

**PHARMACODYNAMICS OF PHENYLPROPANOLAMINE:
ASPECTS OF SAFETY AND EFFICACY IN HUMANS**

by

LAURI RENÉ PETRIE

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ABSTRACT

Phenylpropanolamine (PPA), a synthetic sympathomimetic amine, is widely used as a nasal decongestant and as an appetite suppressant. Much controversy exists regarding the efficacy of the drug as an anorectic agent, the related adverse reactions caused by the relatively high doses required for appetite suppression and the potential of this drug for abuse.

Whilst numerous studies have been carried out to assess the central and cardiovascular safety of PPA and many investigations have been performed to evaluate efficacy in terms of weight loss in humans, there is a relative paucity of information regarding the effects of PPA on appetite and food intake.

A pilot trial was conducted to determine the feasibility of a multidimensional approach to evaluate the safety and efficacy of PPA as an anorectic agent in humans. Eight normotensive caucasian women who were overweight participated in a randomised double-blind cross-over comparison of PPA (75 mg) and placebo and were dosed to steady-state on a 12-hour fixed-dose schedule for a period of eleven weeks. Aspects of efficacy evaluated included the effects of PPA on hunger, appetite and satiety, salivation, macro-nutrient food intake and body weight. Standardised scales were used to quantitatively assess the possible subjective mood and behavioural reinforcing effects of PPA. Supine systolic and diastolic blood pressures were monitored continually throughout the trial.

In addition, peak and trough blood samples were taken to monitor serum concentrations of PPA reached at steady-state and patient compliance with

the dosing schedule. An adaptation of a published reverse-phase high-performance liquid chromatographic (HPLC) assay for PPA in serum using U.V. detection at 210 nm is presented.

A significant decrease in body weight, salivation, total food intake and carbohydrate consumption was demonstrated following PPA administration. Phenylpropanolamine produced significant decrements in subjective reports of hunger and appetite, whilst apparently having little effect on satiety. No significant changes were observed for blood pressures and PPA did not produce significant mood alterations or behavioural reinforcing effects.

The study demonstrates the feasibility of using this multi-faceted approach, with certain design modifications, to evaluate the overall safety and efficacy of PPA as an appetite suppressant.

CHAPTER 1

GENERAL INTRODUCTION

Phenylpropanolamine hydrochloride is a synthetic member of the extensive class of sympathomimetic amines and is structurally and pharmacologically related to amphetamine and ephedrine. Phenylpropanolamine, however, produces similar but not equipotent biochemical and central effects (1). Phenylpropanolamine (PPA) is widely employed as the active component of over-the-counter (OTC) nasal decongestant and appetite suppressant preparations. More recently, PPA has begun to emerge in a multitude of street-stimulants (2).

The most frequently reported adverse reaction associated with the use of phenylpropanolamine is increased blood pressure but other reactions such as psychotic disturbances have also occurred (3).

1.1 PHYSICO-CHEMICAL PROPERTIES OF PHENYLPROPANOLAMINE

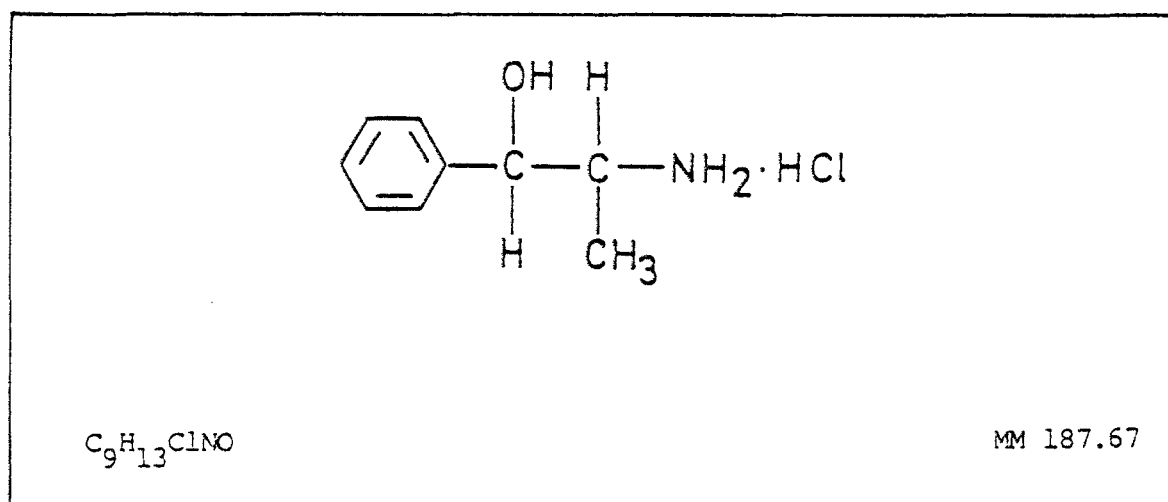
1.1.1 Description

Phenylpropanolamine hydrochloride or d7-norephedrine can be named in various ways (4):

- (a) α -(1-aminoethyl)benzenemethanol hydrochloride
- (b) α -(1-aminoethyl)benzyl alcohol hydrochloride
- (c) ($\pm$)-2-amino-phenylpropan-1-ol hydrochloride
- (d) 2-amino-1-phenyl-1-propanol hydrochloride
- (e) α -hydroxy- β -aminopropylbenzene hydrochloride
- (f) 1-phenyl-2-amino-1-propanol hydrochloride

FIGURE 1.1

Chemical structure of phenylpropanolamine hydrochloride



1.1.2 Synthesis

Phenylpropanolamine hydrochloride is prepared by reacting benzaldehyde in 95% ethanol in the presence of sodium hydroxide to form α -(1-nitroethyl)benzyl alcohol with subsequent reduction of this nitro-alcohol to the corresponding amino compound. A stream of hydrogen chloride passed into a suitable solution of the base yields the hydrochloride (5).

1.1.3 Physical Properties

1.1.3.1 Solubility

Phenylpropanolamine hydrochloride is soluble in 2.5 parts of water and in 9 parts of 95% alcohol and insoluble in chloroform and solvent ether (4).

1.1.3.2 Specific Rotation

The specific rotation $[\alpha]_D^{25}$, of phenylpropanolamine hydrochloride in water is 0° (6).

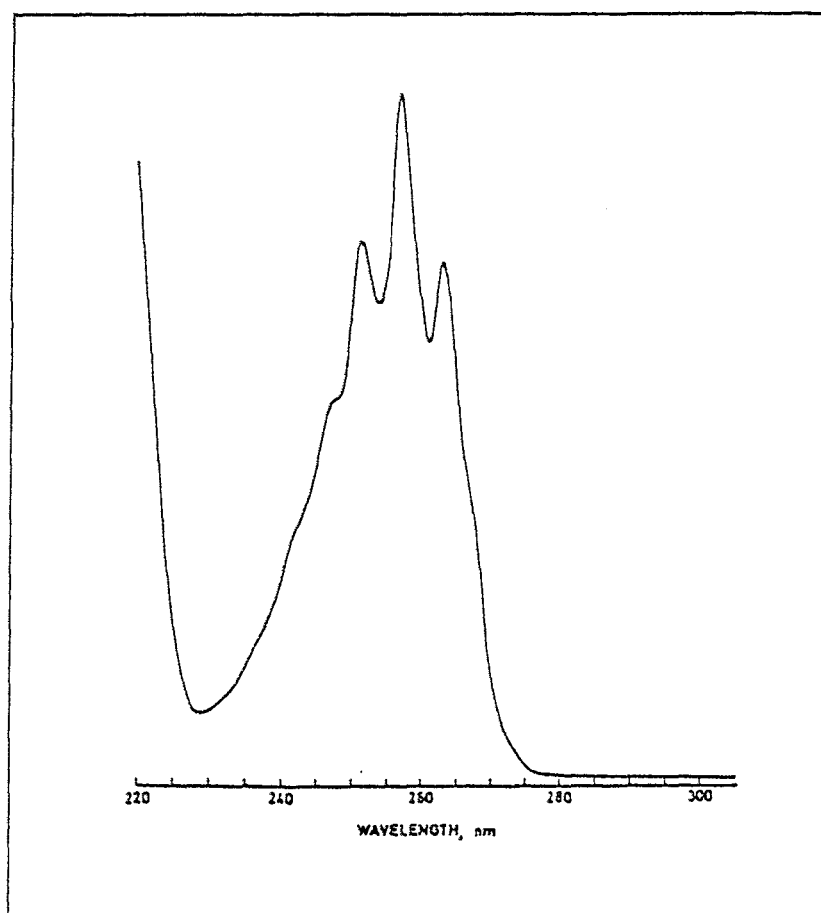
1.1.3.3 Dissociation Constant

The pKa of phenylpropanolamine hydrochloride determined potentiometrically at 20°C is 9.44 ± 0.04 (7).

1.1.3.4 Ultraviolet Spectrum

The ultraviolet spectrum of phenylpropanolamine hydrochloride in methanol at a concentration of 1 mg/ml was obtained with a Beckman Acta MVI ultraviolet spectrophotometer. The spectrum obtained in methanol is shown in Figure 1.2 and depicts shoulders at 267, 248 and 243 nm (8).

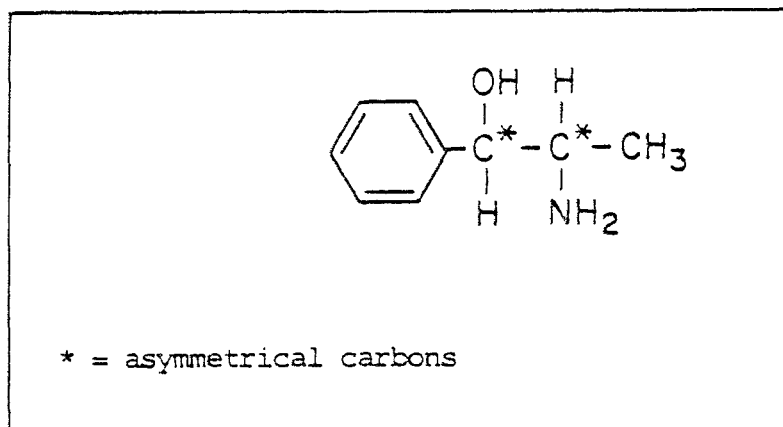
FIGURE 1.2 Ultraviolet spectrum of phenylpropanolamine hydrochloride in methanol



1.2 STEREOCHEMISTRY OF PHENYLPROPANOLAMINE

Simplified line drawings of phenylpropanolamine or d, l-norephedrine as it is chemically known, reveal that both the α - and β -carbon atoms are asymmetric or chiral (Figure 1.3). It is clear that around each of these carbon atoms four spatial arrangements occur and thus four stereoisomers of PPA exist. Evidence of confusion about and a nonchalant approach to the distinctions between the isomers of PPA abounds in the literature. In many reports, part of this confusion has resulted due to the presumptive, non-probative nature of urine drug screening tests using immunoassays, which depend on a relatively nonspecific antibody. Most of the phenylisopropylamines will cross react and a "positive" result may reflect the presence of a norephedrine, amphetamine or ephedrine isomer; or even similar compounds such as phentermine or diethylpropion (9).

