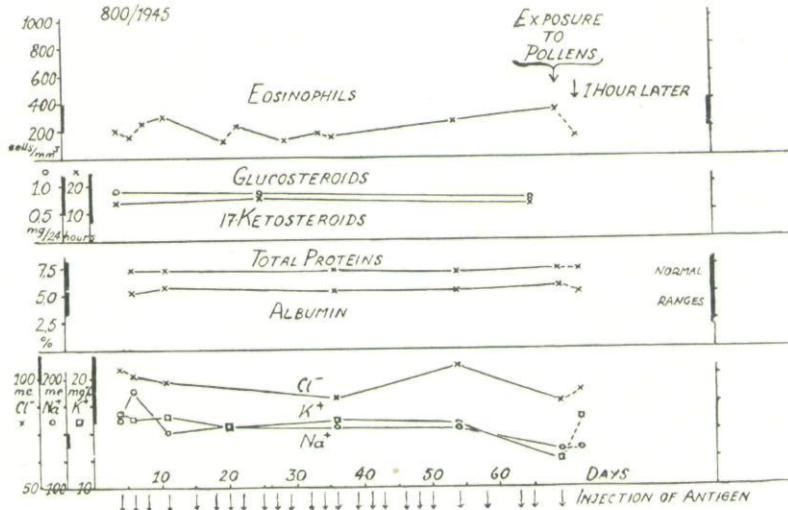


Fig. 1.

Case 2 (Rec. No. 2128/1945).

Man, aged 31, lawyer.

No history of disposition to allergic diseases in the family.

On first admission in 1945: For 5 years the patient had had symptoms of sneezing and rhinitis in the months of June, July and August.

Examination of urine: No abnormality.—Hb.%: 100.—B.P.: 120/80.—S.R.: 1 mm./1 hour.—Roentgenography of the lungs: No abnormality.—Roentgenography of the sinuses was not performed.

The patient was treated with extract of mixed pollen in 1945, 1946, 1947, 1948, 1949 and 1950.

No local or general reactions appeared during the desensitization treatment in spring 1951.

After the exposure test with inhalation of Timothy pollen there was slight rhinitis and 3 attacks of sneezing occurred.

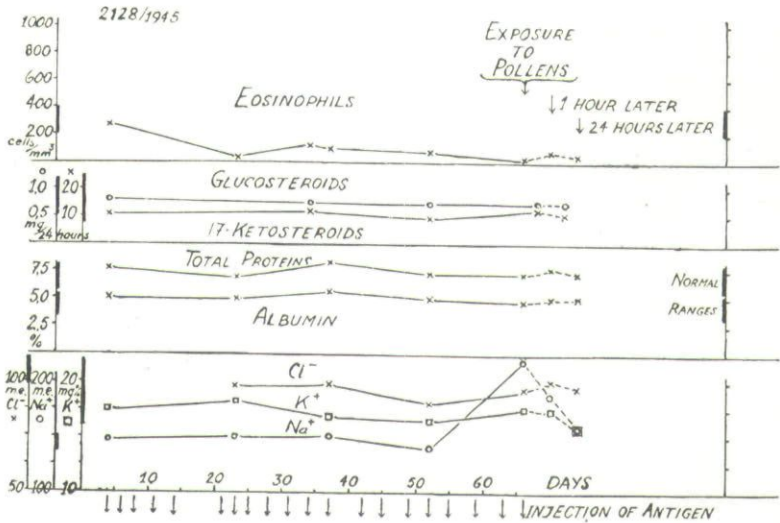


Fig. 2.

Case 3 (Rec. No. 423/50).

Man, aged 25, law student.

A male and female cousin of the patient had asthma. The father suffered from eczema. Otherwise no history of disposition to allergic affections in the family.

For some years the patient has had slight "hay fever" rhinitis, which had become greatly aggravated during the two years prior to his first admission to the clinic in 1950.

