greater than that found by Register and Sarett (1951) but not out of keeping with those reported by Girdwood (1951), Mollin and Ross. (1952), Heinrich (1954), Jones, Mills, and Capps (1957), and Linnell *et al.* (1968) in smaller series of normal subjects and by Girdwood (1951), Mollin and Ross (1952), and Heinrich (1954) in patients with pernicious anaemia. The mean value of daily urine vitamin B₁₂ in the non-vitamin B₁₂-deficient subjects was 164 ng./day, which is higher than that previously found by direct measurement but less than that calculated by Hall (1964) from kinetic studies. The significance of mean values is doubtful, however, as the distribution of daily urine vitamin B₁₂ values is lognormal, as is the distribution of serum vitamin B₁₂ levels in normal subjects (Gräsbeck 1961).

The results are of interest in relation to the proportionate losses of vitamin B₁₂ from the body by the renal and intestinal routes. Serial whole-body measurements in normal and in vitamin B₁₂-deficient subjects given radioactive cobalamins orally or parenterally have shown that the daily loss of vitamin B₁₂ from the body is a function of the total body stores amounting to 0.1-0.2% of stores per day (Heyssel, Bozian, Darby, and Bell, 1966; Adams and Boddy, 1968; Boddy and Adams, 1968). Thus with stores of 2,000 µg. the daily loss will be 2-4 µg.: from the results it is clear that the contribution to this total by the urine loss will be small. With a fall in body stores to say 100 µg. and a fall in serum vitamin B₁₂ level to subnormal values the total daily loss will amount to 100 to 200 ng., and the contribution to this total by the urinary loss will be proportionately greater than in normal circumstances and may then account for half of the total loss.

The correlation between the serum and urine vitamin B₁₂ was found in normal and vitamin B₁₂-deficient subjects. Whether the measurements are correlated in disease states accompanied by a high serum vitamin-B₁₂ level, such as chronic myeloid leukaemia (Beard, Pitney and Sanneman, 1954; Mollin and Ross, 1955; Miller and Sullivan, 1958), renal failure (Matthews and Beckett, 1962), or hepatic disease (Holdsworth,

Atkinson, Dossett, and Hall, 1964; Neale, Caughey, Mollin, and Booth, 1966; Rachmilewitz and Eliakim, 1968) has not been investigated, and further study of this aspect may be necessary to comprehend the problem of vitamin B₁₂ balance in disease states.

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Effect of Ergotamine and Ergometrine on Forearm Venous Compliance in Man

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Summary: The effect of ergotamine and ergometrine on the venous compliance of the forearm has been studied in normal persons. Ergotamine tartrate (0.25 mg. intravenously) led to a fall in venous compliance amounting to 49%, on average, while ergometrine maleate (0.25 mg. intravenously) caused a reduction of 41%; these changes were statistically significant. The potent veno-constrictor action of these ergot alkaloids appears to be a major component of the circulatory response to small doses and may be important in provoking the harmful cardiovascular side-effects (such as angina and pulmonary oedema) that are sometimes observed in patients with pre-existing heart disease.

Introduction

The ergot alkaloids have been widely used in medicine and obstetrics for many years, and the risk of gangrene from excessive dosage is well recognized (Goodman and Gilman,

1965). There is, however, some risk of harmful side-effects with standard clinical doses in patients with certain cardiac abnormalities. Thus ergotamine may aggravate the symptoms of angina pectoris in patients with ischaemic heart disease (Friedman *et al.*, 1959), while ergometrine is believed to carry some risk of precipitating pulmonary oedema if given post partum to patients with mitral stenosis (Barnes, 1965). The mechanism of these untoward effects is not clear, though possible explanations have been advanced.

In analysing the circulatory side-effects of the ergot alkaloids it is important to understand their action on the peripheral circulation. The complex effect of these drugs on the arterial system has been studied in detail (Dale, 1906; Rothlin, 1947; Bluntschli and Goetz, 1948; Barcroft *et al.*, 1951), but their effect on the venous system has received little attention. We

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have therefore investigated the action of the two commonly used ergot alkaloids, ergotamine and ergometrine, on the venous compliance of the human forearm. The results show that both alkaloids are potent venoconstrictors in clinically used doses.

Methods

Forearm venous compliance was estimated by measuring the change in forearm volume that occurred when the local venous pressure in the forearm was varied between two arbitrary but fixed levels; the method has been described in detail elsewhere (Robinson and Wilson, 1968). In brief, a sphygmomanometer cuff on the upper arm was inflated to about 30 mm. Hg and maintained at this pressure for three minutes to allow equilibration to occur. The cuff was then deflated during one minute and the change in forearm volume recorded simultaneously with the change in forearm venous pressure; forearm volume was measured by means of a mercury-in-rubber strain gauge, and forearm venous pressure by means of a short length of nylon catheter introduced into the radial vein and connected to a Satham 23 D pressure transducer. Forearm venous compliance was normally expressed as the change in volume per 100 ml. of forearm for a fall in pressure from 25 to 5 mm. Hg. In some patients the forearm venous pressure did not fall to 5 mm. Hg in every study, and in these a slightly different pressure interval was used; in any one experiment, however, the same interval was used for every measurement.