FIGURE 1.3 Chiral (asymmetrical) carbon atoms

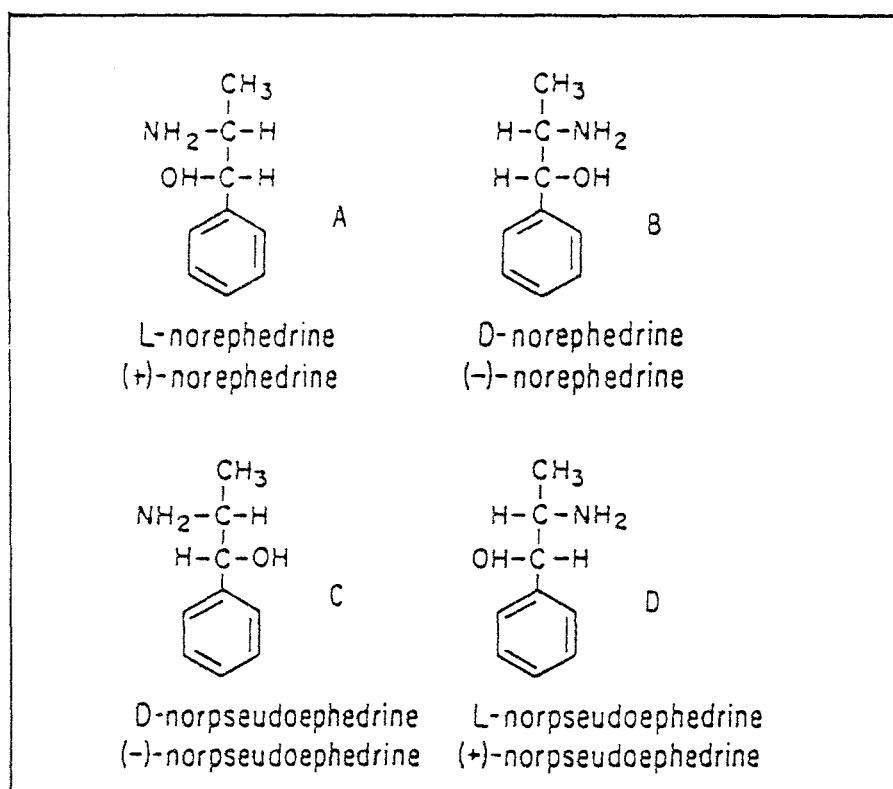


A synthetic reaction essentially yields a racemic mixture composed of equal parts of the (+) and (-) isomers. Phenylpropanolamine, widely marketed and used clinically, consists of a racemic mixture of (+)- and (-)-norephedrine enantiomers (Fig 1.4). Isomeric distinction is of great importance, as enantiomers and diastereomers are not interchangeable and have different pharmacodynamic properties and effects (10, 24).

Numerous reviews of chiral drug action greatly clarify this issue. Results show that (+)-norpseudoephedrine is a potent stimulator of locomotor activity, whilst corresponding isomers of PPA produce stimulation only at doses approaching the lethal range (11). In other studies, results suggest that 7-norephedrine and d, 7-norephedrine are capable of direct activation of vasopressor α -adrenoreceptors, while d-norephedrine has a non-significant effect (12,48).

FIGURE 1.4

Configurational characteristics of PPA isomers



Analytical methods to quantitatively assess norephedrine enantiomers using indirect (diastereomers) and direct (chiral stationary phases) approaches have been published (13-16) and several researchers have reported norephedrine resolution (17, 18). A direct enantiomeric high-performance liquid chromatographic separation of PPA has recently been reported by Wainer *et al* (19).

1.3 PHARMACODYNAMIC PROPERTIES OF PHENYLPROPANOLAMINE

1.3.1 Mechanism of Pharmacologic Action

Phenylpropanolamine hydrochloride (PPA.HCl) belongs to the β -phenylethylamine class of drugs, called sympathomimetics, whose actions closely mimic sympathetic responses. The primary pharmacologic effects of sympathomimetics such as phenylpropanolamine are summarised in Table 1.1.

The main neurotransmitter of the sympathomimetic adrenergic fibres is the catecholamine, norepinephrine (NE), the others being epinephrine and dopamine. Sympathomimetic amines cross the cell membrane of the adrenergic neurones, usually through an active transport process. Within the axon varicosity, the drug crosses the storage vesicle membrane and displaces NE in the intragranular pools which may then act at the adrenoreceptor sites of effector cells, undergo enzyme deactivation by catechol-O-methyltransferase (COMT), or reaccumulate in the cytoplasm of the neuronal axon (20).

Systems	Effects
Central nervous system	Stimulant (psychomotor, locomotor) Analgesic Drugseeking ("addicting") Anorexiant
Cardiovascular system	Vasoconstriction Increased blood pressure, heart rate, cardiac output, etc. Arrhythmias Hypertensive crisis Tachycardia
Metabolic	Increased basal metabolic rate Accelerated blood sugar/carbohydrate metabolism Accelerated blood lipids/fat metabolism Accelerated gastrointestinal mobility/secretions Decreased weight
Other	Mydriasis Decreased uterine contractility

TABLE 1.1 Pharmacologic actions of sympathomimetic agents

The classic studies of Liebman and Tredelenberg (21) established that PPA exerts its sympathomimetic effects via a combination of direct and indirect actions with relatively low potency in this respect. Indirectly-acting amines typically exhibit tachyphylaxis, that is, a decrease in the intensity of drug response as the releasable stores of noradrenaline are depleted following repeated administration of the amine (20).

Phenylpropanolamine is absorbed systemically after oral administration, crosses the blood-brain barrier and acts as a central nervous system (CNS) stimulant via its sympathomimetic activity (22). This activity is related primarily to the blockade of presynaptic neuronal catecholamine uptake, increased release of norepinephrine, inhibition of monoamine oxidase and stimulation of post-synaptic alpha receptors (23). Phenylpropanolamine has a low potency for producing central stimulation and increased locomotor activity (9).

Investigations by Levitt *et al* (25) showed that PPA causes negligible effects on endogenous norepinephrine release, even at toxic doses. In contrast, several studies have demonstrated that PPA inhibits re-uptake of radio-labelled NE via the high-affinity uptake₁ mechanism. There is no direct evidence that PPA causes depletion of NE in the adrenergic terminals and no studies have tested whether PPA could be taken up into the amine storage granules and released as a false transmitter (25).

Phenylpropanolamine possesses both α_1 - and β_1 - adrenergic agonist properties and as such has been labelled a partial agonist. The alpha effects are predominantly vasoconstrictive in nature although urethral and uterine smooth muscle are also affected. The beta effects are occasionally seen as increased heart rate although tachycardia is seldom noted in humans or animals with intact cholinergic mechanisms (26). Published reports lack clarity with regard to possible PPA β_2 -agonist activity.

1.3.2 Mechanism of Anorectic Action

The mechanism by which PPA exerts its anorectic action is uncertain, despite the numerous central and peripheral theories that have been proposed.

It has been established that the anorexic effects of PPA are not mediated by ventromedial hypothalamic effects and that local application to the lateral hypothalamus selectively suppresses food, but not water intake (97). It has been suggested that the anorectic effects of PPA are mediated by NE release or by direct noradrenergic effects in the prefrontal region of the lateral hypothalamus (27). Although this explanation does not seem feasible as PPA does not cause significant release of noradrenaline from the noradrenergic neurons (31), it has been shown by Cairns *et al* that PPA may produce anorexia via catecholaminergic mechanisms (28). A recent study by Wellman (166) suggests that although PPA has weak actions on dopaminergic neurons, its anorexic activity, in contrast to that of amphetamine, is not mediated via a dopaminergic system.

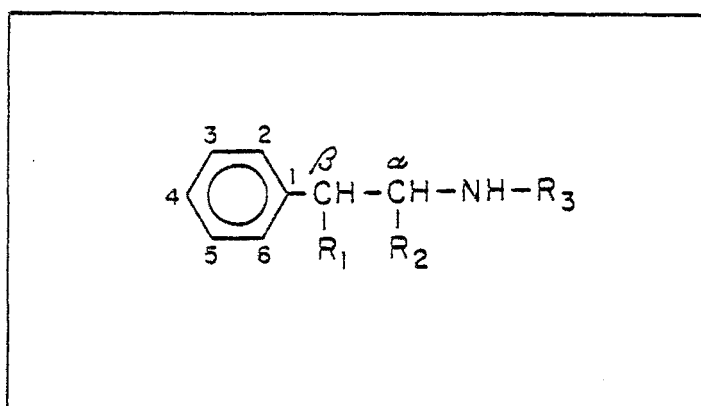
Phenylpropanolamine may cause weight loss, in part, from an excitatory action on brown adipose tissue thermogenesis which is regulated by the sympathetic nervous system and stimulated by β -agonists (29). This suggestion is partly supported by the absence of effects of β -adrenergic blockade on PPA-induced thermogenesis (31). Phenylpropanolamine causes a dose-dependent release of free fatty acids from adipose tissue *in vitro*. It has been shown that phenylpropanolamine increases the gastric transport time in rats and produces a dose-dependent increase in the gastric retention of food (30).

Although numerous animal studies have investigated the effects of PPA on blood glucose and glucose utilization, in attempts to determine whether PPA's anorexic action is mediated by a possible glucostatic mechanism, no consistent data have been produced (31). Altered physiological states may influence the effects of PPA. In a study by Resnick *et al* (32), PPA produced greater hypoglycaemic effects in diabetic as compared with control rats. Another postulated mechanism of the peripheral effects of PPA is conditioned taste aversion, as PPA has been shown to be an aversive stimulus when administered to rats on this paradigm (33).