Examination of the urine: No abnormality.—Hb.%: 98.—B.P.: 120/70.—S.R.: 4 mm./1 hour.—Roentgenography of the lungs: No abnormality.—Roentgenography of the sinuses: No abnormality.

The patient was treated in 1950 with extract of mixed pollen.

No local or general reactions appeared during the desensitization treatment in spring 1951.

After the exposure test with Timothy pollen there was occasional sneezing and slight rhinitis.

Case 4 (Rec. No. 1353/51).

Woman, aged 22, medical student.

One of the patient's grandfathers had suffered from asthma of unknown cause. Otherwise no history of allergic affections in the family.

Since 1944 the patient had been troubled with rhinitis and a burning sensation in the nose and eyes in the months of June and July. The symptoms were most pronounced in clear, sunny and calm weather.

In 1950 she had been treated by an ear specialist with helisen without any improvement in her condition.

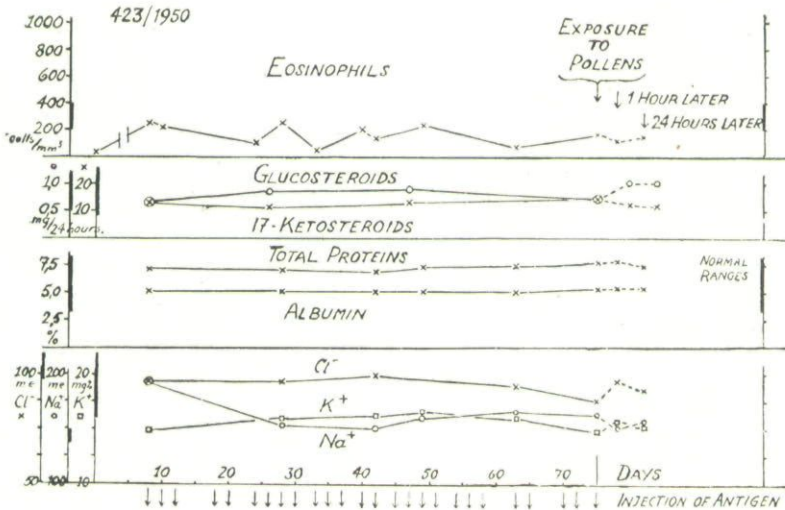


Fig. 3.

During the past year the rhinitis has been accompanied by dyspnoea.

Examination of the urine: No abnormality.—Hb. %: 95.—B.P.: 120/80.—S.R.: 2 mm./1 hour.—Roentgenography of the lungs: No abnormality.—Roentgenography of the sinuses: Diffuse swelling of the mucous membrane of the maxillary sinuses.

At the intracutaneous test with mixed pollen a commencing general reaction was observed and the patient had to be given adrenalin locally (with application of a tourniquet to the arm for 20 min.) and also intramuscularly.

Pronounced local reactions were observed during the desensitization treatment.

The exposure test with Timothy pollen gave a pronounced reaction with rhinitis, lachrymation and general indisposition. The patient felt unwell for three days, in spite of administration of an antihistaminic preparation.

Case 5 (Rec. No. 3792/50).

Woman, aged 22, assistant at the Meteorological Institute.

A cousin of the patient's mother gets attacks of asthma on contact with cats. Another cousin has "hay fever" rhinitis.

The patient applied to the clinic in 1950 on account of a presumably allergic rhinitis which had lasted as long as she could remember and which apparently was brought on when in the vicinity of dogs and cats, and also when she was

