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THE MODE OF ACTION OF UNSPECIFIC THERAPY IN ALLERGIC DISEASES

By

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INTRODUCTION

Allergic diseases have for many years been treated with so-called unspecific therapy. A variety of therapeutics belong to this type of treatment: induced fever (produced by injections of typhus vaccine, coli vaccine, "Pyripher", external heating etc.), injections of peptone, tuberculine, milk, colloidal sulphur in an oil solution, certain vaccines (e.g. pertussis), treatment with autogenous blood or urine, radiation therapy with x-rays, ultraviolet light etc.

All these different forms of therapy can obviously not act in the same way. It is generally thought that the favourable effect of all these forms should depend on either the fever or the "tissue reaction" or both. The "tissue reaction" is said to result from a local breakdown of the tissue proteins resulting from an inflammation produced by the injected substances (*Urbach & Gottlieb*, 1946).

How the relief of the allergic symptoms is obtained has been a matter of speculation. Thus *Weichardt* (1915) declared that an increase of the resistibility of the organism was produced, *Serafini et al.* (1946) stated that some hemochemical alterations are attained, and *Hansen* (1957) thought that an activation of the protoplasm has occurred.

Unspecific therapy was probably introduced as a consequence of some clinical observations e.g. the amelioration of asthmatic symptoms after an attack of high fever, which one tried to

imitate. Animal experiments confirmed the clinical findings. *Gernez & Eloire* (1937), for instance, state that artificial fever prevents anaphylactic shock in guinea pigs, and *Grifoni* (1953) has shown that the sensibilisation of the skin is reduced during such fever. On the basis of Selye's hypothesis regarding the role of the anterior pituitary and adrenocortical hormones in "stress" *Schwartz* (1950) concluded after some studies of the variations in the blood eosinophil count and the urinary 17-ketosteroid output that the effect seen in unspecific therapy is caused by a stimulation of the ACTH production, and *Rose* (1955) declared that an increase of the adrenocortical activity was a probable mechanism.

Unspecific therapy is extensively used. The conceptions of the mode of action produced by such therapy are very divergent and still somewhat unclear. It seemed therefore interesting to study this action more closely, especially the effect on the adrenocortical activity.

MATERIAL AND METHODS

The present investigations have been performed on patients suffering from allergic diseases, especially from bronchial asthma. They were all hospitalized. None had been treated with ACTH or corticosteroids. During the period of treatment they had no or only slight symptoms. The patients are classified according to sex and age in Table 1.

1. *Induced fever.*

Forty of the patients belong to this group. They were treated with a single intravenous dose of 50–80 milj. killed *Bacillus alkaligenes*. This injection was given at 8 a.m. and the body temperature was then measured every hour. At about 3 p.m. the temperature peak was obtained (usually between 39° 0–39° 5 C.)

2. *Sulphur oil injections.*

Eighteen patients were treated with a series of intramuscular injections of colloidal sulphur 5 mg/cc suspended in an oil

containing 4 per cent benzocain. They were given a primary dose of 0.4 cc, after two days interval 0.8 cc was given, after a further two days they received 1.2 cc etc. up to a final dose of 2.0 cc in most cases. All injections were given at 8 a.m.

TABLE 1
Authors' material classified according to sex and age.

Age group years	Induced fever		Colloidal sulphur injections		Total
	Males	Females	Males	Females	
10-19	—	—	2	—	2
20-29	5	5	3	2	15
30-39	3	2	4	—	9
40-49	2	4	1	—	7
50-59	5	7	5	1	18
60-69	—	7	—	—	7
Total	15	25	15	3	58

All patients were studied with reference to their 3 p.m. temperature and their 24-hour urinary excretion of 17-keto and 17-ketogenic steroids, estimated by Norymbersky's methods.

The investigations were started two days before the first injection. The values obtained in these two days are considered basal. To avoid the influence of the great age variations in steroid excretion, the values obtained after these first two days are given in per cent of the basal value of each patient. The body temperature and steroid excretion were then determined during the treatment period and for a further two days. Due to technical difficulties with the urine collection the total number of urinary analyses is somewhat lower than the number of patients.

The results obtained have been treated statistically according to *Snedecor* (1957). The means (M) and the standard errors of the mean (S.E.) are given in the Tables. Statistically significant differences have been calculated by variance analysis and is said to occur when $P < 0.05$.

RESULTS

1. *Induced fever.*

The results are shown in Table 2. Following injection of the bacterial suspension the body temperature rises to a mean value of $39^{\circ}.1$ C. This increase is statistically significant. The temperature during the following days does not differ significantly from the basal values. The urinary excretion of 17-keto and 17-ketogenic steroids is significantly higher during the treatment day.

TABLE 2
Urinary steroid excretion in patients treated with induced fever.

