

tibility-accentuating factors of extremes of temperature and ultraviolet rays. The explanation may be that, in persons on the verge of being clinically affected, increased intensity of these factors will precipitate them into active disease, but as their resistance is stronger than that of persons who would ordinarily get the disease, they dilute the fatality-rate. Conversely, milder temperature and irradiation effects mean that only the persons of very low nutritional status are affected, the fatality-rate being thus concentrated.

If this hypothesis is correct, a law emerges to the effect that, when in an epidemic incidence rises but fatality drops, a factor is at work increasing susceptibility; and, when incidence decreases but fatality rises, a factor is at work decreasing susceptibility, and a background of malnutrition to the epidemic may be suspected. This can apply only if death-time is well within the graph time-unit. That this law may be valid was shown by me in 1935 (Corkill 1936). A community given prophylactic vitamin A had fewer cases but a higher death-rate than a comparable community not so treated, suggesting that a factor—i.e., vitamin A—decreasing susceptibility was involved.

#### CONCLUSIONS

It is concluded that susceptibility to meningococcal meningitis is a deficiency state, and that climate is an important factor in epidemics in that ultraviolet irradiation activates mass susceptibility and causes epidemics, and extremes of temperature accentuate this susceptibility. Clouds and humidity are beneficial in that they reduce ultraviolet radiation; the association of rainfall is incidental.

An important point is that in an epidemic, before populations are turned out wholesale from their villages to obviate the very important factor of overcrowding, it should be secured that their temporary shelters give adequate protection from bright sunlight and cold winds; otherwise the weighty factor of exposure is thrown into a scale-pan already heavily dipped by the factors of malnutrition and, presumably, a heavy carrier-rate. This has been a matter of experience in the Nuba mountains and, it is understood, in Darfur.

#### SUMMARY

(1) Popular opinion in the Northern Sudan associates epidemics of meningitis with the dry season and their closure with the onset of the rains; but rain is merely an incidental factor.

(2) Since humidity and clouds are associated with the closure of epidemics, and temperature extremes increase susceptibility to the disease but decrease the fatality-rate, and sunlight is associated with the disease, it is suggested that clouds and humidity close epidemics by decreasing solar irradiation. Susceptibility to meningococcal meningitis may be regarded as a deficiency state, being activated by seasonal advent of heavy ultraviolet irradiation. Laboratory evidence of activation of deficiency states by ultraviolet irradiation is given, and the tribal populations involved are shown necessarily to be deficient in protein and vitamins A, B<sub>2</sub>, and C. Classical deficiency diseases occur among them.

(3) A similar argument applied to northern latitudes explains the local epidemiology of epidemic meningitis.

(4) A new law relating graph phenomena in an epidemic to a malnutritional background is tentatively formulated.

(5) It is concluded that quarantine measures disregarding the factor of exposure may be very harmful.

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#### REFERENCES

- Corkill, N. L. (1936) *J. trop. Med. (Hyg.)*, **39**, 1.  
 Frank, M. (1937) *Arch. Kinderheilk.* **110**, 91.  
 Maurice, G. K. (1938) personal communication.  
 Mouriquand, G., Rollet, J., and Courbières, M. (1935) *C.R. Soc. Biol. Paris*, **118**, 1455.  
 Riding, D., and Corkill, N. L. (1932) *J. Hyg., Camb.* **32**, 258.  
 Schiøtz, C. (1935) *Norsk Mag. Laegevidensk.* **96**, 1 (Abstr. in *Lancet*, 1935, 1, 243).

## EFFECT OF FOLLICULAR HORMONE ON MENOPAUSAL FLUSHES

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ALTHOUGH the efficacy of ovarian follicular hormone in menopausal disorders is generally recognised, much remains to be learnt about the dosage. This paper reports the use of comparatively small doses in 51 cases where the menopause had been induced with radium. The indication for treatment was the symptom generally called "flushings" or "hot sweats," and since this is the best-defined, as well as the commonest, of all the many menopausal complaints, it was used as an index of therapeutic action.

Whatever part other endocrine or nervous influences may play in causing these flushes, they certainly follow the withdrawal of the ovarian influence, and administration of ovarian hormone is rational. In judging its effect, however, one must remember that the patients are apt to be in a highly suggestible state. Thus in 100 cases at the normal menopause Pratt and Thomas (1937) found that the general condition benefited as much from lactose tablets and injections of sterile oil as from preparations containing ovarian hormones. In the present inquiry I have tried to eliminate the psychological factor by asking the women to take written notes of the number, severity and duration of the "flushes," and by substituting dummy tablets of lactose in every fifth patient treated.

In the majority of cases hormone therapy was started 8–12 weeks after radium was used, and, although "flushes" have developed in this interval, it is my experience that as a rule a considerably longer time elapses before the mental changes become apparent.

In women over 40 the interval between the radium treatment and the onset of "hot flushes" varies considerably, but the average time is probably four to eight weeks. In surgical castrates and younger women the onset is much quicker. Werner (1935) found an immediate onset in 44 out of 53 castrates; though he also said that some women might have a period of delayed onset varying from six months to six years. In all my cases "flushes" had developed to various degrees by the eighth week after radium treatment.

#### DOSAGE AND RESULTS

Most authorities, including Kaufmann, have expressed the belief that large doses of hormones

are necessary to produce relief in castrates; but Bishop (1938) reports that 0.6 mg. of oestrone daily by mouth controlled the "flushings" of a surgical castrate aged 20.