Forearm blood flow was measured by venous occlusion plethysmography with a temperature-compensated mercury-in-rubber strain gauge. A wrist cuff occlusion pressure of 200 mm. Hg was used with a collecting cuff pressure of 50 mm. Hg. Flows were recorded for 10 seconds in each 15 seconds, and each value shown is the mean of 10 measurements.

Blood pressure was measured by sphygmomanometer. In experiments in which central venous pressure was recorded a long nylon catheter was introduced into an arm vein and advanced to a central position; it was then connected to a Satham 23 D pressure transducer. The zero level for venous pressure was taken as mid-chest.

Ergotamine was given as the tartrate and ergometrine as the maleate; the weights of the drugs refer to the salts.

Experiments were carried out in six normal volunteers. The studies were performed with the subjects lying comfortably on a bed, and they were allowed to rest for at least half an hour before any measurements were made. An intravenous infusion was set up in the arm not being used for measurements and an infusion of 0.9% saline was maintained by a constant-rate syringe driver throughout the experiment. A minimum of three control measurements of venous compliance were obtained, and forearm blood flow and arterial pressure were recorded. The saline infusion syringe was then changed for one containing the ergot alkaloid under study in solution in saline, and a total of 0.25 mg. was given over 10 minutes. Five further measurements of venous compliance were made at 10-minute intervals beginning 10 minutes after completion of the infusion, and when ergometrine was being studied an additional measurement was made immediately the drug had been given. Forearm blood flow and arterial pressure were recorded 20 and 40 minutes after the infusion had been completed.

In one study with every subject saline was infused for 10 minutes after the control measurements and a further two measurements were obtained at 10-minute intervals before the alkaloid was infused. The fact that the alkaloid was not being given during the first infusion was known to the experimenters when they acted as subjects, but was not known to the other volunteers. In one subject the forearm venous compliance was recorded at 10-minute intervals over a

period of one and a half hours without administration of any drug.

Statistical comparisons were made by Student's *t* test as adapted for use with paired data.

Results

Effect of Saline (Six Subjects).—The average of the two control measurements of venous compliance was 1.74 ml./100 ml./25-5 mm. Hg.† while the average at 10 and 20 minutes after infusion of saline was 1.68 ml./100 ml. (Table I).

TABLE I.—Effect of Saline on Forearm Venous Compliance and Forearm Blood Flow. Results are Shown as the Mean $\pm$ 1 Standard Deviation

	Venous Compliance (ml./100 ml./25-5 mm. Hg)	Forearm Blood Flow (ml./100 ml.)
Control 1.. ..	1.72 $\pm$ 0.31	2.2 $\pm$ 0.6
Control 2.. ..	1.76 $\pm$ 0.27	—
10 minutes after saline ..	1.67 $\pm$ 0.41	—
20 minutes after saline ..	1.69 $\pm$ 0.37	2.1 $\pm$ 0.8

The changes are not statistically significant.

Forearm blood flow averaged 2.2 ml./100 ml. before saline and 2.1 ml./100 ml. after.

Effect of Repeated Measurement of Venous Compliance (One Subject).—In the subject in whom venous compliance was measured at 10-minute intervals for one and a half hours the values obtained showed little variation and the level had only a slight tendency to fall with time (Fig. 1).

Effect of Ergotamine (Five Subjects).—In every subject there was a large fall in forearm venous compliance after ergotamine (Table II and Fig. 1). This change was already well

FIG. 1.—Effect on forearm venous compliance of ergotamine tartrate and ergometrine maleate in one subject. The drugs were infused intravenously in a dose of 0.25 mg. over the time shown; in the control study no infusion was given. The pressure interval used for measurement of venous compliance varied slightly from study to study.

developed at 10 minutes, but the maximum effect was not attained until 40 minutes, at which time the decrease in compliance amounted to 49% on average. When compared with the immediately preceding control measurements, the fall in venous compliance was highly significant at each interval. Forearm blood flow increased by 14% on average at 20 minutes, but had returned to the control value by 40 minutes; the changes were inconsistent, however, and the increase at 20 minutes was not statistically significant. Calculated mean arterial pressure increased by 14% at 20 minutes and 17% at 40

† In some subjects the pressure interval used differed slightly from the standard limits of 25-5 mm. Hg, but the same interval was used for all measurements in any one experiment.

minutes; these changes have not been analysed statistically since the measurements were not obtained by direct recording.