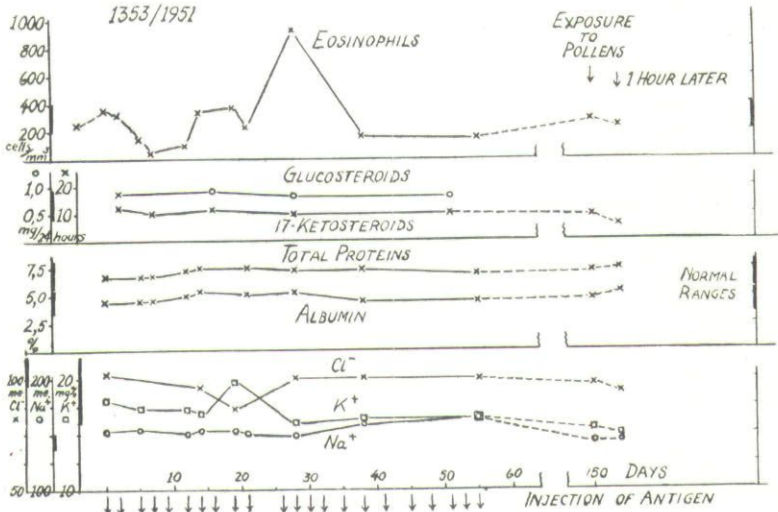


Fig. 4.

dusting. There is pronounced exacerbation of the symptoms in the summer in clear, dry weather. The patient does not think she can stand the smell of flowers.

Examination of the urine: No abnormality.—Hb.%: 85.—B.P.: 120/80.—S.R.: 9 mm./1 hour.—Roentgenography of the lungs: No abnormality.—Roentgenography of the sinuses: No abnormality.

There was no local or general reaction during the treatment.

The series of injections was not concluded and the exposure test was not carried out as the patient was getting married.

Case 6 (Rec. No. 4147/50).

Woman, aged 25, secretary.

A cousin of the patient's father had asthma of unknown cause. Otherwise no history of disposition to allergic affections in the family.

The patient has been suffering from asthma and chronic "colds" since the age of 5 years. The attacks proper of asthma and rhinitis occur only in July

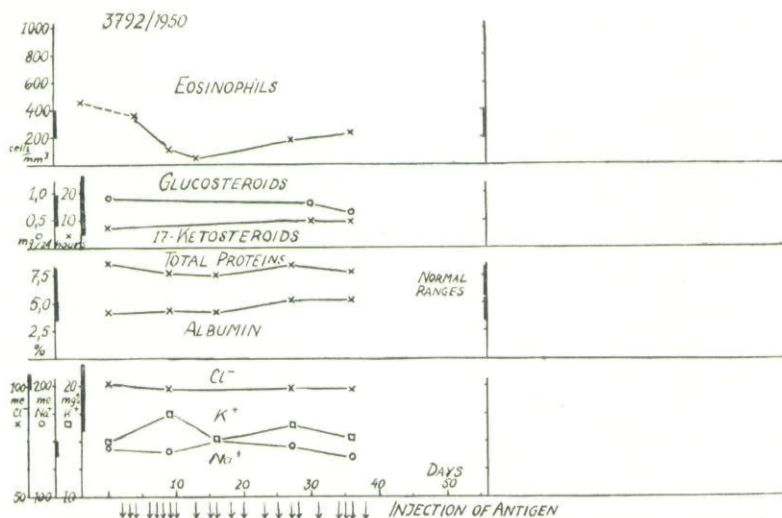


Fig. 5.

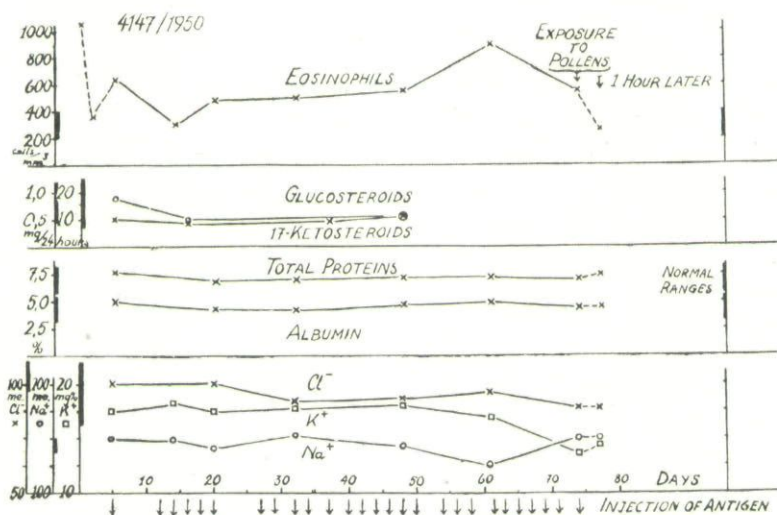


Fig. 6.