When the castration is brought about by radium, the cessation of the ovarian secretion is less sudden, and patients of more mature age are probably less affected by the loss of this secretion. In this investigation all the patients were over 40, most of them being about 45. Compared with the normal standards, very small doses of hormone have been given—so small, in fact, that noticeable results were hardly to be expected. But satisfactory results were obtained in nearly every case, although few were completely relieved. A gradual readjustment of the endocrine balance was aimed at, instead of mere postponement of the severe symptoms by massive doses of hormone. Although injection is usually more efficient the hormone was given by mouth. Apart from expense, this is the most practical method for practitioners who deal with large numbers of these patients and find it difficult to give frequent hypodermic injections.

The 51 women were treated over periods varying up to six months. In most cases treatment began between the eighth and twelfth weeks after the radium. The preparation of follicular hormone used was Gynœstryl (Roussel) of which each tablet contains

0.025 mg. of œstradiol. The largest daily dose given was 8 tablets (0.2 mg. of œstradiol).

The procedure, in an average case, was as follows. The patient was given 4 tablets daily, and the dose was increased to 6 or 8 tablets, according to the result at the end of fourteen days. After four weeks at the increased dose, if the "flushes" were sufficiently controlled to cause the patient no discomfort, the tablets were reduced to 6 or 4, and finally to 2. Any improvement noted was as a rule maintained and it proved unnecessary to revert to a larger dose. The accompanying table shows the number of "flushes" in twenty-four hours at the beginning of treatment and the lowest number this could be reduced to with the above dosage of hormone. The effect on the severity and duration of the "flushes," as noted by the patient, is also recorded.

One in every five cases treated was given dummy tablets of lactose, presented in a similar packing. In these patients, although some said that the severity and duration of the "flushes" were lessened, there was no reduction of the number in twenty-four hours.

#### DISCUSSION

The results indicate that œstradiol reduces the number, severity and duration of "hot flushes" after a radium menopause. In 11 cases, as shown by the table, a complete cure resulted, the average period of treatment being about four weeks; but these were mostly patients with a small number of "flushes" daily, before treatment started. In only 5 cases did treatment fail to reduce the number of "flushes," and in 4 of these their severity lessened. In assessing results one had to rely on the patients' statements, and the emotional instability of women at the menopause reduces the value of such evidence. But the use of dummy tablets and the written notes help to eliminate this source of error.

Since administration of follicular hormone over long periods is expensive, a knowledge of the efficacy of small doses by mouth may be of use to practitioners. Throughout this investigation, therefore, the doses were kept extremely low, although no doubt they could in many cases have been increased with advantage, and complementary injections might have given even better results. The cost averaged 3s. 6d. per week per patient.

#### SUMMARY

(1) Follicular hormone (œstradiol) was administered to 51 women suffering from "hot flushes" after an artificial menopause induced by radium.

(2) The hormone was given only by mouth and the dosage purposely kept very low so as to estimate the effect of the limited quantities likely to be available for such cases in general practice.

(3) In nearly all cases the number and severity of the "flushes" were reduced, and most of the less severe cases were cured.

(4) After the tablets had been gradually withdrawn there was seldom any recurrence of symptoms within the next six months.

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#### REFERENCES

- Bishop, P. M. F. (1938) *Brit. med. J.* 1, 939.  
Pratt, J. P., and Thomas, W. L. (1937) *J. Amer. med. Ass.* 109, 1375.  
Werner, A. A. (1935) *Endocrinology*, 19, 695.

EFFECTS OF FOLLICULAR HORMONE ON VASOMOTOR FLUSHES AFTER ARTIFICIAL MENOPAUSE

Case	Number of flushes in 24 hours.		Severity	Duration	Highest daily dose in tablets
	Before treatment	After œstradiol			
1	3	0	—	—	4
2	About 24	8	Less	Shorter	8
3	4	2	Less	Same	6
4	7	2	Less	Shorter	6
5	3	0	—	—	4
6	14	8	Less	Shorter	8
7	4	1	Less	Same	6
8	4	3 a week	Same	Same	6
9	6	0	—	—	6
10	2	0	—	—	6
11	8	8	Less	Shorter	8
12	7	5	Less	Shorter	8
13	4	3	Less	Shorter	4
14	4	2	Same	Same	6
15	3	1 a week	—	—	6
16	15	4	Less	Shorter	6
17	8	3*	Less	Same	6
18	6	3	Less	Shorter	8
19	8	3	Less	Same	6
20	4	1	Less	Shorter	4
21	4	0	—	—	6
22	2	0	—	—	4
23	4	1 a week	Less	Same	4
24	10	4	Less	Shorter	6
25	1	1	Same	Same	6
26	2	0	—	—	4
27	3	1*	—	—	8
28	12	12	Less	Shorter	8
29	6	2	Less	Shorter	6
30	5	0	—	—	6
31	2	1*	—	—	6
32	2	2	Less	Shorter	8
33	4	0	—	—	6
34	4	2	Less	Shorter	6
35	6	2	Less	Same	6
36	5	3	Less	Shorter	4
37	5	4	Less	Shorter	4
38	About 30	12	Less	Shorter	8
39	7	1*	Less	Shorter	6
40	6	4	Same	Same	8
41	10	3	Less	Shorter	8
42	5	1	Less	Shorter	4
43	12	4	Less	Same	8
44	3	0	—	—	4
45	12	4	Less	Same	6
46	2	0	—	—	4
47	5	2	Less	Same	4
48	4	4	Less	Same	8
49	8	4	Less	Shorter	6
50	4	1	Same	Same	6
51	8	4	Less	Shorter	8

\* Sometimes nil.