Effect of Ergometrine (Five Subjects).—Forearm venous compliance showed a large fall in every subject after ergometrine. A significant reduction in compliance was already apparent at the completion of the infusion and reached its maximum by 40 minutes, when it amounted to 41% on average (Table II). The change from the control values was

oped more slowly than that to ergometrine (Fig. 1). Ten minutes after the completion of the infusion, only 48% of the eventual response had occurred on average with ergotamine, whereas 77% had occurred with ergometrine; this difference was highly significant ($P<0.01$).

Effect on Central Venous Pressure (Two Subjects).—In one subject the central venous pressure was measured together with the forearm venous compliance before and after ergot-

TABLE II.—Effect of Ergotamine and Ergometrine on Forearm Venous Compliance, Forearm Blood Flow, and Calculated Mean Arterial Pressure. Results are shown as the Mean $\pm$ 1 Standard Deviation

	Ergotamine (five subjects)			Ergometrine (five subjects)		
	Venous Compliance (ml./100 ml./25.5 mm. Hg)	Forearm Blood Flow (ml./100 ml.)	Mean Arterial Pressure (mm. Hg)	Venous Compliance (ml./100 ml./25.5 mm. Hg)	Forearm Blood Flow (ml./100 ml.)	Mean Arterial Pressure (mm. Hg)
Control 1	1.68 $\pm$ 0.39	2.2 $\pm$ 0.6	84 $\pm$ 4	1.90 $\pm$ 0.38	1.9 $\pm$ 0.8	81 $\pm$ 4
Control 2	1.71 $\pm$ 0.30			1.84 $\pm$ 0.46		
Immediately after drug				1.52 $\pm$ 0.45		
10 minutes after drug	1.31 $\pm$ 0.26			1.24 $\pm$ 0.40		
20 minutes after drug	1.04 $\pm$ 0.25	2.5 $\pm$ 0.5	96 $\pm$ 5	1.12 $\pm$ 0.46	2.2 $\pm$ 1.1	88 $\pm$ 10
30 minutes after drug	0.93 $\pm$ 0.24			1.12 $\pm$ 0.48		
40 minutes after drug	0.86 $\pm$ 0.22	2.2 $\pm$ 0.5	98 $\pm$ 7	1.10 $\pm$ 0.41	1.9 $\pm$ 0.7	86 $\pm$ 8
50 minutes after drug	0.86 $\pm$ 0.23			1.15 $\pm$ 0.45		

The fall in venous compliance following administration of the drugs is significant at the 1% level for all measurements except that immediately following ergometrine which is significant at the 5% level. The changes in forearm blood flow are not statistically significant.

significant at each interval. Forearm blood flow tended to increase in some subjects, but the average change for the whole group, which was an increase of 16% at 20 minutes and a return to the control level at 40 minutes, was not significant. The calculated mean blood pressure increased by 9% at 20 minutes and by 6% at 40 minutes.

Comparison of Speed of Action of Ergotamine and Ergometrine.—The venoconstrictor response to ergotamine devel-

amine, and in another before and after ergometrine. In both subjects the decrease in venous compliance was accompanied by a clear increase in central venous pressure, which amounted to 4.2 mm. Hg after ergotamine and 3 mm. Hg after ergometrine (Figs. 2 and 3).

Discussion

For many years it has been known that the natural ergot alkaloids exert a direct constrictor effect on the arterial system (Dale, 1906; Rothlin, 1947; Bluntschli and Goetz, 1948; Barcroft *et al.*, 1951). The present study indicates that ergotamine and ergometrine also have a potent constrictor effect on the forearm veins in man when given in doses that are in the lower range of those used clinically. It is of interest that there was a clear difference in speed of action between the two drugs, the venoconstriction after ergometrine appearing much more rapidly than that after ergotamine; a similar difference in speed of action is seen in the effect of the two alkaloids on the uterus (Smith, 1938). Several earlier observations are consistent with the occurrence of venoconstriction after ergot preparations. Thus Dale (1906) noted a fall in the leg volume of a cat when an extract of ergot was given; Freis *et al.* (1949) found a decrease of vascular distensibility in the extremities in man after dihydroergocornine; and Lands *et al.*, (1950) recorded a large reduction of leg volume in the dog after intra-arterial ergotoxine. It does not appear to have been appreciated, however, that these changes might reflect an action of the alkaloids on the veins in addition to the arteries. In the present investigation only ergotamine and ergometrine were studied, but it seems probable that their venoconstrictor action will be found to be shared by other alkaloids of the group.

