and that in the colon was decreased significantly ($0.05 > p > 0.01$) from 3.9 ± 0.8 (6) to 1.7 ± 0.7 mV (4). The inhibitory effect of indomethacin cannot be attributed to a nonspecific action since it did not significantly affect ($p > 0.05$) the maximum increase in potential difference induced by acetylcholine (3.5 ± 0.3 mV (6) in the jejunum and 6.3 ± 1.0 mV (6) in the colon). These observations support the hypothesis that the increased transintestinal potential difference induced by bradykinin is mediated by an increased production of endogenous prostaglandins.

Cyclic AMP is thought to be involved in the secretory states induced by both prostaglandins[13] and bradykinin[7], and this lends further support to the suggestion of a link between bradykinin and prostaglandins. Bradykinin not only increases the transintestinal potential difference in vivo but is also effective in an in vitro preparation, indicating a direct action on the tissue. Sheets of rat jejunum and colon respond to the addition of 50 µg bradykinin to the serosal fluid with transient rises in the potential differences of 1.3 ± 0.2 mV (6) and 3.2 ± 0.8 mV (7), respectively. From simultaneous resistance measurements the change in the current generated by the tissues can be calculated using Ohm's law. In the jejunum bradykinin increased the current by 17.4 ± 3.1 µA/cm^2 (6) and in the colon by 31.7 ± 6.6 µA/cm^2 (7). Thus the rise in potential difference results from an alteration in net ion transport and does not simply reflect a change in tissue resistance. The carcinoid tumour secretes many biologically active substances and 5-hydroxytryptamine has already been implicated as the cause of the diarrhoea associated with this syndrome[14]. In view of the action of bradykinin demonstrated in this study it would appear that the kinins may also play a contributory role.

1 D.L. Wilhelm, A. Rev. Med. *22*, 63 (1971).
2 G.E.G. Sladen, in: Transport across the Intestine, p. 14. Ed. W.L. Burland and P.D. Samuel. 1972.
3 R.A. Frizzell and S.G. Schultz, J. gen. Physiol. *59*, 318 (1972).
4 C.J. Edmonds and J. Marriott, J. Physiol. *194*, 457 (1968).
5 P.T. Hardcastle and J. Eggenton, Biochim. biophys. Acta *298*, 95 (1973).
6 J.R. Vane, Br. J. Pharm. *35*, 209 (1969).
7 A.D. Crocker and S.P. Willavoys, J. Physiol. *253*, 401 (1975).
8 S. Fasth and L. Hultén, Acta chir. scand. *139*, 699 (1973).
9 J.G. Browning, J. Hardcastle, P.T. Hardcastle and P.A. Sanford, J. Physiol. *272*, 737 (1977).
10 P.J. Piper and J.R. Vane, Nature *223*, 29 (1969).
11 J. Eggenton, R.J. Flower, P.T. Hardcastle, P.A. Sanford and D.H. Smyth, J. Physiol. *238*, 79 P (1974).
12 J.R. Vane, Nature New Biol. *231*, 232 (1972).
13 D.V. Kimberg, M. Field, J. Johnson, A. Henderson and E. Gershon, J. clin. Invest. *50*, 1218 (1971).
14 M. Donowitz and H.J. Binder, Am. J. dig. Dis. *20*, 1115 (1975).

The transcendental meditation technique, adrenocortical activity, and implications for stress

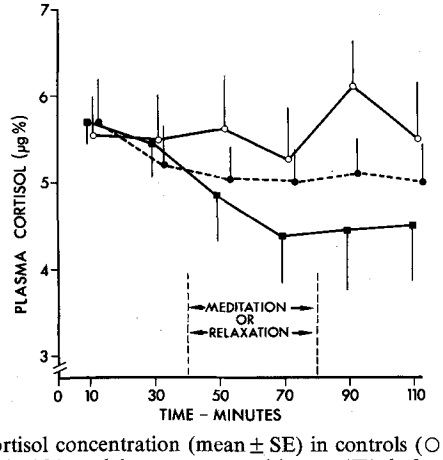
R. Jevning, A.F. Wilson and W.R. Smith

Department of Medicine, University of California, Irvine (California 92717, USA) and Maharishi International University, Fairfield (Iowa 52556, USA), 5 September 1977

Summary. The practice of the transcendental meditation technique in subjects eliciting this state regularly for 3–5 years is correlated with acute decline of adrenocortical activity not associated with sleep during the practice.

