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"ENDOCRINE ALLERGY"

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The concept of "endocrine allergy" has been introduced on the basis of the rather unlikely hypothesis that allergic signs and symptoms manifesting themselves chiefly or exclusively in relation to puberty, menstruation, or menopause are due to an allergic reaction to the patient's own sex hormones. We must realize, however, that "endocrine allergy" is to be regarded as a clinical concept only, as it has never been proved that an individual may become allergic to his own cells or the products of these within the organism. Nevertheless there is some sense in regarding patients with so-called "endocrine allergy" as a well-defined group in comparison with other patients; the usual susceptibility tests rarely reveal releasing allergens, and symptomatic treatment is generally the only possible one, e.g. with antihistamines, bronchospasmolytics, and the like.

Numerous papers have been published on "endocrine allergy", of which the most important will be mentioned below. Several authors claim to have proved that the condition is due to allergy to sex hormones. *Geber*, for instance, in 1921 provoked an attack of urticaria within a rash-free phase in a patient suffering from premenstrual urticaria, by injecting auto-serum obtained within the premenstrual urticarous phase. In 1939 *Geber* reported on successful desensitization by subcu-

taneous injection of such serum.—However, Geber's results probably only suggest that the patient's serum premenstrually contains such large amounts of some allergen or other that the allergic symptoms will manifest themselves in this phase, or that she is more susceptible premenstrually.

In 1935 Salén published five cases of bronchial asthma during menses, with very strong cutaneous reaction to extract of the patient's own menstrual blood. This seems less unlikely, since the blood is decomposed in the uterus and possibly thereafter may return to the blood stream. By desensitizing the patients with an extract of menstrual blood he succeeded in preventing the symptoms from occurring during one or more monthly periods, which previously had not occurred. In four cases, however, there was a polyvalent allergy with positive cutaneous reactions to other extracts and symptoms intermenstrually, too, whereas the fifth case seemed to be "pure", with attacks of asthma solely during menstruation. The latter patient experienced only one symptom-free period, as she died in status asthmatus within the next. Castration had very reasonably been contemplated in this case, but had been limited to partial X-ray castration.

In 1945 *B. Zondek* and *Bromberg* published a paper on "endocrine allergy", in which a detailed account is given of skin tests with sex hormones (oestradiol, oestrone, progesterone, and pregnanediol). These tests were negative in all normal women, but positive in about three-fourths of the patients with a history suggesting "endocrine allergy". In a number of these latter patients the authors had also succeeded in producing a positive Prausnitz-Kuestner test. In addition to patients suffering from the current allergic diseases, this series comprised patients with pruritus vulvae, acne in relation to menstruation, "premenstrual tension", and intensive menstrual pains. Between one-half and one-third of the patients had eosinophilia. Some of the patients with a positive skin test were desensitized with the positively reacting hormone, resulting in one-third cured, one-third improved, and the remainder unchanged.

Hartman in 1947 published a paper on the same subject. He classified his patients suffering from bronchial asthma, vasomotor rhinitis, urticaria, Quincke's oedema, and migraine in three groups according to the time of occurrence of their symptoms: (1) menopausal, (2) premenstrual, and (3) menstrual. In group 1, comprising 78 patients, all except two, who received androgenic hormone, were desensitized with oestrogenic hormone. Improvement was allegedly obtained in 84 per cent. In group 2, comprising 68 patients, 20 out of 52 suffering from migraine and urticaria were treated by vitamin B injections. Only one-third of these improved. The remaining patients within this group were either desensitized with oestrogenic hormone or received methyl-testosterone by mouth, which gave improvement in about 80 per cent. The methyl-testosterone treatment here seems to have had a small advantage over desensitization with oestrogenic hormone. The total result for group 2 was 67 per cent improved. Group 3 comprised 54 patients, all treated with 1–2 mg oestradiol dipropionate or oestradiol benzoate 2 to 4 days before menstruation, by which 83 per cent improved. The results are not reliable, however, because, among other things, so many of the patients had only migraine or urticaria.