Our experiments have been limited to the forearm, but it is likely that the constrictor response affects a significant proportion of the systemic venous bed, since the central venous pressure rose substantially in the two subjects in whom it was measured. A rise in venous pressure, as measured in the antecubital fossa, has been noted after ergometrine (Brown *et al.*, 1947), and those workers suggested that it might result in part from a decreased capacity of the vascular reservoir. A rise in venous pressure in an antecubital vein was also observed by Freis *et al.* (1949) after dihydroergocornine, but it was thought to be caused by increased arterial flow.

The demonstration of the potent constrictor effect of ergot-

FIG. 2.—Effect of ergotamine tartrate (0.25 mg. intra-venously) on venous compliance and central venous pressure.

FIG. 3.—Effect of ergometrine maleate (0.25 mg. intra-venously) on venous compliance and central venous pressure.

amine and ergometrine on the veins suggests that a fall in the compliance of the systemic venous reservoir may be an important component of the circulatory changes that follow the administration of clinical doses of these alkaloids. This action may also be an important factor in the production of certain of the harmful side-effects that are occasionally observed. The aggravation of angina pectoris that sometimes follows the administration of ergotamine has been assumed to result from coronary arterial spasm, but there is no evidence to confirm this view. The constrictor action on the veins could provide an alternative explanation: the rise in central venous pressure that results will tend to increase the size of the heart and so augment the metabolic needs of the left ventricle, and this change would be expected to facilitate the development of angina pectoris in response to exercise or other stress. It is interesting to note that the circulatory actions of ergotamine are almost exactly the reverse of those of the organic nitrates which probably relieve angina partly as a result of the venodilatation that they produce.

The occasional occurrence of pulmonary oedema in women with mitral stenosis who have been given ergometrine immediately after delivery is usually attributed to a sudden transfusion of blood resulting from the powerful uterine contraction. Brown *et al.* (1947), however, who suggested this mechanism, also put forward the idea that a decreased capacity of the vascular reservoir might play a part. The finding that ergometrine induces a rapid constriction of the forearm veins

provides strong support for this view, and the resulting rise in central venous pressure may well be an important factor in the precipitation of pulmonary oedema in patients with impaired cardiac function.

The potent effect of ergotamine and ergometrine on the veins should be considered whenever these drugs are used clinically. The venoconstriction that they produce is haemodynamically equivalent to the administration of a rapid blood transfusion, and this should be borne in mind before either alkaloid is given to a patient who has a cardiac disorder.

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Coccidian-like Nature of *Toxoplasma gondii*

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Summary: Specific pathogen-free domestic cats were fed with tissue cysts containing *Toxoplasma gondii*. In two infected cats large numbers of oocysts were produced in the faeces; no oocysts were observed in the faeces of the uninfected control cat. Five days after the feeding of the toxoplasms profuse schizogonic and gametogonic stages were observed in the epithelial cells of the small intestine of one infected cat. A single schizont was observed in an intestinal epithelial cell of a second cat six days after being fed the tissue cysts. There was no evidence of schizogony or gametogony in the uninfected control cat. The stages observed in the intestinal epithelium are identical with those of the well-known endogenous cycles of coccidian parasites. The appearance of these stages, together with the nature of the oocyst, indicates that *T. gondii* is a coccidian parasite closely related to the genus *Isospora*.

Introduction

Toxoplasma gondii is probably the last protozoan parasite of medical importance whose life cycle has yet to be elucidated. Much information has been compiled on its epidemiology,

pathology, immunology, serology, and other aspects of its effect on the life of man and other animals, but it is only relatively recently that a clearer understanding of its life history and transmission has emerged. It was thought that the elucidation of its natural transmission mechanism would provide a clue to the life cycle. This has indeed been proved to be the case.

Research on transmission of toxoplasmosis employing cats was initiated by Hutchison (1965). He showed that a resistant form of *Toxoplasma* could be transmitted in the faeces of cats which had been fed with chronically infected toxoplasmic carcasses. Hutchison (1967) put forward the hypothesis that this resistant form of *Toxoplasma* was transmitted within nematode ova, but subsequent work by ourselves and others has cast doubts on the validity of this hypothesis (Jacobs, 1967; Dubey, 1968; Hutchison *et al.*, 1968; Frenkel *et al.*, 1969; Hutchison and Work, 1969a; Sheffield and Melton, 1969; Work and Hutchison, 1969a).

It was next shown by Work and Hutchison (1969a, 1970b) that the infective unit passed in cat faeces was a cyst. Moreover, they pointed out that this cyst showed remarkable similarities to the coccidian oocyst of *Isospora* (Hutchison and Work, 1969b; Work and Hutchison, 1969b). In the absence of evidence of schizogony and gametogony, however, they tentatively called their cyst "the new cyst" rather than an oocyst. Siim *et al.* (1969), using coccidian terminology, showed that within the oocyst there were two sporocysts each containing four sporozoites, thus strengthening the hypothesis that *T. gondii* is related to the genus *Isospora*. The purpose of

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