Day	Treatment	Body temp. °C		Urinary excretion of steroids in per cent of the basal values				
				No. of ana- lyses	17-ketogen		17-keto	
		M.	S. E.		M.	S. E.	M.	S. E.
1 basal	—	374.	± 0.03	40	100	—	100	—
2 values				40				
3	Induced fever	39.1	± 0.07	40	215	± 24	148	± 12
4	—	37.7	± 0.08	39	145	± 15	118	± 11
5	—	37.3	± 0.07	23	107	± 13	95	± 8

M. = Mean.

S.E. = Standard error of the mean.

2. *Sulphur oil injection.*

The results are given in Table 3. The mean values of the body temperature appears to be some-what higher during the treatment, but this difference is not statistically significant. The same is true of the steroid values.

DISCUSSION

The two types of unspecific treatment chosen for this investigation represent the two different hypothetical mechanisms, which have been considered important for the effect, viz. fever and "tissue reaction".

It has been shown by the present investigation that artificial fever, induced in patients with allergic diseases, gives rise to a

stimulation of the adrenocortical production, shown as a 1.5 to 2 times increase of the basal 24-hour urinary corticosteroid excretion. It therefore seems likely that the improvement of the symptoms of allergic diseases seen after induced fever is due to a stimulation of the adrenocortical activity.

TABLE 3
Urinary steroid excretion in patients treated with sulphur oil injections.

Day	Mg of colloidal sulphur injected	Body temp. °C		No. of analyses	Urinary excretion of steroids in per cent of the basal values			
					17-ketogen steroids		17-keto steroids	
		M.	S. E.		M.	S. E.	M.	S. E.
1 basal	—	37.2	± 0.04	18	100	—	100	—
2 values	—	37.3	± 0.10	14	102	± 3	101	± 14
3	2	37.3	± 0.06	16	125	± 22	115	± 10
4	—	37.2	± 0.08	14	130	± 25	158	± 32
5	—	37.5	± 0.15	17	120	± 13	119	± 12
6	4	37.6	± 0.09	16	141	± 16	117	± 12
7	—	37.3	± 0.08	17	119	± 10	119	± 12
8	—	37.5	± 0.14	17	123	± 15	132	± 12
9	6	37.6	± 0.08	17	118	± 15	101	± 9
10	—	37.3	± 0.06	17	144	± 23	123	± 14
11	—	37.8	± 0.17	16	151	± 19	132	± 14
12	8	37.7	± 0.09	17	149	± 13	133	± 13
13	—	37.4	± 0.13	16	114	± 16	135	± 20
14	—	37.7	± 0.16	15	111	± 14	122	± 15
15	10	37.6	± 0.10	14	123	± 17	133	± 39
16	—	37.2	± 0.08	14	116	± 21	89	± 3
17	—							

Sulphur oil injections are generally considered effective due to the produced "tissue reaction". In connection with such therapy sometimes a small fever reaction is seen. This reaction is generally looked upon as favourable, but in the present investigation no such reaction was noticed. Nor did the urinary steroid output increase. This applies not only to the whole group of patients but also to all individuals. It is, however, possible that some other type of "tissue reaction" therapy without simultaneous fever, might cause a stimulation of the

adreno-cortical production. An amelioration of asthmatic symptoms is for instance often seen after major surgery and it has been shown that in connection with this the urinary excretion of corticosteroids is increased. (*Frankson et al.* 1956).

The general opinion is that unspecific therapy has a positive effect, but control investigations for instance with placebo (cf. *Helander* 1959) have not been visible in the literature. It seems probable that after such an investigation at least some of the types of therapy which were listed in the introduction would have been laid completely aside. It is possible that unspecific therapy may have some favourable effect which is not due to any adrenocortical stimulation, but it has not been proved that such is the case. In the present paper it has been showed that sulphur oil injections do not stimulate the adrenal cortex. The therapeutical results thus must depend on some other action. Induced fever gives an increase of the steroid production. This way to increase the adrenocortical activity is very inconvenient. If the motive for giving unspecific therapy in allergic diseases, is to increase the corticosteroid production, it seems to us more practical to use a short-term steroid treatment directly.

SUMMARY

The body temperature and 24-hour urinary output of 17-keto and 17-ketogenic steroids have been studied in 40 patients, who were treated with induced fever and in 18 patients, who obtained a series of injections of sulphur oil.

In the patients treated with induced fever a significant increase of the body temperature to a mean value of $39^{\circ}.1$ C was obtained. At the same time the urinary output of steroids increased to about 1.5 to 2 of the basal value. The therapeutical effect seen after induced fever is probably due to this increase of the adrenocortical activity.

After injections with sulphur oil no such increase of body temperature or steroid excretion was seen. Thus the effect of this type of unspecific treatment is not due to any adreno-cortical stimulation.

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