Allergic diseases developed during pregnancy have likewise been treated as "endocrine allergy", and apparently with success. *Turiaf & Zizine* in 1950 reported cases of "asthma of pregnancy" in which the asthma had disappeared after brief desensitization with lutein. They treated 21 patients, but no cure rate is given. In the same paper mention is also made of treatment of asthma in relation to puberty, menstruation, and menopause, and different lines of treatment, partly with oestrogenic hormones and partly with androgenic, are indicated, but no results are stated.

The above-mentioned paper by *Zondek & Bromberg* contains a detailed description of the technique of skin tests with hormones and the interpreting the reactions. Further, different forms of reaction are described. *Wolf et al.* (1953), in one of their latest papers dealing with this question, ar-

rived at the conclusion that such cutaneous reactions are unreliable and difficult to interpret, because, for instance, the reactions to both the hormone skin test and the control test with the solvent may flare up in relation to the following period of menstruation.

PRESENT INVESTIGATIONS

On the assumption that it might have a favourable influence on certain patients with supposed "endocrine allergy" to reduce or arrest their production of oestrogenic hormones, 35 patients between the ages of 23 and 55 were treated with androgenic hormone (testosterone propionate). This treatment is commonly supposed to inhibit the production of gonadotrophic hormones in the pituitary body and consequently the ovarian production of oosterogenic hormones, which testosterone is even supposed to neutralize to some extent. Although small quantities of testosterone are believed to be produced in the ovaries (its presence in the androgenic fraction of the ovarian hormones has never been proved, but is regarded as likely), no influence has been attributed to this on the occurrence of allergic symptoms in patients with so-called "endocrine allergy". As is evident from the dosage of testosterone, injected intramuscularly in ordinary doses (see below), the treatment has by no means been intended as a desensitization, because, as stated above, an individual has never been demonstrated to become allergic to one of their own hormones, and desensitization therefore seems irrational.

The total series of patients comprises:

16	patients with	bronchial asthma
4	"	" vasomotor rhinitis
10	"	" Quincke's oedema
2	"	" urticaria
3	"	" migraine

The past histories were all suggestive of "endocrine allergy", i.e. the allergic signs and symptoms had come on

at puberty or menopause, or were closely related in time to menses. However, we had to give up verification of the diagnosis by skin tests, because, as *Wolf et al.*, we found the reactions to be unreliable. Thus, for instance, a marked positive reaction to oestrone was observed in two controls with no allergic disease. One of these also developed late reaction about the "middle day" of progesterone injection. The patients were all treated with testosterone propionate intramuscularly. The dosage varied somewhat, dependent on the response, but as a general rule menopausal patients received 25 mg i.m. once or twice weekly the first 4 weeks, and thereafter 25 mg every 2 or 3 weeks, until the menopausal troubles and the allergic phenomena had subsided. Patients with premenstrual or menstrual allergic symptoms were generally given 25 mg (one patient only 12½ mg) 10 to 14 days and 3 to 7 days before menstruation. This may cause menstruation to set in a few days before or after the expected date; of other side-effects we noticed only in a small number of cases a tendency to headache and increase in weight. As might be expected, no signs of masculinizing on these doses were seen in any of the patients, of whom several had been under treatment for more than 6 months.

Table 1 shows that the whole series of cases has so far been under treatment for from 1 to 8 months. Treatment is being continued of all the patients who have responded favourably. The response was prompt, if there was any, so that already after 1 to 2 injections it was possible to judge whether there was any reason to continue. None of the patients treated with an primarily poor result benefited by prolonged treatment.

The results are illustrated in table 2, classified according to disease and type of "endocrine allergy". It appears that out of 35 patients treated, 17 became symptom-free and 7 definitely improved, while 11 remained unimproved. However, among the latter there were three with Quincke's oedema (the last three in table 1) who later proved also—and mainly—to be food allergics, having become symptom-free on a

TABLE I
Clinical observations in 35 patients suffering from "endocrine allergy" treated with androgenic hormone.

