

between successive cycles in the same subject. Nevertheless, with occasional exceptions<sup>4 9 11-13</sup> there are very few published data which can be described as greatly superior. We do not seek to present arguments for or against the existence of the accepted clinical concepts. We are not aware of any previous attempts to define ranges in this manner, even though several cut off points have been described, ranging from 9.6 nmol/l (3.0 ng/ml)<sup>14</sup> to 38 nmol/l (12.0 ng/ml).<sup>13</sup> In addition, it is worth while re-emphasising that the principles of management of anovulation and defective luteal phase are quite different. There is well accepted and effective treatment for anovulation but little or no controlled evidence that current treatment of luteal phase deficiency is of any value. Thus it is of obvious therapeutic importance to distinguish the two conditions.

Another important feature of this study is the definition of the clinical cut off points as multiples of the follicular phase median. The purpose of this is as follows. It is well known that different assay systems (especially radioimmunoassay systems using different sets of reagents) give different numerical results. Thus an individual laboratory cannot rely entirely on published normal ranges or definitions of abnormality. Equally, the smaller unit cannot do its own clinical trial to define these ranges; even the quite simple investigation described here required appreciable time and effort. It should, however, be possible for any unit to collect a small group (10-20) of samples from apparently normal subjects in the follicular phase—a process aided by the fact that values are stable over this period and exact timing is not important. A median may be derived from this set of values and the multiples of the median then used to extrapolate an upper limit for the follicular phase or "anovular" values and a range for defective luteal function. For convenience, the limits so defined may be rounded to the nearest whole number. In this way the small unit can calculate with reasonable confidence a set of clinical action lines which would otherwise require a lengthy and tedious clinical study.

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## Penile erection: possible role for vasoactive intestinal polypeptide as a neurotransmitter

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### Abstract

Concentrations of vasoactive intestinal polypeptide were measured in blood drawn from the cavernous spaces of corpus cavernosum of the human penis during tumescence and erection, and the effect of injecting the polypeptide into the cavernous spaces was studied. A significant release of the polypeptide was shown during

tumescence and erection. Injection of exogenous vasoactive intestinal polypeptide induced erection.

These findings support the concept of vasoactive intestinal polypeptide as a neurotransmitter in penile erection and suggest that it might have a clinical use in patients suffering from erectile dysfunction.

### Introduction

The 28 amino acid peptide vasoactive intestinal polypeptide has been found in nerve fibres throughout the body.<sup>1</sup> Evidence has been put forward that it functions as a neurotransmitter in several non-adrenergic, non-cholinergic physiological events.<sup>1-2</sup> An essential part of the mechanism leading to penile erection is non-adrenergic, non-cholinergic relaxation of vascular and cavernous smooth muscle.<sup>3-6</sup> The recent finding in the male genital tract of nerves containing vasoactive intestinal polypeptide that seemed to innervate blood vessels,<sup>7-9</sup> and the relaxant effect of the polypeptide on cavernous smooth muscle, suggest that it may act as a neurotransmitter in penile erection.

In the present study we investigated the local release of vasoactive intestinal polypeptide during erection and the effect of administering the polypeptide direct into the cavernous body.

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## Subjects and methods

**Release of vasoactive intestinal polypeptide**—Nine men (aged 24-60) participated in 12 experiments. All had given written informed consent, and the study had been approved by the local ethical committee. Two men were normal volunteers, and seven were being evaluated because of erectile dysfunction (psychogenic in two; due to vascular insufficiency in four; and neurogenic and arteriogenic (after injury) in one). Erection was induced by means of visual sexual stimulation in the two normal men<sup>6</sup>; by intracavernous injection of 80 mg papaverine in five men (one with psychogenic, four with vasoconstrictive dysfunction)<sup>10</sup>; and by a continuous infusion of saline in four (two with psychogenic, two with vasoconstrictive dysfunction).<sup>11</sup> Two men received both infusion of saline and, later, papaverine. Blood samples were drawn from the cavernous body before and during erection for measurement of immunoreactive vasoactive intestinal polypeptide.<sup>12</sup> The plasma concentration of the polypeptide was corrected for the dilution during the saline infusion by determination of the packed cell volume. Peripheral venous blood samples were collected simultaneously during the experiment.