1.3.3 Structure-Activity Relationships

The functional groups attached to a drug can greatly affect its physico-chemical properties, which can significantly modify both receptor activity and distribution to the biophase.

FIGURE 1.5 Sites of potential structural variance of sympathomimetic phenylethylamines



Phenylpropanolamine contains a two-carbon chain separating the phenyl group and the amino nitrogen. Phenylpropanolamine contains no substitution on the aromatic 3,4-dihydroxyphenyl ring and therefore exhibits relatively low potency as a sympathomimetic amine. The lack of substitution of the catechol nucleus increases the oral effectiveness of PPA and renders it insensitive to catechol-O-methyltransferase. Non-catecholamines can manifest both α - and β -effects, mainly by indirect mechanisms. The methyl group attached to the α -carbon of PPA renders it insensitive to oxidation by monoamine oxidase (MAO) thus greatly prolonging the duration of action of the compound (34).

Phenylpropanolamine contains no substitution on the amino nitrogen and hence has relatively little selectivity for β -adrenergic activity. Beta-hydroxyl substitution markedly reduces distribution of PPA in the central nervous system, decreases the lipid solubility and increases the polarity. For example, the chlorform/water partition coefficients for dextroamphetamine, ephedrine and PPA are 146, 0.015 and 0.001, respectively

(35). Hydroxyl substitution on the beta-carbon may sometimes be accompanied by an enhancement of peripheral α - and β -effects. Beta-hydroxyl substituted compounds are considered indirect agonists (20, 30), that act by enhancing the release of stored catecholamines and/or by inhibiting the uptake of catecholamines (37).

1.4 PHARMACOKINETIC PROPERTIES OF PHENYLPROPANOLAMINE

1.4.1 Absorption and Distribution

Following oral ingestion of an aqueous solution of PPA, absorption is rapid, being completed in less than 2.5 hours (4, 170). However, absorption can be altered by various factors, particularly the presence of absorbents such as activated charcoal (38). Phenylpropanolamine, being a weak base, will not be readily absorbed from an acidic stomach because of ionization. However, in the more alkaline stomach, absorption does occur at rates determined by the dissociation constant and the lipid solubility of the unionized form. Although the pKa of PPA is 9.4, it is almost completely absorbed in the small intestine due to the large surface area available for absorption (7).

Phenylpropanolamine is not highly bound to proteins in the blood (4, 10). As large differences in pH between the blood and gastric contents exist, weak bases such as PPA are, to a small extent, passively concentrated in the stomach. PPA is highly distributed in organ tissues with negligible body fat localization, as evidenced by its tissue distribution in dogs 2 hours after administration; kidney > lung > liver > spleen > brain > heart > muscle > plasma > fat > cerebrospinal fluid (4). Water soluble forms that are metabolically stable, poorly penetrate cellular barriers to reach further sites of metabolism, or central sites of action. PPA has been found to have an apparent volume of distribution of 300 litres (8).

1.4.2 Metabolism

Comparatively little information is available concerning PPA metabolism and excretion. The drug is referred to by Axelrod as a "metabolically stable entity" (39). Considerable species variation has been reported in the metabolism of PPA. In studies with humans, it was found that approximately 90% of the drug was excreted in urine over a 24 hour period, predominantly

unchanged. (40). Sinsheimer *et al* (41) found that, in humans, 86% of a dose of PPA was excreted unchanged with only 4% occurring as transformation products, the major biotransformations being parahydroxylation to 4-hydroxynorephedrine and oxidative side chain deamination to hippuric acid. Phenylpropanolamine is also metabolised by phenylethanolamine-N-transferase to the corresponding N-methylated metabolite.

In the rabbit and rat, 80-90% of [^{14}C] of small oral doses of [^{14}C]-PPA is excreted in the urine within 24 hours, with 1-2% of the dose being detected in the faeces. In the rat, 60% occurs as the unchanged drug and 35% as 4-hydroxynorephedrine. Small amounts of 4-hydroxyhippuric acid and 1,2-dihydroxy-1-phenylpropane were also detected. In the rabbit, however, 76% is excreted as deamination products consisting of 31% 1,2-dihydroxy-1-phenylpropane, 27% 1-hydroxy-2-oxo-1-phenylpropane and 24% benzoic acid (4). Phenylpropanolamine appears as a major metabolite of cathinone (44) and as a minor metabolite of amphetamine, methamphetamine (42) and ephedrine (43).

1.4.3 Excretion

The elimination half-life of PPA.HCl in humans has been reported as 3.9 hours and the elimination rate constant as 0.18 hr^{-1} (8, 10, 45, 170). In a study with humans under controlled urinary pH conditions, acidification of the urine resulted in the excretion of largely unchanged PPA.HCl (46). Conversely, basic urine conditions resulted in a lower fraction of unionized drug causing extreme tubular reabsorption with little influence on metabolism and the renal clearance of PPA decreased by 33.5% (167, 168). Phenylpropanolamine is excreted by glomerular filtration (47).

1.5 USES OF PHENYLPROPANOLAMINE

Phenylpropanolamine hydrochloride is widely used as an over-the-counter (OTC) nasal decongestant and weight control aid and has been the focus of continual debate for many years. Independent FDA advisory panels have reviewed the clinical evidence of PPA as an OTC drug and found it to be safe and effective at appropriate doses in approved formulations (2). Numerous clinical studies have been performed that support the conclusions of these government reviews (51-61). Nevertheless, much controversy exists regarding the safety of PPA (49) and the potential of this drug for abuse

(*vide infra* section 1.6) (50).

Phenylpropanolamine, first synthesized in 1910 (4), was developed and used as an alternative to ephedrine, with significantly fewer side effects, for parenteral maintenance of blood pressure in hypotensive patients. However, with the advent of more effective pressor medications, PPA has become obsolete in this respect. One of the earliest clinical uses of PPA was as a nasal decongestant and it is still used in this regard for the treatment of colds and sinusitis and for symptomatic relief of allergic conditions caused by hayfever, allergic rhinitis, urticaria, angioneurotic oedema and bronchospastic conditions accompanying allergic asthma (64, 81, 82).

Phenylpropanolamine is often used in combination with analgesics, antihistamines, anticholinergics, caffeine, atropine-like drugs and other products to reduce the discomforts of upper respiratory tract symptoms (65). PPA is present in numerous solid and liquid oral formulations (66), and is administered in doses of 12.5 to 50 mg every 3 to 8 hours. Although oral administration may provide a longer duration of action, systemic use may be complicated by undesirable sympathomimetic effects such as agitation, insomnia, increased blood pressure, blurred vision, nausea and epigastric pain, for example (67). Topical nasal solutions and gels containing PPA in concentrations of 1% to 3% are also available (68). While topical application has the advantage of more rapid onset of action, prolonged use causes rebound vasodilation or rhinitis medicamentosa, thereby limiting the usefulness of this route (69).

By a direct stimulatory action on the α -adrenoreceptors, PPA causes constriction of the microvasculature of the edematous nasal mucosa which reduces the blood flow to the turbinates, resulting in shrinkage of the swollen mucosa and promoting relief from nasal stuffiness (70). Phenylpropanolamine has an anti-allergic effect (76), moderately inhibits mucosal secretion (71, 72) and is useful in improving air flow in the nasal passages (75). PPA has been used with some success for the symptomatic treatment of perennial rhinitis (73, 74). Decongestant-antihistamine preparations incorporating PPA to partially counteract the drowsiness caused by antihistamines have been found to be efficacious in treating nasal congestion frequently accompanying acute otitis media with effusion

in children (77).

Phenylpropanolamine in dosages of 50 mg twice daily seems to be of some use in relieving stress during incontinence by stimulating the alpha-adrenoreceptors at the proximal urethra, resulting in sphincter contraction, increased bladder outlet tone and improved bladder storage (78, 79, 143). It has been reported that PPA, when administered in conjunction with oestrogens, causes a more effective elevation of the urethral pressure in elderly women with urinary incontinence (80).

The usefulness of sympathomimetic agents such as PPA in correcting, at least partially, retrograde ejaculation in the presence (82-84) or absence (85) of neurogenic dysfunction, has been demonstrated in occasional reports. Phenylpropanolamine, in doses of 25-75 mg, has recently been indicated to alleviate symptoms in patients with orthostatic hypotension after general treatment measures have failed (86). PPA has been reported to be of some benefit for adults who suffer from mild or sporadic snoring (87) and in combination with paracetamol and phenyltolamine citrate, may be useful in cluster headache (Horton's Headache) (88).

In a recent report (89), PPA was found to be beneficial in antagonizing several, mainly unwanted, effects of diazepam, without diminishing the tranquilizing properties of the anxiolytic.

Clinically, PPA has been used for over 40 years as an appetite suppressant, following the appearance of an article by Hirsch (52), in which he concluded that PPA was effective in controlling the appetite of patients on an anti-obesity diet.

The first controlled clinical trial of PPA as an appetite suppressant was published by Fazeekas *et al* in 1959 (90), in which the authors intimated that PPA did not possess significant anorexiant potential. However, the study was severely criticised as the result of several basic flaws in the experimental design (91). The criticisms raised included: The study population consisted of mentally deficient individuals whose diets were not restricted during the study and who were not necessarily motivated to lose weight, and therefore may not be directly indicative of a normal

population. The design of the trial was questioned in terms of the "double-blind" conditions imposed and because spontaneous weight loss was not estimated. In addition, compliance was impossible to verify as some patients went home on weekends and blood levels of the drug were not monitored. Finally, there appeared to be an interaction between IQ and drug effectiveness (2,91).

Numerous animal studies have demonstrated that PPA significantly reduces body weight and food intake (92, 95, 96, 169). In a systematic study using rats, Tainter (93) found that PPA caused loss of body weight that was not due to changes in energy output or metabolism. However, PPA slowed the rate of passage of food through the gastrointestinal tract. Food intake was reduced, but after approximately one week, tolerance to PPA developed and food intake returned to normal (93). More recently, phenylpropanolamine was found by Rosofsky *et al* (94) to disrupt postprandial satiety in rats as evidenced by changes in behavioural sequence.

Much research has gone into the evaluation of the use of PPA as an appetite suppressant. One problem in assessing the efficacy of an anorectic agent is quantitation of the response. In numerous studies, weight loss and degree of appetite suppression have been used as measures of anorectic efficacy (55-63). However, although weight reduction was the major criterion for proving efficacy, very little emphasis was placed on the effects of PPA on appetite, and the methods used to monitor appetite except in one study by Hoebel *et al* (62).