Pt.	Age	Disease	Allergic disposition	Type of "endocrine allergy"	Eosinophils pr. mml.	Previously demonstr. cutan. allergy.	Effect of hypoderm. sensitization	Effect of testosterone treatm.	Duration of treatm. in mths.	Remarks
1.	9/56 K.L.	38	Q.Ø.	—	præ.	38	—	++	6	
2.	200/56 M.H.	54	Q.Ø.	++	clim.	188	—	++	5	
3.	464/56 M.K.-L.	23	A.B.	+	præ.	118	—	++	2	
4.	722/56 E.H.	39	Q.Ø.	—	præ.	—	—	+	8	
5.	992/56 H.H.	45	R.V. A.B.	++	clim.	500	+	++	4	
6.	1300/56 T.L.-M.	36	Q.Ø.	+	præ.	188	+	++	3	
7.	2244/56 E.A.	31	Q.Ø.	—	men.	18	+	—	2	exacerbation
8.	2209/56 A.J.	34	R.V.	+	præ.	169	+++	++	2	
9.	1793/55 I.N.	44	A.B.	—	clim.	1094	+	+	3	
10.	1771/55 N.A.	49	A.B.	—	clim.	281	+	++	2	
11.	3614/55 A.J.	49	R.V. A.B.	—	clim.	662	+	+	5	

12.	1939/44 G.N.	47	A.B. R.V.	—	clim.	450	—	++	3	
13.	2960/50 K.N.	55	A.B.	—	clim.	590	+++	+	3	*
14.	478/54 F.B.	36	Mig.	+	men.	505	—	—	2	exacerbation
15.	1369/54 E.P.	35	A.B.	—	præ.	1088	+++	++	4	
16.	121/55 I.G.	36	Q.Ø. R.V.	+	men.	205	—	—	6	
17.	599/55 B.J.	24	A.B.	+	præ.	175	+++	++	6	headache
18.	2417/55 H.H.	52	A.B.	—	clim.	1756	—	+	5	
19.	2866/55 L.T.	33	A.B. R.V.	—	præ.	980	—	++	5	
20.	4334/55 I.S.	33	Urt. Q.Ø.	—	præ.	119	—	+	6	migraine
21.	E.J.	44	Mig.	+	præ.	901	—	++	2	
22.	4129/52 O.G.	39	Mig.	+	men.	56	—	—	1	
23.	654/47 J.R.	44	A.B.	++	clim.	213	+	—	2	exacerbation *
24.	3119/45 E.M.	49	A.B.	—	clim.	166	+	—	2	*
25.	2186/56 A.T.	50	Q.Ø. A.B.	—	clim.	506	—	++	3	*
26.	4613/54 K.L.	45	R.V.	—	præ.	62	—	—	2	

TABLE 1 (cont.)

Pt.	Age	Disease	Allergic disposition	Type of "endocrine allergy"	Eosinophils pr. mm.	Previously demonstr. cutan. allergy	Effect of hypoderm. sensitization	Effect of testosterone treatm.	Duration of treatm. in mths.	Remarks
27. 2661/55 K.J.	41	A.B.	+	præ.	260	+	—	—	2	
28. 4422/51 R.P.	52	A.B. R.V.	—	clim.	1200	—	—	++	2	
29. 3204/44 B.R.	31	A.B.	++	præ.	1650	+++	+	++	2	*
30. 739/56 K.P.	33	Urt.	—	men.	108	—	—	++	4	
31. 2462/47 I.E.	35	A.B.	—	præ.	840	+	—	+	2	*
32. 2878/48 S.R.	46	A.B.	—	clim.	232	+	—	++	2	
33. 258/55 B.B.	25	Q.Ø.	—	men.	200	—	—	—	3	**
34. 2396/54 E.H.	49	Q.Ø.	—	clim.	125	—	—	—	2	**
35. 36/56 A.D.	52	Q.Ø.	+	clim.	106	—	—	—	4	**

Abbreviations: A.B. = bronchial asthma

R.V. = vasomotor rhinitis

Q.Ø. = Quincke's oedema

Mig. = migraine

Urt. = urticaria

clim. = menopausal

men. = menstrual

præ. = premenstrual

* Under continual prednisone treatment

** Food allergic

++ symptom-free

+ greatly improved

— no response

TABLE 2

Clinical results in 35 patients suffering from so-called endocrine allergy, treated with androgenic hormone.