Increased adrenocortical hormone levels in the circulation are well established correlates of both acute and chronic stress[1]. However, natural states characterized by acutely decreased adrenocortical activity have not been identified. The technique of transcendental meditation (TM) is a widely practiced, reportedly relaxing[2] mental practice which requires no special circumstances except ordinary considerations of comfort[2]. This practice has been reported to induce, within 30 min, a physiologic state characterized by decreased oxygen consumption, carbon dioxide elimination, and arterial lactate; major redistribution of blood flow[4]; and EEG changes[3]. To see whether these apparent relaxing effects are reflected in endocrine changes, change of plasma concentration of cortisol was measured. Also, since the beneficial effects purportedly associated with meditation may be simply due to sleep or drowsiness accompanying relaxation, the endocrine changes were correlated with occurrence of sleep. We report here a marked decline of plasma cortisol consistent with complete inhibition of adrenocortical activity in long-term practitioners during meditation. This decline was not found to be related to sleep during meditation. The conclusions of this study are at variance with those of Michaels[5].

Materials and methods. Plasma cortisol values were measured in 30 normal day-active young adult volunteers (University students). 15 long-term regular practitioners (8 men and 7 women, ages 22–29) and 15 controls (7 men and 8 women, ages 20–27), were studied; the controls were restudied after 3–4 months of regular TM practice. The long-term practitioners had been practicing the technique from 3 to 5 years. Transcendental meditation is practiced twice daily for 20–40 min by the regular practitioner. All observations were made between 12.00 and 16.00 h, a period of relative stability of mean plasma cortisol concentration[6].



Plasma cortisol concentration (mean ± SE) in controls (○) restudied controls (●) and long-term practitioners (■) before, during and after meditation or rest.

A time series experimental design[7] was used (multiple unit, single intervention) with a pre- and post-intervention period. Experimental observations were made for 120 min, divided into 3 40-min periods. During the pre-meditation or pre-relaxation period (0–40 min), subjects sat with eyes open. Subsequently (40–80 min), they were instructed to close their eyes and start meditation, or in the case of controls, simply to rest or relax. During the post-meditation or post-relaxation period (80–120 min), they continued to sit but with eyes open again. Since drowsiness (EEG stage 1) or sleep (EEG stages 2, 3, 4) may occur during TM[8], we monitored a unipolar electroencephalogram (EEG), electromyogram (EMG), and electro-oculogram (EOG) according to standard methods[9]. Questionnaires were administered in which subjects judged the quality and normalcy of meditation or rest periods after the experiment.

Prior to beginning measurements, an arterial catheter was placed p.c. into a brachial or radial artery. Blood samples were taken every 20 min (2 samples in each of the 40-min periods). Plasma cortisol was measured by the competitive protein binding method of Murphy et al.[10]. For analysis of the trend of cortisol concentration, curvilinear regression analysis of variation over time with a test of significance of the coefficients was used in statistical treatment of the data[11,12].

Results and discussion. Trend of cortisol concentration (mean ±SE) over course of the experiment in controls, restudied controls, and long-term practitioners is shown in the figure. Pre-relaxation and pre-meditation initial values (μg%; mean±SE) at 10 and 30 min for controls were: 5.5±0.5, 5.4±0.6; for restudied controls: 5.8±0.5, 5.1±0.5; for long-term practitioners: 5.7±0.6, 5.4±0.8. Cortisol values in long-term practitioners declined rapidly (27%) during meditation ($p < 0.01$; significance of regression). The decline of cortisol concentration approximated 1.5 mg/100 ml. The trend of mean cortisol concentration in long-term practitioners differed significantly ($p < 0.03$) from that of the control group. Subjects reported comfortable, usual TM or relaxation experience during the measurements.