**Effect of exogenous vasoactive intestinal polypeptide**—Five other healthy men with no erectile complaints (aged 21-52) volunteered for this study. All gave written informed consent after the study had been approved by the local ethical committee. Local cavernous blood flow was continuously determined by a <sup>133</sup>Xe washout technique.<sup>6,13</sup> Tumescence was measured with a strain gauge around the penis.<sup>6</sup> Highly purified, sterile vasoactive intestinal polypeptide<sup>14</sup> (20 and 200 pmol) in saline or saline alone was administered as a bolus into the cavernous body in randomised order via a 27 gauge needle without preceding anaesthesia.

Statistical analysis was by Wilcoxon's test for pair differences; p values less than 0.05 were considered to be significant.

## Results

**Release of vasoactive intestinal polypeptide**—Eight of the nine men showed an increase in the median concentration of vasoactive intestinal polypeptide in the cavernous blood during erection (table I). No change

TABLE I—Concentration of vasoactive intestinal polypeptide (VIP) in corpus cavernosum at rest and during full erection or tumescence (figures are medians and interquartile ranges of results obtained in 11 experiments in eight men)

Time (min)	0	5	10	15	20
VIP (pmol/l)	2.0 (0.2-2.0)	20 (11.24)	28 (12.5-31)	51 (9.63)	45 (12.65)

Stimulation was started immediately after t = 0; tumescence or erection was obtained after two to four minutes and was unchanged during the period of observation. The increase in concentration during erection and tumescence was significant ( $p < 0.05$ ). Conversion: SI to traditional units—VIP: 1 pmol/l  $\approx$  3.3 ng/l.

TABLE II—Effect of intracavernous injections of vasoactive intestinal polypeptide (VIP) (20 and 200 pmol) on penile erection\* and local cavernous blood flow† in five normal men (figures are medians and total ranges of results obtained in five experiments)

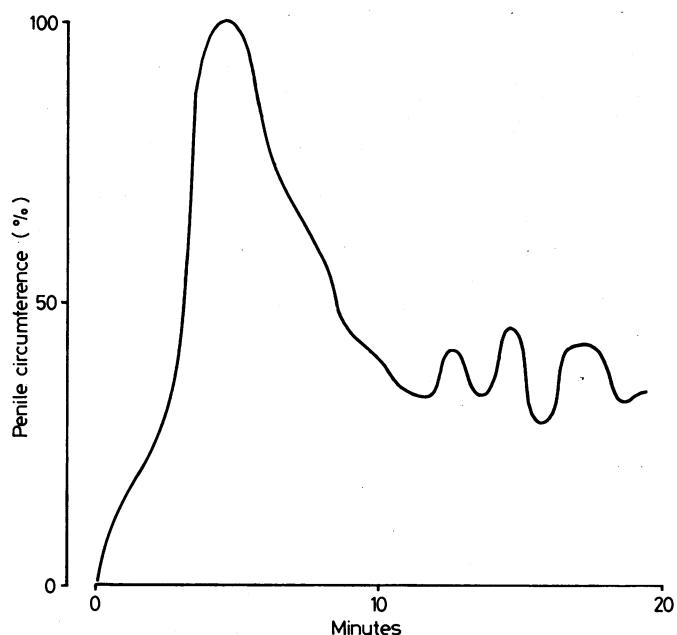
	Baseline	VIP 20 pmol	VIP 200 pmol
Incremental penile circumference (mm)	0 (0.0)	0 (0-10)	11 (5-25)
Elimination coefficient/min	4.6 (2.4-7.1)	2.6 (1.0-3.0)	0.9 (0.4-2.7)

\*Measured as increase in penile circumference on a strain gauge.

†Measured by <sup>133</sup>Xe washout.

in the concentration of the polypeptide could be detected in control samples from peripheral blood. In the patient who had neurogenic and arteriogenic impotence after injury it was impossible to obtain tumescence by means of either an injection of papaverine or an infusion of saline. In this patient the concentration of vasoactive intestinal polypeptide in cavernous blood stayed low (less than 4 pmol/l) throughout the experiment.

**Effect of exogenous vasoactive intestinal polypeptide**—Vasoactive intestinal polypeptide (200 pmol) induced various degrees of tumescence in all subjects and in one patient induced full erection (figure). No effect was observed after saline or after 20 pmol of the polypeptide. The effect was maximum within two to four minutes and lasted 15-30



Effect of intracavernous injection of vasoactive intestinal polypeptide (200 pmol) on penile erection in one normal man, expressed as the increase in penile circumference measured with a strain gauge (full erection = 100%; flaccidity = 0%).

minutes. The penis remained slightly enlarged for several hours. A significant decrease in the local cavernous elimination of <sup>133</sup>Xe and a significant increase in penile circumference were found in all cases (table II).