		Symp- tom-free	greatly improved	no re- sponse
Bronchial asthma	menopausal	4	3	2
	premenstrual	5	1	1
	menstrual	0	0	0
Vasomotor rhinitis	menopausal	1	1	0
	premenstrual	1	0	1
	menstrual	0	0	0
Quincke's oedema	menopausal	2	0	2
	premenstrual	2	1	0
	menstrual	0	0	3
Urticaria	menopausal	0	0	0
	premenstrual	0	1	0
	menstrual	1	0	0
Migraine	menopausal	0	0	0
	premenstrual	1	0	0
	menstrual	0	0	2
Total		17	7	11

suitable regimen. These must therefore be supposed to have been incorrectly treated. Among the remaining eight patients there were two (Nos. 23 and 24 in table 1) whose asthma had for several years been repressible only by means of intense corticosteroid treatment. We therefore cherished no illusions about successful treatment of these patients, although they were menopausal; and the result was thus as expected. Of the six patients left, who did not respond to treatment, four had their symptoms during menstruation. According to Hartman, suitable treatment with oestrogenic hormone might possibly help these patients.

The total number with allergic phenomena of the type of "endocrine allergy" treated with testosterone propionate thus

amounted to 32. Of these, 24 (75 per cent) responded favourably. It is evident that we can only expect satisfactory results of the treatment in menopausal patients and in patients whose allergic symptoms occur premenstrually. Only one of our patients with symptoms during menstruation responded to the treatment.

31 of the 32 patients were examined for eosinophilia. In 14 (about 44 per cent) the counts of eosinophilic cells gave raised values ranging from 450 to 1756 per mml. 13 of these improved, while one (No. 14 in table 1) remained unchanged, as might have been expected, since it was a patient suffering from migraine during menstruation.

The total result of 53 per cent symptom-free and 22 per cent improved must be regarded as relatively satisfactory, as the majority of these patients would otherwise have had to manage with symptomatic treatment with antihistamines, bronchospasmolytics, or the like, which as a rule has been found of little effect in such cases. Further, the treatment described here seems to have no side-effects worth mentioning, when the dosage of testosterone is kept within the stated limits, even if the treatment is extended over a fairly long period.

The "ideal patient" for treatment with testosterone should thus be one with eosinophilia and symptoms occurring chiefly or exclusively premenstrually or at the menopause. Before treatment is instituted, the patient should be submitted to a series of susceptibility tests, to exclude other causes of her allergic disease.

DISCUSSION

It is beyond the scope of the present work to discuss the justification of the concept of "endocrine allergy". There seem, however, to exist several cases which, with our present knowledge, cannot be explained in any other way.

The hormonal conditions existing about the periods of menstruation and menopause will briefly be mentioned. The pituitary body produces two gonadotrophic hormones, one

follicle-stimulating and the other luteinizing. By measuring the amount of oestrin in the urine during the menstrual cycle (oestrin is a breakdown product of oestradiol, which is supposed to be produced in the ovarian follicles) we find two peaks of excretion, of which the former is presumed to coincide with the ovulation and the latter with the highest activity of the corpus luteum, i.e. with the time of maximum progesterone production. The oestrin excretion falls markedly immediately before menstruation. During the menopause the production of oestrogenic hormone decreases, while at the same time a considerable rise occurs in the production of gonadotrophic hormone from the pituitary body.

It seems as if the appearance of allergic phenomena in association with menstruation and menopause may bear a certain relation to quantitative changes in the proportion of the sex hormones, but this has not yet been proved. *Zondek*, however, adheres to the view of a "genuine" allergy to endogenous hormones.