Two reports have appeared in the literature concerning the effects of PPA on food intake. Hoebel *et al* (62,63) reported that subjects taking PPA experienced a suppression in liquid food intake and noted a significant reduction in supper size and the total amount of snacks eaten, when compared to placebo. Recently, Klesges *et al* (98) reported that PPA (in chewing-gum form) caused a significant reduction in total caloric, fat, carbohydrate and protein intake from baseline to subsequent weeks following a cessation of smoking.

Objective assessment of the safety and efficacy of PPA as an appetite suppressant has been difficult as clinical trials have not always been convincing. Weintraub (99) reviewed a number of PPA clinical trials, published and unpublished. His criticisms related primarily to those designs intended to show efficacy, and did not cite evidence of bias regarding safety data. Concerns raised by the author included design defects, failure to include a run-in period, inconsistent handling of treatment group comparability and "drop-outs", inclusion criteria, problems with ancillary therapy and improper approaches to caloric restriction.

Several appetite suppressant products are currently available in the United States and include traditional dosage forms such as tablets and capsules, as well as novel dosage forms such as chewing-gum and breath-mints. Smaller dose products are usually contained in immediate release formulations, while those containing higher doses are available only as sustained release preparations. Recommended daily dosages vary, but none exceed 75 mg.

As with other medications, some adverse drug reactions attributed to PPA may be related to its serum concentration. Pharmaceutical scientists, in an attempt to decrease the incidence of concentration-dependent adverse reactions have developed an osmotically controlled drug delivery system for PPA, called OROS (Osmotic Release Oral System) and this formulation is marketed as Acutrim. OROS tablets release medication, following zero order kinetics, from a core of active PPA within a semi-permeable membrane. Recently, in a controlled clinical trial Acutrim did not produce any serious cardiovascular effects and in combination with individualised caloric restriction and physician-managed behaviour modification was found to be more effective than placebo in reducing body weight in overweight women (59).

1.6 SIDE EFFECTS OF PHENYLPROPANOLAMINE

In evaluating reports of adverse drug reactions, it is often difficult to identify the contribution of a specific substance, as drug interactions, pre-existing disease conditions and the possibility of overdoses may, individually or jointly, come into play. In addition, accepting patient drug identification without analytical verification of the drug in question in body fluids, is fraught with problems.

Numerous reports of adverse reactions to products containing PPA have been cited in the literature, the most frequently documented reaction being an increase in blood pressure. On the basis of chemical structure and pharmacologic activity, there is no doubt that PPA in sufficient doses is capable of α - and β -agonist action, with potential for evoking hypertension, tachycardia, headaches, arrhythmias and encephalopathy.

Hypertensive responses have been reported after ingestion of single doses of PPA in previously normotensive subjects (100-102), and in patients with special sensitivity to adrenergic pressor agents (103, 104). In a controlled clinical trial, patients taking a double dose of PPA experienced transient hypertension (105). Tachyphylaxis to the blood pressure elevating effects of PPA has been suggested as a possible explanation for the adverse reactions occurring after a single dose of this drug (106). There is evidence that a strong dose-response relationship exists for PPA's hypertensive effect (106-108), as most cases of *ad hoc* blood pressure increases occur following the ingestion of more than 50 mg of PPA (106). However, there have been sporadic reports of increased BP after doses lower than 50 mg (100). In a recent study by Dowse *et al* (109), which detailed the effects of 3 different dosages of racemic PPA as single doses on BP in normotensive human subjects, it was found that no significant changes in BP occurred following the 25 mg dose, whereas statistically significant increases in BP occurred following the 50 and 100 mg doses. However, although serum concentrations of PPA increased linearly with increasing doses of PPA, the authors concluded that no clear-cut correlation could be found between serum concentrations and BP effects.

The reports by Horowitz *et al* (103, 107) which detailed elevated BP's and adverse reactions emulating CNS stimulation in healthy subjects receiving a single dose of Trimolets (an Australian 85 mg IR product) have been widely discussed. There appears some confusion regarding whether the active ingredient contained in this preparation was PPA or (+)-norspseudoephedrine, one of its most centrally active isomers (2).

Additional evidence suggests that PPA-induced hypertension may result in cerebrovascular haemorrhage (110, 111), myocardial injury (112) and cardiac arrhythmias (113, 114). A number of cases of adverse cardiovascular events

have been reported (115). While some case reports fail to specify the exact dose of PPA consumed, most indicate that patients took overdoses of either cough-cold or diet-aid products containing PPA. Three cases of raised blood pressure accompanied by elevated levels of serum creatinine kinase and cardiac-iso-enzymes associated with myocardial infarction have been reported (112). Excessive adrenergic stimulation has been suggested as a causative factor in myocardial necrosis (112).

The increased blood pressure associated with ingestion of therapeutic (116) and excessive doses (117, 118) of PPA has been implicated in causing cerebrovascular haemorrhage with angiographically defined vasculitis, and deaths resulting from these conditions have been ascribed to PPA (114, 116, 118, 119). Although four published case reports (111, 116, 119, 120) have cited a relationship between the ingestion of products containing PPA and subsequent occurrence of stroke related symptoms, the number of cases was small and none could confirm any association between PPA and intra-cranial haemorrhage.

Although blood pressure increased significantly following a single intravenous dose of PPA (0.44 mg/kg), these increases did not correlate with serum concentrations of the drug (121). In controlled repeated-dose trials of sustained release (SR) and immediate release (IR) PPA formulations, in healthy (53, 60, 61) and hypertensive (55, 122, 131) subjects, no clinically significant pressor responses were observed. A similar scenario was demonstrated in a one-day dosage regime comparison of either 25 mg IR tds or 75 mg SR, in normotensive volunteers (51). However, in a similar study by Blackburn *et al*, a clinically unimportant but statistically significant pressor effect occurred in the first 6 hours after ingestion and was greater in the sustained release group (123).

Several case reports (124-129, 142) of psychiatric or affective disorders related to the ingestion of nasal decongestants, appetite suppressants, or "look-alikes" (*vide infra*) containing PPA are cited in the literature. Symptoms of psychotic episodes include auditory and visual hallucinations, confusion, disorientation, delusions, aggression, bizarre and impulsive behaviour, mania, paranoia, agitation, anxiety and depression.

In one report by Dietz (130) acute CNS effects also included hyperventilation, which was probably the result of stimulation of the medullary respiration centre. The most consistent characteristic shared by many of these patients is a positive past psychiatric record. The products containing PPA more than likely exacerbated trait-related symptoms in patients presenting these histories and caused acute drug-induced brain syndromes in those with no psychiatric history. All cases required medical attention and hospitalization was necessary in cases where combination products, in particular those containing caffeine, had been taken.

Presumably because the legal manufacture and availability of amphetamines was severely limited following the passage of the Controlled Substances Act of 1970, a new source of stimulant drug abuse emerged and continues to the present time. Phenylpropanolamine (in combination with caffeine and ephedrine) began to appear in a multitude of amphetamine "look-likes" or "street" stimulants, which were not controlled by prescription. Associated with the abuse of these "look-alike" combination products there have, quite predictably, been reports of amphetamine-like reactions, CNS toxicity and overdose cases (130). PPA has often been implicated as the culprit in such reports, presumably due to its structural similarity to amphetamine. However, there is evidence that the pharmacological activity of PPA is markedly distinct from that of amphetamine (AMP) (165), that PPA does not possess AMP-like euphorogenic or dependence potential (135) and that animal models and epidemiological studies have shown PPA to have a low potential for abuse (132-137). The sale of these combination products was, however, banned in the United States in 1983 (2).

Acute renal failure with tubular necrosis (138) and non-traumatic rhabdomyolysis (139) have been reported following PPA overdose. Caperton (140) reported alleviation of significant complications of Raynaud's phenomenon in three young women following discontinuation of PPA-containing products. He speculated however, that caffeine may have augmented possible vasospastic effects.

PPA has been implicated in causing blurring of eyesight in susceptible people. A recent report suggests that PPA was the precipitating factor in causing bilateral acute angle closure glaucoma through pupil dilation in

a hypermetropic woman (141).

1.7 INTERACTIONS OF PHENYLPROPANOLAMINE WITH OTHER DRUGS

With any widely used drug, it is of major medical importance to establish the effect of its concomitant use in the presence of pre-existing disease states or with other medications. Many reports of adverse drug reactions following the use of PPA are attributed to circumstances in which numerous other drugs, in addition to PPA, were used.

Other sympathomimetic agents should not, even in acceptable doses, be used concurrently with PPA as summation of adrenergic effects is likely to cause adverse reactions (144). A number of reports of interactions occurring between monoamine oxidase inhibitors (MAOI) and sympathomimetic amines, including PPA, appear in the literature (145-148). Concomitant administration of an indirectly acting sympathomimetic amine and a MAOI is likely to cause a sharp increase in blood pressure, accompanied by tachycardia, chest pains and severe occipital headache, and may result in intracranial haemorrhage, cardiac arrhythmias, circulatory failure and death. The results of a controlled clinical study have demonstrated concordance of the adverse pressor effects caused by MAOI-PPA interactions (149).

The inhibition of monoamine oxidase (MAO) in the terminal axon by MAOI causes an increase in levels of norepinephrine at the storage site, which when released by sympathomimetic amines, causes extensive excitation of the receptor neurones resulting in hypertensive crisis (150). However the results of a study performed by D'Mello (151) show that PPA is a poor substrate for MAO and suggest that other enzymes are involved in its metabolism.

A case has been cited of a subject who consumed cheese prior to ingestion of PPA and experienced a hypertensive episode, which could have been due to tyramine present in the cheese acting synergistically with the effect of the sympathomimetic amine (152). Other foods rich in tyramine include red wine, beer, pickled herrings, chocolate and others may act conjointly with PPA to produce an adverse cardiovascular event (148).

Phenylpropanolamine provoked a hypertensive episode in a patient who was taking methyldopa and oxprenolol. Methyldopa is known to potentiate the pressor effects of sympathomimetic amines and it has been postulated that beta-blockade may produce similar effects by permitting unopposed vasoconstriction to adrenergic stimulation (153). The mechanism was, however, not supported as the beta-blocker propranolol, blocked PPA-induced cardiovascular responses (108).