and August, and the patient has been hospitalized several times at this period of the year. During the remaining months she is greatly troubled by dyspnoea, especially at night. Since childhood she has suffered from swelling of the tongue and lips after eating nuts, and from urticaria on the legs after contact with grass.

Examination of the urine: No abnormality.—Hb.%: 96.—B.P.: 120/70.—S.R.: 5 mm./1 hour.—Roentgenography of the lungs shows horizontal ribs and low diaphragm.—(Vital capacity: 1.6 l).—Roentgenography of sinuses: No abnormality.

No local or general reactions in connection with the desensitization.

Inhalation of Timothy pollen after the treatment gives violent attacks of sneezing and rhinitis.

DISCUSSION

As mentioned in the introduction, the hypothesis has been advanced that specific desensitization might be due to some action of the adrenal cortex whereby the organism becomes immunized.

By increasing or substituting the secretion from the adrenal cortex with administration of ACTH (pituitary adrenocorticotrophin) or with cortisone (compound E) it has been practicable to demonstrate a fall in the number of eosinophil cells in the blood stream and/or an increase in the urinary content of 17-ketosteroids or 11,17-oxysteroids. It will be appropriate to mention here that other reactions of significance to an appraisal of the present material are: a decrease in the globulin content, an increase in the chlorine and sodium content, and a decrease in the potassium content of the blood (11).

From the graphs it will be seen that no significant decrease in the eosinophil count occurred in any of the patients. Table 5 shows the cell count before as well as after the treatment.

No change was demonstrated in the excretion of neutral 17-ketosteroids or glucosteroids during the desensitization. Table 6 gives the values obtained before the institution of the treatment, on discontinuation of the treatment and afterwards.

From these results it must therefore be concluded that it

TABLE 5
Eosinophil Count before and after Desensitization.

Patient No.	800/45	2128/45	423/50	1353/51	3792/50	4147/50
Before treatment ..	200	275	250	362	362	625
After " "	338	29	173	150	225	556
Difference	+69%	-88%	-31%	-58%	-37%	-11%
Average for all 6 patients				-26%		

TABLE 6
Excretion of 17-ketosteroids and Glucosteroids before and after Desensitization.

Patient No.	800/45		2128/45		423/50	
	17-keto.	Gluco.	17-keto.	Gluco.	17-keto.	Gluco.
Before treatment ...	13.9	0.92	10.8	0.80	13.1	0.63
After treatment	13.3	0.72	9.6	0.72	14.3	0.72
Normal values mg./24 hours (Hamburger)	7.8-25.5	0.50-1.21	7.8-25.2	0.5-1.21	7.5-25.8	0.53-1.25

Patient No.	1353/51		3792/50		4147/50	
	17-keto.	Gluco.	17-keto.	Gluco.	17-keto.	Gluco.
Before treatment ...	12.7	0.87	7.6	0.85	10.0	0.86
After treatment	10.0	0.90	9.3	0.63	11.3	0.53
Normal values mg./24 hours (Hamburger)	4.6-16.5	0.4-0.16	4.6-16.5	0.4-0.96	4.5-16.9	0.42-0.98

Examination of the serum protein showed no changes of significance either before or after the treatment. The only specimen that showed a change in the albumin/globulin ratio (Case No. 4147/50) was also submitted to electrophoresis¹; here the results were identical with those of the usual examination.