It is indisputable that the sex hormones may have an influence on allergic diseases. In 1953 *Klaus Jensen*, in a follow-up study comprising 76 women with bronchial asthma or vasomotor rhinitis, investigated the course of the disease during pregnancy and found an unchanged course in about 20 per cent, whereas the chances of improvement or exacerbation were approximately equal (about 40 per cent of improvement and 40 per cent of exacerbation). In the individual patient the change proved to be the same during each pregnancy. Unfortunately no information could be procured as to whether the disease had borne any relation to menstruation before the pregnancy.

Erik C. Christiansen estimated the cholinesterase activity in human plasma and used the reciprocal value of this as an expression of the oestrogen concentration, because injection of oestrogenic hormone has been found to effect a fall in the serum cholinesterase activity. Inhibition of the oestrogen production should accordingly effect a higher serum cholinesterase activity with a consequent more rapid breakdown of

acetylcholine. That this may be of importance in allergic conditions is shown by *Barnard* (1952), in which he mentions the therapeutic use of cholinesterase, injected intravenously, to seven patients suffering from antihistamine-resistant penicillin-urticaria, and for treatment of "peptone shock" in dogs and cats. Favourable results were allegedly achieved from this treatment. *Morgan* in 1953 described two cases of cholinogenic urticaria, in which the skin test with acetylcholine gave a much stronger reaction than in normals, and in which there was found a low serum cholinesterase activity. Further, attacks could be released by substances with acetylcholin action and checked by atropine. He believes, however, that the clinical picture of cholinogenic urticaria becomes fully developed only if histamine is present. *Halpern*, in an experimental work from 1956, arrived at the result that histamine alone is responsible for the anaphylactic reaction. *Massino*, on the other hand, found that acetylcholine is liberated from the tissues and the blood in the state of anaphylactic shock and during the course of allergic reactions. *Barnard et al.* (1953) observed that in humans the histamine action cannot be prevented by simultaneous injection of cholinesterase.

The question of the significance of histamine and acetylcholine in allergic conditions has not been clarified; in particular some uncertainty seems to prevail regarding the role of acetylcholine. Most likely, however, this plays a rather significant part in certain allergic conditions, e.g. "endocrine allergy".

Though the mechanism of response to testosterone treatment is rather obscure, there is much evidence to suggest that the effect is of a purely symptomatic nature, because the symptoms generally recur if the treatment is discontinued. Briefly we may say that testosterone causes a manifest allergy to become latent during the treatment.

Finally, in assessing the result of the treatment, we must also consider the fact that in "endocrine allergy" the symptoms occur at points of time when women are somewhat off their

balance both physically and especially mentally. The sense of well-being which under such conditions generally follows soon after an injection of testosterone will therefore have a stabilizing effect on the patient, so that the mental factor, which often must be considered in allergics, will be reduced or disappear. However, the fact that the action of testosterone seems to be superior to that of ACTH and corticosteroid in some patients is evidence to suggest that the action of testosterone is not limited to a "stabilizing" effect on the results of treatment.

Thus, as seen in table 1, four out of six patients under continual prednisone treatment could stop corticosteroid treatment after starting testosterone.

SUMMARY

The concept of "endocrine allergy" is explained, and various problems concerning diagnosis and possibilities of treatment are discussed. The results of treatment of 32 patients with signs and symptoms of so-called "endocrine allergy" are reviewed. Of these patients, who were all treated with androgenic hormone in ordinary doses, 53 per cent became symptom-free, while 22 per cent obtained considerable improvement. The patients who responded to treatment were almost exclusively such as presented allergic symptoms in relation to the menopause or premenstrually, whereas allergic symptoms occurring during menstruation remained uninfluenced. By this treatment we were able to help a number of patients on whom other treatment, except perhaps ACTH or corticosteroid therapy, had had little or no effect. Finally, the cause of the response is discussed. This may be due in part to inhibition of the oestrogen activity, causing an increase of the serum cholinesterase activity and consequently a more rapid breakdown of acetylcholine, which is supposed to play a part in certain allergic conditions, including "endocrine allergy".

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