## Discussion

In the present study the concentration of vasoactive intestinal polypeptide in cavernous blood was shown to increase up to 20-fold during penile tumescence and erection. This change must be due partly to local release of the polypeptide, as the concentration of the polypeptide in the peripheral circulation was unchanged throughout the experiment, and partly to the simultaneous decrease in cavernous blood flow, as a constant release of the polypeptide accompanied by a decrease in local blood flow would lead to an increased concentration. The observed changes in local blood flow during tumescence and erection, however, were not of sufficient magnitude to account for the total rise in the concentration.<sup>6</sup> A similar release of vasoactive intestinal polypeptide during erection induced by electrical stimulation of pelvic nerves has recently been shown in the dog.<sup>15</sup>

Intracavernous administration of vasoactive intestinal polypeptide produced tumescence or erection. We did not give doses higher than 200 pmol owing to the risk of priapism. Although we do not know the concentration at the synapse between the endings of nerves containing the polypeptide and smooth muscle cells, the doses used in the present study were probably lower than or within the physiological range.

From the results of this and previous studies we conclude that vasoactive intestinal polypeptide fulfils several of the classical criteria for a neurotransmitter in penile erection in man: it is present in nerve fibres with nerve endings around cavernous smooth muscle and blood vessels<sup>7-9</sup>; it is released when erection is induced; and when applied exogenously it mimics the action of the endogenously released transmitter and displays identical pharmacological characteristics.<sup>8,9</sup>

The recent observation that phenoxybenzamine (an alpha adrenoceptor blocking agent) injected intracavernously produces full rigid erection in normal and in certain impotent men is of interest,<sup>16</sup> as this compound also has a relaxing effect on cavernous smooth muscle. Thus vasoactive intestinal polypeptide, papa-

verine,<sup>10</sup> and phenoxybenzamine may possibly have a role in diagnostic procedures for erectile dysfunction. None of the drugs, however, should be recommended yet for general therapeutical use.

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## Blood pressure control during weight reduction in obese hypertensive men: separate effects of sodium and energy restriction

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### Abstract

The separate and combined effects of dietary energy and sodium restriction on regulation of blood pressure were investigated in 30 middle aged obese men with essential hypertension attending the outpatient department. In group 1 ( $n=15$ ) a basal period with no dietary restriction was followed by a period taking an energy reduced diet (5.1 MJ; 1230 kcal), the sodium intake being supplemented and hence unchanged (1:ErSn). In group 2 ( $n=15$ ) the basal period preceded a control period with no intervention, which was followed by taking a diet restricted in energy (5.1 MJ; 1220 kcal) and sodium (2:ErSr). During period 1:ErSn there were reductions in heart rate and urinary noradrenaline output but not in systolic or diastolic blood pressure. Body weight decreased by 4.9-11.7 kg and urinary sodium excretion

did not change. In period 2:ErSr urinary sodium output was reduced by 81.4 (SEM 17.8) mmol(mEq)/24 h and there was a weight loss of 8.2 (SEM 0.7) kg. Systolic and diastolic blood pressures fell significantly, as did the heart rate and urinary noradrenaline excretion.

These results show that in hypertensive obese men a moderate weight reducing diet decreases indices of sympathetic nervous system activity. Reduction of blood pressure to the normotensive range was observed only when there was a concomitant restriction of sodium intake.

### Introduction

Reducing weight by decreasing the energy intake lowers the blood pressure in most obese hypertensive patients.<sup>1-8</sup> Nevertheless, weight reduction has not been widely considered as a possible alternative to drug treatment of hypertension, probably owing to the disappointing long term results of weight reduction in obesity.<sup>9</sup> Also the concomitant decrease in dietary salt may have been thought to be responsible for the hypotensive effect of weight loss.<sup>10</sup> In recent years, however, several long term studies<sup>11-13</sup> have shown a convincing effect of weight reduction on blood pressure control in mild hypertension. In addition, some suggest that the weight reduction by itself and not the restriction of salt is the factor responsible for the blood pressure lowering effect,<sup>6,7</sup> although this remains controversial.<sup>13</sup> As an alternative mechanism of reduction in blood pressure with weight loss some authors have reported a hypotensive effect of

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