On the average we found that rest and TM periods were associated with almost identical amounts of sleep: 70% of meditation or rest time was spent in wakefulness, 22% in stage 1 and 8% in stages 2 and 3. There was no correlation between total sleep time and cortisol decline and therefore sleep alone cannot account for the decline observed. Also, TM differs from sleep in this effect since sleep is not correlated with acute alteration of plasma cortisol[13]. These conclusions do not support the hypothesis of Pagano et al.[8] that sleep during meditation is responsible for its beneficial effects.

Since a close qualitative relationship between ACTH and cortisol secretory episodes exists in normal individuals[14], it seems likely that the acute decline of plasma cortisol reflects lessened pituitary-adrenal activation and not a non-specific increase in the metabolic clearance of cortisol; this is further supported by the fact that blood flow to the liver, the principal site of cortisol degradation, actually declines markedly during TM[4]. Based upon the assumption of a 70-min half life for circulating cortisol[6,14], a 27% decline of cortisol concentration in 30 min is consistent with complete inhibition of pituitary-adrenal activity. If no secretion of cortisol occurred for 30 min, plasma levels would decrease to $C_o e^{(\ln 0.5) \times 30/70} = C_o \times (0.74)$; i.e., a 26% decrease.

This report is the 1st documentation of self-induced decrease of adrenocortical activity; whether stylized practices of rest or relaxation-induction other than TM would have a similar effect is a matter of conjecture.

1 E. Bajusz, Physiology and Pathology of Adaptation Mechanisms. Pergamon Press, Oxford 1969.
2 D. Kanellakos and J.S. Lukas, in: The Psychobiology of Transcendental Meditation, p. 17. Benjamin, Menlo Park 1974.
3 R.K. Wallace, H. Benson and A.F. Wilson, Am. J. Physiol. *221*, 795 (1971).
4 R. Jevning, R. Smith and A.F. Wilson, Am. J. Physiol., in press.
5 R.R. Michaels, M.J. Huber and D.S. McCann, Science *192*, 1242 (1976).
6 E.D. Weitzman, K.D. Fukushima and C. Nogeire, J. clin. Endocr. Metab. *33*, 14 (1971).
7 G. Glass, V. Willson and J. Gottman, Design and Analysis of Time Series Experiments. University of Colorado Press, Boulder 1975.
8 R.R. Pagano, R.M. Rose and R.M. Stivers, Science *191*, 308 (1976).
9 A. Rechtshaffen and A. Kales, UCLA National Institutes of Health Publication 204.
10 B.P. Murphy, W. Engelberg and C.J. Pattee, J. clin. Endocr. Metab. *23*, 293 (1963).
11 C.W. Dunnett, in: Statistics in Endocrinology, p. 163. Ed. J. McArthur and T. Colton. MIT Press, Cambridge 1967.
12 G.W. Snedecor and W.G. Cochran, in: Statistical Methods, p. 434, 447. Iowa State University Press, Ames, Iowa 1973.
13 E. Weitzman, C. Nogeire and M. Perlow, J. clin. Endocr. Metab. *38*, 1018 (1974).
14 T.F. Gallagher, K. Yoshida and H.D. Roffwarg, J. clin. Endocr. Metab. *36*, 1058 (1973).

Electrogenic hyperpolarization in canine cardiac Purkinje fibres exposed to calcium ionophores[1]

J.M. Gelles and R. Zeiler

Department of Medicine, Downstate Medical Center of the State University of New York, 450 Clarkson Avenue, Brooklyn N.Y. 11203, USA), 17 October 1977

Summary. The Ca ionophores markedly enhance the increase of intracellular Ca occurring during Na-free perfusion and the hyperpolarization observed upon Na readmission may be due to rapid restoration of intracellular Na and resultant stimulation of both electrogenic sodium and calcium efflux.

Ca efflux from cardiac muscle is dependent upon external Na and Ca[2,3]. When intracellular calcium concentration (Ca_i) is increased, Na-dependent Ca-efflux increases[4]. X-537A and other Ca ionophores which increase Ca_i cause hyperpolarization of the membrane potential in canine cardiac Purkinje fibres (CPF)[5,6]. The present study was undertaken to determine whether this effect of X-537A was dependent upon the presence of Na during exposure to the ionophore.

Methods. Details of the tissue bath and experimental set-up