The hypotensive effect of guanethidine may be blocked by PPA (154), and sensitization to the effects of sympathomimetic agents may occur following the administration of bethanidine, whose action is analogous to guanethidine in hypertensive crisis (155). It has been proposed that PPA and hypotensive agents, including debrisoquine, and tricyclic antidepressants may compete for neural reuptake (106).

An unexplained death, attributed to ventricular arrhythmia, occurred in a woman taking thioridazine and a PPA-containing product. However, this profound effect may have been coincidental, as the patient had shown T-wave abnormalities while taking chlorpromazine, suggesting a predisposition to adverse effects from the phenothiazine class of drugs (114).

Reports have appeared in the literature of hypertensive reactions occurring when PPA is taken concurrently with indomethacin (156). The authors concluded that cyclooxygenase inhibitors, such as indomethacin and aspirin, influence the prostaglandins system by reducing the prostaglandin-controlled negative feedback mechanism of catecholamine release at sympathetic nerve endings.

There is evidence that the administration of general anaesthetics may sensitize the myocardium to the potential for PPA-induced cardiac arrhythmias (154).

Two reports have been published of women taking oral contraceptives, who experienced hypertensive episodes following PPA ingestion (157, 158). Factors that can induce hypertension following oral contraceptive use can also increase sensitivity to the pressor effects of PPA.

Individuals who consume large amounts of caffeine-containing products such as coffee, chocolate and cola are at a greater risk of suffering adverse reactions to phenylpropanolamine. Both PPA and the trimethylated xanthine, caffeine, have different, but synergistic mechanisms of action, although caffeine causes more potent CNS stimulatory effects (159). These two drugs in combination have the potential to cause psychotic episodes, cardiac arrhythmias (119, 120), as well as cardiovascular accidents. In a recent study (160), it was shown that PPA administered concurrently with caffeine, caused an increase in the plasma caffeine concentrations, resulting in elevated blood pressures. The authors suggest that PPA either enhances absorption or inhibits elimination of caffeine which may explain increased reports of side effects after their combined use.

In a recent study by Zimmerman *et al* (167), urinary alkalinization with sodium bicarbonate depressed the renal clearance of PPA producing higher post-absorptive plasma concentrations and a small but significant increase in diastolic blood pressure.

1.8 CONTRAINDICATIONS OF PHENYLPROPANOLAMINE

Phenylpropanolamine is contraindicated in pregnancy as it could affect the foetus indirectly through effects on uterine blood flow or uterine contractility during labour (161). It has also been shown that drugs with alpha-adrenergic agonist activity are associated with increased risk of malformations (162).

Expectant and postpartum mothers should be advised against taking any sympathomimetic agent, including PPA, as they may be most susceptible to major affective disorders during these periods (163). Psychotic episodes were experienced by two women who ingested diet aids while pregnant (128).

Phenylpropanolamine is contraindicated in patients who have a familial history of psychosis, as susceptible subjects may develop psychiatric complications following the use of PPA-containing products (128). Conditions that impair the balance and control of the sympathetic nervous system such as autonomic dysfunction, may increase vulnerability to the hypertensive effects of PPA (164). There is also evidence to suggest that individuals with genetically low MAO levels may be more liable to

experience the blood pressure elevating effects of PPA (106).

Phenylpropanolamine is contraindicated in patients with cardiovascular or gastro-intestinal disease, hepatic or renal dysfunction, thyroid or endocrine disorders, hypertension and asthma. The adrenergic properties of PPA may lead to elevated glucose levels and is thus contraindicated in diabetes (165).

CHAPTER 2EVALUATION AND TREATMENT OF OBESITY**2.1 ETIOLOGY OF OBESITY**

Many view obesity, at best, as a set of bad habits and at worst, as an extreme flaw or evidence of moral depravity in the form of gluttony or sloth. The dilemma of obesity is of great concern to the population at large as well as to the medical profession and the treatment of obesity has become the focus of increasing scientific scrutiny.

The etiology of obesity is unknown but the mechanism is simple. The condition develops when energy intake exceeds energy expenditure and an individual's body weight significantly exceeds the norm or ideal body weight (65, 172). Obesity is best viewed as a multifactorial problem involving metabolic, neurological, psychological and socio-economic factors, some of which may be genetically determined. Obesity is generally defined as the excessive accumulation of fat in the storage regions of the body. Excess calories are stored in the form of triglycerides in a cellular unit called an adipocyte. Anatomically, the triglycerides may be stored in pre-existing adipose cells resulting in an increased cell size, or new adipocytes may be formed producing an increase in cell number (172). Functionally, adipose tissue synthesizes and stores fatty acids in triacylglycerols and releases these fatty acids as a source of metabolic fuel (178).

Obesity can be classified according to the age of onset, by etiologic causes and by the anatomic and regional distribution of adipose tissue. When hypercellularity occurs in childhood ("early-onset obesity"), there is an increased number of fat cells and in adulthood ("maturity-onset obesity"), as the number of fat cells is usually fixed, the adipose tissue is enlarged (173). Etiologic causes of obesity include hyperinsulinism, Cushing's syndrome, hypothyroidism and hypogonadism. In addition, obesity can be induced by dietary changes (178).

2.2 BIOLOGICAL ALTERATIONS IN OBESE INDIVIDUALS

The topographical differences in adipose tissue distribution in obesity are well known. Android obesity is characteristically displayed by obese men who typically show enlarged fat depots located on the upper part of the body. However, this type of obesity can be seen in women, particularly during menopause accompanied by other signs of virilization. Gynoid obesity is typical in women who display an excess accumulation of fat deposits in the lower parts of the body and can be seen in men (173, 174). It has been shown that adipocytes localised in the femoral and gluteal regions in women are larger than those in the abdominal areas. Recent functional studies indicate that the specific metabolic pattern of adipocytes in these two regions is regulated by female sex hormones (173). These adipocytes tend to accumulate triglycerides by an increased lipoprotein lipase activity combined with a low lipolytic activity and mobilize fat less effectively than abdominal adipocytes. Consequently, it is extremely difficult to shift the excess weight in the form of adipose tissue in gynoid obesity. The male type of fat distribution, with enlarged abdominal or truncal fat depots, involves fat that is easier to mobilize (173).

There is a large body of evidence to suggest that the majority of obese people show some impairment of carbohydrate metabolism, which may be improved by substantial weight reduction. In addition, obese persons generally show glucose intolerance and an addiction to high carbohydrate diets (176) which would greatly augment insulin levels (177). Insulin has a stimulating effect on fat synthesis and the high blood levels often found in the obese and which are increased following a glucose pre-load may cause rapid accumulation of fat stores (175).

A consistent correlation has been found between the concentration of very low-density lipoproteins (VLDL) and obesity, and that weight reduction is the best treatment for hypertriglyceridemia resulting from the elevated levels of hepatically synthesized VLDL. In contrast, the high-density lipoproteins (HDL cholesterol) are consistently reduced in obese males and females. The concentration of HDL cholesterol is inversely related to the incidence of cardiovascular risks associated with obesity. In general, HDL cholesterol increases with weight loss while the ratio of total cholesterol to HDL cholesterol decreases (175).

The concentration of free fatty acids (FFA) and their turnover are increased in obese subjects. There is enhanced basal lipolysis in large fat cells and an increased response of large fat cells to lipolytic agents. It has been reported that obese persons tend to have lower concentrations of fat-mobilizing substance (FMS) in urine during fasting as opposed to normal control subjects similarly treated. FMS appears to be of pituitary origin and present in man during active fat catabolism and periods of severe carbohydrate deprivation. It is known, in addition, that obese people usually have low levels of growth hormone (GH) which has fat mobilizing and anti-lipogenic effects (173, 175).

In obese men and women the concentration of serum testosterone is decreased probably due to the reduction of sex hormone binding globulin (SHBG), which transports the testosterone in the serum. Obese subjects also generally display an enhanced conversion of androstenedione to estrone in fibroblasts by the stromal elements in adipose tissue, and obese women exhibit a reduced turnover in estradiol (175).

Adrenal secretion of cortisol and excretion of urinary cortisol metabolites are significantly increased in obesity. While the adjustments that occur in thyroid hormone function in obese subjects are complex, it is known that in obese fasting subjects, total thyroxine (T4) levels remain normal but serum triiodothyronine (T3) levels decline (175, 178).

It is thus evident that differences in metabolic and hormonal balance do often exist between obese and non-obese individuals and that in some obese individuals there may be a relative defect in fat mobilisation and an increased tendency to fat synthesis as a consequence of these imbalances. Some of the alterations occurring in obese individuals, such as hyperinsulinemia, impaired GH response and hormonal changes are reversible with weight loss. However, the changes that occur in adrenal or thyroid function, may not change following weight loss (172, 173).