¹ The electrophoresis was carried out by Mr. Birch Andersen, C.E., of Statens Seruminstitut, Copenhagen, to whom I wish to express my best thanks for his kind assistance.

was not practicable to demonstrate any increased effect of the glucosteroids during the specific desensitization.

No significant difference was observed on comparison of the values obtained for potassium, sodium and chlorine and the conclusion may therefore be drawn that no increased activity of the mineralocorticoids takes place during the specific desensitization.

In order to obtain an idea of the effectivity of the specific desensitization after the treatment was concluded, all the patients (with the exception of one) were submitted to a test with inhalation (by sniffing) of Timothy pollen. As previously mentioned, the reactions to this test were recorded and from the results obtained it is quite evident that the two patients, who regularly attended the clinic for treatment during six years, showed very slight clinical reactions that hardly inconvenienced them at all. At the same time as the test was made with Timothy pollen an opportunity was taken to repeat the previous examinations on these patients.

As will be noticed from the graphs in Figs. 1-6, no changes worth mention were observed in the values for potassium, sodium, chlorine and protein (verified by electrophoresis). It was not practicable in all of the patients to carry out the examination of the excretion of 17-ketosteroids and glucosteroids and consequently no definite statement can be made as to these values—only 1 out of the 3 patients examined showed an increase in the excretion of glucosteroids amounting to 33 % while the excretion in the two others remained unchanged.

The eosinophil counts are recorded in Table 7.

As will be seen from this table, a not inconsiderable decrease was recorded in the number of eosinophil cells. If we eliminate Case 2128/45, whose eosinophil count before and after inhalation of pollen extract was extremely low, it will be seen that the average decrease in the eosinophil count amounted to 37 % one hour after the exposure test (all figures taken: 35 %).

This decrease which is significant in 3 instances is in direct contrast to the results obtained after exposure tests on

TABLE 7
Eosinophil Count in Patients before and after Inhalation of Timothy Pollen after Specific Desensitization.

	Stand- ard devi- ation	2128/45	Stand- ard devi- ation	423/50	Stand- ard devi- ation	1353/51	Stand- ard devi- ation	3792/59	4147/50	Stand- ard devi- ation	Average
Before exposure	338	45	13	173	31	282	42	not	556	58	1378
1 hour after exposure	150	81		125		242		made	288		886
Difference	—56%	(+179%)		—28%		—14%		—48%			—35%

(The standard deviation is calculated according to $\sqrt{6.25 \times \text{counted figure.}}$)

TABLE 8
Eosinophil Count, before and after Inhalation of Timothy Pollen, in Patients not previously submitted to Specific Desensitization.

Patient No.	Diagnosis	Eosinophil count				Difference	Clinical reaction
		Before treatment	Standard deviation	After treatment	Standard deviation		
3506/51	Pollen allergy	525	57	376	39	—37%	Severe asthma
2634/51	"	175		325	45	+88%	Sneezing and rhinitis
2597/51	"	650		1000 ¹	56	+54%	None
2300/51	"	148		288	42	+42%	Sneezing and rhinitis
Total ...		1498		1989	average	+33%	

¹ Double count.

patients that had not previously received any treatment. A few examples are given in Table 8.

From the findings recorded in Tables 7 and 8 the conclusion might be drawn that the reaction of patients who had not previously been treated was different from that of the treated patients after the direct exposure test with Timothy pollen. Whether an increased glucosteroid secretion into the blood stream does take place, however, is a hypothesis the writer will not assert here.

SUMMARY

In order to ascertain whether specific desensitization produces any increased activity of the adrenal cortex, a number of tests were carried out in the spring of 1951 with six patients suffering from hay fever. Two of these patients had been given specific desensitization treatment for a period of six years, two others had been treated for one year only, and the remaining two had received no treatment at all.

Examination of the values obtained for the potassium, sodium, chlorine and protein contents of the blood, the eosinophil count and the excretion of 17-ketosteroids and glucosteroids in the urine afforded no indication that such an increased activity takes place.

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