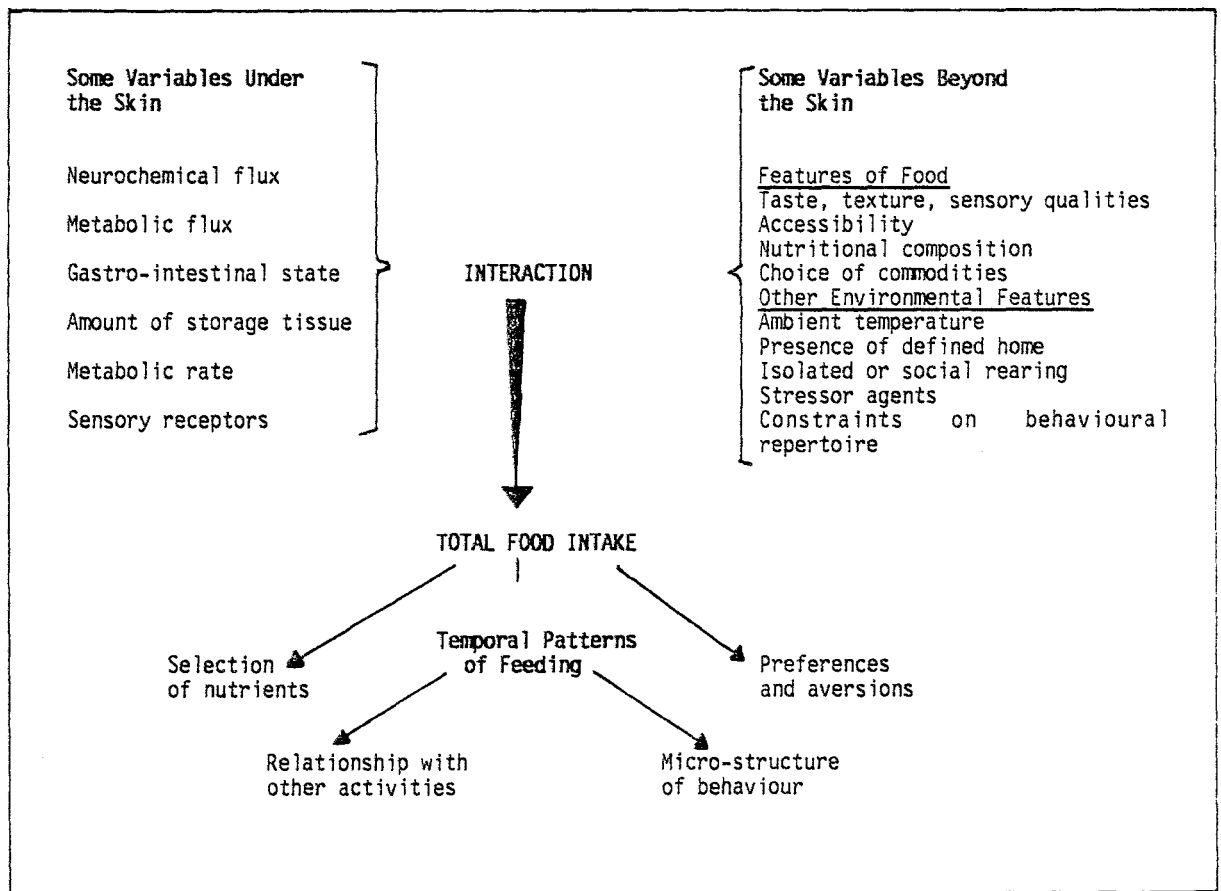
2.3 REGULATION OF ENERGY BALANCE

Because of the complex nature of the relationship between man and his diet, it is difficult to separate the physiological basis of human eating behaviour from the vast overlay of non-physiological factors that may

influence food intake (179, 180). For this reason, it has been difficult to carry out meaningful investigations of food intake regulation in human subjects and researchers have usually sought answers to questions relating to man by observing feeding behaviour in laboratory animals (180).

Feeding behaviour is best viewed as an interaction between two domains: events conducted under the skin and events occurring beyond the skin. Figure 2.1 lists some of the pertinent features of the external environment. Naturally, many of these are concerned with the nature of the food supply including its temperature, flavour, texture, composition and variety. Alterations in these parameters alone are often sufficient to cause large changes in food consumption and body weight (181).

FIGURE 2.1 Feeding depicted as an interaction between two domains
Reproduced from Hill and Blundell (250)



2.3.1 Physiological Factors Affecting Food Intake and Weight

Table 2.1 depicts numerous physiological signals which may trigger the functioning of the complex system which tends to match nutritional input to bodily or somatic requirements. Some of the biological factors that must be considered include the role of taste, gastro-intestinal factors, hormonal and nutrient blood levels and the central nervous system (182).

General Type of Signal	Example
Oropharyngeal Signals:	depending on the taste, texture, temperature of food
Gastro-intestinal events:	stomach contractions and distension, intestinal distension
Hormonal signals:	insulin, prostaglandins, cholecystokinin
Metabolites carried in blood:	glucose, free fatty acids, amino acids, glycerol, lipid mobilising substance
Factors associated with body weight:	amount of fat tissue, number of fat cells, size of fat cells
Factors influencing energy utilization:	thyroxine, growth hormone, corticosteroids

TABLE 2.1 Physiological signals believed to influence food consumption
Reproduced from Blundell (182)

2.3.2 Mechanisms of Food Intake Regulation

The regulation of food intake is a complex biological process that involves regulatory mechanisms at biochemical, organic, behavioural, endocrinologic, social and even cultural levels. Obviously, any anorectic drug, could theoretically affect regulation of food intake at any of these levels and may well act at several to reduce hunger and decrease food intake.

Several theories involving both central and peripheral sites have been proposed to explain the multifactorial mechanisms by which food intake and hence body weight is regulated. For many years research on energy regulation focused on the hypothalamus. This was seen as the loci of the brain where taste factors are integrated with glucostatic, thermostatic and lipostatic mechanisms to control both energy metabolism and the psychological aspects of eating (183).

2.3.2.1 Peripheral Theories

Peripheral mechanism theories emphasize the role of peripheral factors such as taste, stomach distension, rate of stomach emptying, rate of nutrient absorption and the role of gastrointestinal hormones such as cholecystokinin, glucagon, bombesin and somatostatin released during a meal. Alterations in concentrations of these hormones, or any of these factors, have been correlated with changes in eating behaviour induced by various experimental manoeuvres such as sham feeding, for example. The neuroendocrine and sensory aspects of the gut have been suggested as the major peripheral mechanisms that signal feelings of hunger or satiety to the central neural network (178, 184-186).

2.3.2.2 Central Theories

The central anatomical regions thought to regulate appetite occur mainly in the hypothalamus. The hypothalamus acts as a transducer by integrating the sensory inputs and maintaining nutritional homeostasis by activating or suppressing food-seeking behaviour. The hypothalamus fulfills its role through a complex pattern of monoamines and neuropeptides acting on hypothalamic interneurons (188).

To date, a large portion of the research to elucidate basic hunger mechanisms has centred on electrical and chemical control of the hypothalamus. The ventromedial hypothalamus has been designated the satiety centre, since electrical stimulation of this area causes inhibition of feeding leading to aphagia, anorexia and weight loss. Conversely, bilateral electrolytic lesions placed in the ventromedial nucleus cause hyperphagia and obesity. The satiety centre is associated with the serotonergic pathway and the ventral adrenergic bundle (183, 189).

The ventrolateral hypothalamus is known as the feeding centre as it appears to be involved in eliciting feeding behaviour. Application of similar electrical treatments to this area produce essentially opposite effects as the medial hypothalamus. The feeding centre is associated with the dopaminergic nigrostriatal tract. Many of the anabolic and catabolic responses evoked after electrical stimulation or destruction of the hypothalamus are mediated by the autonomic nervous system (ANS) and the autonomic hypothesis suggests that obesity is caused by an imbalance in the

ANS (183, 188).

While regulation of feeding behaviour is commonly attributed to ventromedial and lateral hypothalamic sites, evidence continues to accumulate to demonstrate that several extrahypothalamic structures such as the amygdala, the midbrain, the septum pellicudum and others are also involved in this complex regulatory system (183).

As information is transmitted in the hypothalamus by the release of neurohumoral substances, one of the most vigorously investigated parts of central appetite regulation is the role of the monoamine neurotransmitters in the hypothalamus. By injecting various natural compounds, their analogues or drugs into specific regions of the brain, some of the basic neural systems controlling appetite, satiety and several aspects of behaviour reinforcement have been possible to outline (183). The phenylethylamines such as amphetamine (AMPH), phenylpropylamine (PPA) and fenfluramine (FEN) have similar basic structures to the monoamine neurotransmitters, dopamine (DA), epinephrine (E), norepinephrine (NE) and serotonin (5-HT), which are considered to play an important role in the regulation of various brain functions as well as in the mechanism of action of centrally acting drugs (97, 187).

The pioneering research by Leibowitz (97) showed excitation of feeding by an alpha-adrenergic system in the paraventricular nucleus (PVN) by inhibition of part of the ventromedial hypothalamic satiety centre. Alpha-adrenergic agonists, including AMPH, induce feeding in the medial portions of the hypothalamus probably by releasing NE or E, it is not clear which (97). Amphetamine-induced feeding may sound paradoxical, but is easily observed and explained when AMPH is locally applied to the PVN where it could inhibit satiety and aversion (183). The satiety centre is thought to be under positive serotonergic control as the usual effect of serotonin-agonists, such as FEN, is the production of anorexia (183, 188). Injection of NE, DA and E into the perifornical region of the lateral hypothalamus feeding and reward system has an anti-feeding effect. Likewise the injection of drugs which release catecholamines, such as AMPH into the lateral hypothalamus (LH) suppresses feeding and the effect is beta-adrenergic or dopaminergic (189).

Output from the PVN apparently facilitates both satiety and the post-absorptive energy-release phase of metabolism which are inhibited by NE in the PVN. The evidence to date suggests that serotonin counteracts NE in the PVN control of satiety and carbohydrate intake and metabolism. Most anorectic agents are known to act on brain monoamines and while most show a preferential action for a particular monoaminergic system, they can also affect other systems in the brain (183).

More recently, research has focused on three interesting classes of compounds a) opiates such as enkephalin and dynorphin, b) brain-gut peptides such as cholecystokinin and neurotensin, and c) compounds related to phencyclidine (PCP) or angel dust (183).

Various studies have shown that both exogenous and endogenous opiates can stimulate food intake (190), and appear to preferentially increase the intake of foods with a high energy content (188). Support for this role of the opioids is the ability of the opiate receptor antagonist, naloxone to inhibit the appetite in a variety of species, including man. More specifically, dynorphin, an endogenous opiate peptide that contains leucine enkephalin at its amino terminal apparently induces eating by stimulating kappa opiate receptors. Stress-induced eating may also relate to increased activity of the endogenous opioid system (185, 188).

In contrast to the opioid peptides, the release of most other neuropeptides such as the calcium lowering hormone, calcitonin and corticotrophin-releasing factor (CRF) appear to inhibit rather than stimulate feeding (185, 188). CRF is available in higher concentrations during stress, in some depressed patients and in some disease states such as anorexia nervosa (191, 192). Overactivity of CRF may play a role in the weight loss these patients may experience (185).

It has been shown that the gut peptides cholecystokinin (CCK), neurotensin and bombesin can all cause malaise at high peripheral doses and that intrahypothalamic and intraventricular injection of these brain-gut peptides selectively inhibits food intake (184). Exogenous CCK has been shown to inhibit the size of a test meal in obese and lean subjects and to decrease appetite, in a dose-related fashion (193). The stimulant PCP is

known to act at sigma opiate receptors and acts as a reinforcer at the nucleus accumbens (183).

2.3.2.3 "Set-Point" Theories

Obesity is regarded by many as a behavioural problem and is frequently treated with behavioural therapy in attempts to modify maladaptive eating patterns. However, resistance of obesity to such treatment raises concerns that its origins may not be behavioural (194). The observation that body size remains fairly constant over long periods of time, following the period of rapid growth, has led some theorists to suppose that body size or some aspect of size such as weight is actively regulated (181).

The "set point" theory is supported by numerous researchers and suggests that biological constancy in body weight is maintained within a narrow range or level of adiposity, by reference to a set point embodied in physiological mechanisms, which in turn controls energy intake and expenditure. Other theorists have argued that features such as total body energy, body fat or weight are not actively regulated about prescribed set values but that apparent constancy is maintained by a natural balance between intake and output (194, 195).

It has been demonstrated by Bray (196) that some obese people attempting to lose weight by drastic caloric dilution show a minimal (3%) weight loss and a large decline (17%) in the resting rate of oxygen consumption. This large decline in metabolic rate with so modest a weight loss suggests the participation of a physiological process actively resisting weight change. This type of obese person who displays a normal capacity to regulate and defend body weight physiologically, albeit at an elevated set point, is extremely difficult to treat as the chances of achieving significant weight loss or of sustaining losses that do occur is greatly diminished. However, the growing evidence that set points can be altered by various neuroanatomical, physiological and pharmacological manipulations may, in time, offer a solution to physiologically regulated obesity (194, 195).

However, some obese patients who lose weight fail to display these rapid adaptive adjustments in resting metabolism, suggesting that this type of obesity results from a regulatory dysfunction. It is likely that

conventional treatments such as dieting, behavioural modification of eating habits and increased expenditure through exercise might well be effective in this type of obesity (194).

It is generally thought that changes in body weight set points can be induced by changes in diet, by drugs or toxic agents and by exercise. It remains uncertain whether the changes in body weight that accompany shifts in female hormones, onset or cessation of smoking and the metabolic changes in body composition associated with aging occur because of a direct influence on intake or output, or because the set point has been changed (194, 195).

2.3.2.4 Appetostat Theories

The group of compounds that may serve as correlates between central and peripheral mechanisms are known as appetostats. Appetostat theories suggest that eating behaviour is modulated by the concentrations of substances such as glucose, insulin, amino acids, free fatty acids and purines. The role of nutrients in appetite control and CNS sensors that regulate nutrient levels have been emphasized by numerous researchers (188).

The glucostatic theory was proposed by Carlson in 1916, modified by Mayer in 1955 (188) and suggests that appetite and hunger are regulated by changes in blood glucose levels or related factors such as glucose utilization, insulin or glucose receptors. Glucoreceptors have been identified and located in the ventromedial hypothalamus and in more caudal regions of the brain, in the liver and in the gastro-intestinal tract. It has been shown that iontophoretic application of glucose and/or insulin increases firing of the medial hypothalamic neurons (188).

The lipostatic theory was proposed by Le Magnen (198) who suggested that free fatty acids and triglycerides released during lipolysis could signal feeding behaviour. Iontophoretic application of free fatty acids caused firing of the lateral hypothalamic neurons (197).

The aminostatic theory proposes that changes in plasma amino acid levels may play a role in food intake regulation (188). Certain amino acids such as γ -aminobutyric acid (GABA) have been shown to act as neurotransmitters and to alter feeding, whereas others such as tyrosine and tryptophan (199), that serve as precursors for monoamines, have been shown to modulate feeding (200).

The proliferation of theories of the control of food intake by nutrients suggests that the brain may possess mechanisms for modulating all of the essential nutrients. As macro-nutrients can be interconverted by cellular metabolism, several theories based on overall energy utilization have been proposed. Brobeck's classic thermostatic theory suggests that body temperature and the heat generated by metabolic fuels is responsible for feeding regulation (188).

It has been shown that a defect in brown adipose tissue of genetically obese mice accounts for their inability to increase metabolism in response to cold stress. In man, however, the evidence of thermogenic defects is equivocal and would be inadequate to explain the etiology or persistence of obesity (178, 201).

Miscellaneous factors thought to be important in the regulation of hunger and food intake include hormones, oral and GI factors, vagal influences, exercise and energy balance. Short-term and long-term regulation of food intake are generally considered to be controlled by independent mechanisms (97).

2.3.3 Psychological Factors in the Control of Appetite

It is generally agreed that eating behaviour is controlled to a large extent by psychological factors. For example, taste preferences, time of eating and contents of a given meal show wide cultural variation, being influenced more by social and psychological factors than by physiological determinants.

Psychological factors that affect eating include stress, palatability and salience of the food, social influences and cognitive decisions. These variables may operate to affect eating indirectly, by increasing or

decreasing hunger or satiety or directly, independent of the individual's state of deprivation or repletion (202).

2.3.3.1 The Externality Hypothesis

It has been suggested that obese individuals are unable to differentiate between internal arousal states and frequently interpret such states as hunger. The internality-externality hypothesis proposed that eating by normal-weight persons was influenced by internal signals such as gastric motility and other peripheral and central cues signalling hunger and satiety. On the other hand, eating by obese people was thought to be influenced largely by external cues such as the taste and sight of food, and the number of highly palatable food cues present (180). It has been proposed that the external cue has two effects, a specific effect that elicits an anticipatory response such as salivation and a nonspecific one that arouses the individual and increases the chances of eating to occur (204). It is known that certain times of the day, as well as visual, gustatory, olfactory and cognitive cues predict food availability and result in responses that characterize caloric depletion (205).

There have been numerous reports of significant (206, 207) and nonsignificant (208, 209) interactions of body weight with variations in the visual and cognitive salience of food cues, and the perceived passage of time. It has also been established that normal-weight individuals compensate for changes in caloric density of meals incompletely and are often inaccurate in their perceptions of internal hunger and satiety cues (179, 210-212). Due to a variety of methodological and definitive problems it is difficult to analyse the studies on responses to external cues in obese and non-obese people. However, it is evident that overweight people are not necessarily more responsive to external cues than leaner controls but that external responsiveness is an individual difference factor that can be identified at birth, or subsequently learned and does have the potential to produce weight gain (203).

2.3.3.2 Palatability

Although palatability was originally considered to be an external food-related cue, it has been shown that this variable is not simply an intrinsic property of food. Hedonic judgements are strongly influenced by

physiological variables such as the individual's acute state of energy excess or deprivation, amount of fat stored and metabolic status (213). Palatability is also related to the nutrient value of the food (214) and reflects the learned history of the person rating the food (215).

Most studies on palatability show that both obese and normal-weight individuals consume more when the food is palatable (206, 207, 215, 216). However, in general, overweight subjects ingest more palatable food than normal-weight subjects and these findings are stronger than the findings that overweight subjects reduce their intake of a meal of low palatability. Studies have been performed to establish whether heightened taste responsiveness, and sweet tastes specifically, relates to the development and maintenance of obesity. It has been demonstrated that subjects of different body weights do not differ in perceptions of taste intensity and that weight loss achieved through dieting increases the perceived intensity of sweet tasting solutions (203).

The presentation of a variety of palatable foods augments intake and it has been postulated that the variety effect may be mediated by perceived changes in palatability. Reduction in palatability has been attributed to the mechanism of sensory-specific satiation, first postulated by Le Magnen (203) and which suggests that the oral satiety mechanism operates through stimulation of food passing through the mouth. Several studies demonstrate that the pleasantness ratings of foods consumed during a meal decrease more than the same ratings for foods not eaten. It has been argued by Rolls *et al* that satiety relies on an interaction between internal satiety signals and sensory food cues such as texture, shape, smell, taste and temperature (203).

2.3.3.3 Restrained Eating

It has been suggested that the obesity-externality correlation is a phenomenon of the fact that obese people are always dieting or restricting their food intake in order to lose weight and that conscious restraint is responsible for externality (217). Early experiments showed that restrained eaters, but not unrestrained eaters, consumed more of a test meal following the ingestion of a high-calorie preload. This paradoxical behaviour, termed "counter-regulation", was thought to occur from disruption of the control

dieters usually exert over their food intake (217). This disinhibition was observed by inducing arousal, administering alcohol or manipulating cognitive variables such as knowledge of the caloric content of the preload. It was also shown that unrestrained eaters eat less and lose more weight, and that the effect is reversed in restrained eaters in response to dysphoric emotions such as anxiety, depression or stress (219).

Several studies have reported that restraint, as measured by a restraint scale or Eating Habits Questionnaire, is more common among obese weight individuals than among normal weight individuals (203, 217). However, the large number of obese persons who identified as restrained eaters may be related to the properties of the restraint scale. Studies suggest that counter-regulation may be most typical for normal-weight individuals (218), as obese restrained eaters ate considerably less than normal-weight restrained eaters following a preload aimed at inducing counter-regulation (203). Factor analyses of the restraint scale yielded two main factors, that is, a weight fluctuation factor and a dietary concern factor (219).

The three-factor restraint questionnaire designed by Stunkard and Messick (219) proposes three discrete factors of the global construct of restraint that is, cognitive restraint of eating, disinhibition and hunger, which allow for the determination of how these aspects of restraint relate to binge eating, obesity and other eating disorders.

2.3.3.4 Psychodynamic Hypothesis

Psychoanalytic theories have led to two universal predictions about obese individuals. First, unconscious conflicts arising from disruptions in personality development that occur with a specific pattern of personality traits, leads to overeating. Several psychological disturbances have been postulated and include lack of emotional satisfaction leading to frustration, "over-compensation", increased drive for oral satisfaction, a true addiction to food, a sexual conflict situation, passive dependence and so on. Second, overeating is a response to emotional distress such as anxiety or depression. However, while it is true that psychodynamic mechanisms are important for some individuals, current evidence suggests that obese persons do not, as a whole, differ from normal-weight

individuals on measures of global psychological adjustment and on standard measures of personality (202, 203, 220).

It is well established that one of the effects of stress, anxiety and/or depression is a loss of, or a reduction in appetite. It is postulated that stress activates the sympathetic nervous system to release stored glucose into the bloodstream, which acts to suppress hunger. Although this is generally the case with normal-weight individuals, overweight subjects more often than not, do overeat in response to stress compared to when calm. It appears that stress appears to affect normal weight, non-dieting individuals by affecting hunger and that the effect of stress in obese, dieting individuals is not mediated physiologically (202).

2.3.3.5 Eating Styles of the Obese

Several researchers have investigated the assumption that obese people overeat. However, a variety of methodological problems intrinsic to both laboratory and field studies have hindered the ability to interpret the data clearly.

Most surveys suggest that energy intake is significantly lower in the overweight than in those of normal weight (221). However, one concern with these retrospective observations is that overweight subjects tend to be biased to the low side when using self-report programs (178). In field studies, measuring food intake is complex as subjects have access to many foods, the observer must remain inconspicuous and observational data are subject to observer bias (180, 203). In laboratory studies, although amount eaten is assessed objectively, subjects have fewer food choices and less control over their eating profile. In addition the fact that they are being observed may influence behaviour (222). If differences occur between obese and normal weight subjects in the amount of food eaten, it may be because they choose different types of food and may not necessarily correlate with degree of overweight or level of weight gain (203).

Behaviour therapists have focussed on eating styles as potentially significant in the etiology and treatment of obesity. Empirical studies have evaluated aspects of the topography of eating such as meal duration, eating rate, and a variety of micro-elements of eating styles such as

choice of eating utensils and number of chews per meal (203, 216).

Laboratory studies that have engaged subjects in some parallel activity during eating to ensure that they are unaware of being observed and more naturalistic studies without distraction have shown that meal duration of obese and nonobese subjects does not differ when all subjects are served identical meals (203). However, in a recent summary of research performed in this area, the authors concluded that the obese tend to eat at a more rapid rate than normal-weight individuals (178).

Rate of eating has been studied with other measures of appetite such as perceived hunger and as an aspect of a stable eating style. Presumably eating faster permits a greater intake before post-ingestive satiety cues occur. Wooley *et al* found that the rate of eating one meal has a positive influence on salivation a putative measure of appetite, at a subsequent meal (203).

Most of the current data provide an inconsistent picture of differences in eating style or amount eaten between overweight and normal-weight subjects. Differences that do emerge may not be causally related to obesity since efforts to modify eating style in behaviour treatment programs have not shown substantial effects on weight loss for all over-weight patients (203).

2.4 CLINICAL ASSESSMENT OF OBESE INDIVIDUALS

Although the factors eliciting or contributing to obesity are numerous and not coherently illustrated as yet, sufficient information is available to demonstrate that the obese are a diverse group with many differences. One of the obstacles in the treatment of obesity is a tendency toward bias of recommendations according to the strengths or background of the clinician or counsellor. A comprehensive assessment of the factors contributing to the development of obesity is essential to allow adequate and pertinent treatment modalities to be instituted.

Clinical and biochemical evaluation of diabetes, hypertension and hyperlipidemia should be included as part of an overall assessment due to a high prevalence of these diseases in obesity. Measurement of basal metabolic rate is of prime importance, as treatment measures will differ according to the individual rate. For example, an individual with a relatively low resting rate of metabolism will benefit more from increased physical activity or changes to aberrant eating patterns than from caloric restriction alone.

For obese persons with psychiatric disturbances such as depression or anxiety, treatment recommendations should be tempered so that the demands of the treatment are modest and achievable without undue stress. Based on clinical judgement of responsiveness to external cues, treatments will vary so that highly responsive people are taught stimulus control, for example. An awareness of the restrained eating phenomenon is useful to aid in alleviation of the concerns of individuals with this type of behaviour.

Likewise it is of tantamount importance to assess the nutritional status of the individual in terms of eating frequency, variety and quantity of foods eaten as well as to evaluate the extent of an individual's activity levels, in order to avoid unrealistic treatment demands (218).

2.5 MEDICAL CONSEQUENCES AND TREATMENT OF OBESITY

The medical consequences of obesity are well recognised. The incidence of cardiovascular, menstrual and reproductive disorders as well as arthritis, gout and hypertension is much higher among obese individuals than normal-weight individuals. Obesity is associated with a number of established risk factors for ischaemic heart disease (IHD) and related conditions. These include hyperinsulinemia, diabetes mellitus, hyperlipidemia and hypertension. It has been established that men who show android fat patterning specifically localized abdominally are more prone to exhibit metabolic complications which may lead to hypertension and IHD (173, 175, 223).

However, the treatment of obesity is a difficult medical problem. Since maintenance of body weight is determined by food intake and energy expenditure it would seem that decreasing body weight would be a simple

matter of reducing food intake, increasing energy output, or both. In practice, however, decreasing body weight is not a simple process; for example, to lose 0.45 kg (1 lb) of body weight one must reduce one's caloric intake by 3500 calories, or run 25 miles. Obviously for an individual who is even moderately overweight, a considerable amount of time and effort is required to effectively lose weight (223,224).

Many traditional as well as novel approaches to weight reduction and weight loss maintenance have been proposed. The multiplicity of treatment approaches include psychotherapy, psychoanalysis, group therapy, behaviour modification, repatterning, surgical and pharmacologic therapy.

Surgical procedures include various types of gastric bypass operations, such as the ileojejunal bypass, for example, as well as horizontal and vertical gastropplasties. Despite numerous technical and medical complications and criticisms to the contrary, surgical procedures, when accompanied by post-surgical follow-up measures and sound treatment practices, remain an effective treatment in terms of both weight loss and weight maintenance in the morbidly obese (225). Mechanical treatments used in the treatment of obesity include jaw-wiring and intragastric balloon bezoars. While jaw-wiring produces clinically significant weight loss, weight regain occurs following the removal of the wires (223, 226). Only a few studies have been performed with the relatively new nonsurgical technique of balloon bezoars (227). However, gastric erosions have been noted in up to 50% of patients with these devices in place and studies in animals have indicated that weight regain occurs once the balloons have been removed (228).

Local fat deposits have also been altered for cosmetic purposes, by a technique called liposuction or suction-assisted lipectomy. With the patient anaesthetised, a suction probe is inserted into an incision made in an area usually covered by clothing, and the tissue is then aspirated through a cannula. Successful operations have usually been performed on younger patients with limited quantities of fat to be removed. However, seromas and infections and other complications such as dimpling and wavy contour have been observed (223).

Emetics and purgatives have been used to control body weight, particularly in eating disorders such as anorexia nervosa. However, the use of these agents should be discouraged as they are socially disruptive, medically dangerous and very resistant to treatment (226).

Physical activity is perhaps the most effective and important intervention necessary for successful weight control. It has been shown that exercise may facilitate weight loss by increasing the metabolic rate, increasing energy expenditure and may decrease appetite resulting in a reduced caloric consumption. Exercise may also enhance the mobilization and utilization of free fatty acids from adipose tissue producing an increased fat weight loss while minimising lean mass loss (223, 226, 228).

The most universally used intervention is that of dieting. Numerous "fad" diets such as "The Beverly Hills" diet and the "Scarsdale" diet, to mention but two, have been and are, used by millions of people in attempts to lose weight rapidly. However, many of these diets are based on unsound nutritional principles and have a high failure rate as weight usually returns to normal following cessation of the diet (223, 226). Very low calorie diets (VLCD) are those which contain less than 800 calories per day and are typically composed of protein with smaller proportions of carbohydrate and fat. These diets frequently consist of smaller quantities of food or can be a pharmacologically manufactured formula; synonyms are "liquid protein" diets or "protein-modified" fasts. When used with adequate patient selection, close medical supervision and a high quality diet, VLCD's produce clinically significant weight loss with minimal complications (228, 229).

A nutritionally balanced, calorically restricted diet may be essential for obesity treatment, but the success rate of even medically sound dieting, including the VLCD's is low when used alone. If used, a diet should be instituted as part of a comprehensive program of nutritional education and behaviour modification to ensure efficacy and maintenance of weight loss.

Behaviour therapy or behaviour modification is employed in the treatment of obesity as a result of maladaptive learned behaviours that concern food intake, energy expenditure and habit control (223, 226, 228, 229).

Techniques used include:

- 1) Control of environmental and intrapersonal stimuli that elicit excessive eating.
- 2) Changes in eating behaviour such as slowing eating rate and increasing awareness of the amount eaten.
- 3) Self-monitoring techniques for systematic recording of dietary intake and weight.
- 4) Social support initiation and relapse prevention programs.

More recently, two new areas, that is cognition and spouse support have been added to the list of factors deemed important in the treatment of obesity. The Master Questionnaire, an obesity assessment device, has been designed "to provide an outcome measure sensitive to the types of changes relevant to the cognitive-behavioural conceptualization of obesity treatment" and to serve as a predictor of changes in obesity status in such programs (230).

It is generally perceived by many, that combining interventions such as behaviour modification, physical activity programs and diets based on sound nutritional practices, is of enormous value in effecting weight loss and sustaining the lost weight.

Pharmacological treatments used to modify appetite have previously been confined to the administration of amphetamine and amphetamine-like compounds. The development of tolerance, potential abuse liability and side effects often outweigh their mild and transient appetite suppressant effects. Medical practitioners have often been either overzealous or totally reluctant in prescribing them. There has been considerable controversy about the value of pharmacological intervention in the treatment of obesity. Although the majority of anorectic preparations on the market are not ideal, when used according to prescribed directions, they may be of great value in the treatment of overweight conditions, particularly when used as adjuncts to low calorie diets and in combination with behaviour modification (188, 223,231).

It has been shown by Weintraub *et al* (232), that failure to consider such factors as a patient's response to a diet-only period, motivation, eating habits, personality and obesity characteristics may partly explain the low discriminatory power of anorexiant clinical trials. The authors suggested that these factors, which were shown to be important determinants of outcome, may help medical practitioners in treating patients in terms of drug selection and treatment strategy (232).

Because conditions of obesity are complex and multifactorial, treatments must reflect individual differences with respect to physiological, psychological and social factors.

CHAPTER 3

EVALUATION OF THE EFFICACY AND SAFETY OF ANORECTIC PREPARATIONS

3.1 PHARMACOLOGICAL TREATMENT OF OBESITY

Most of the appetite suppressant drugs on the market possess many of the pharmacological properties of the neurotransmitter, norepinephrine, and therefore many of these preparations can stimulate the CNS, increase locomotor activity and cause adverse cardiovascular reactions in the form of raised blood pressure and heart rate. It is thus of prime importance to determine the safety and efficacy of anorectic agents in order to establish whether they are clinically useful or not. An anorexiant is deemed efficacious if it reduces hunger and food intake consistently and produces a sustained reduction in body weight. Safety is inferred if the drug in question does not cause increased blood pressure or subjective mood or stimulant effects and shows low abuse liability and little dependence potential (178,223).

3.2 BEHAVIOURAL PHARMACOLOGY OF ANOREXIA

The term behavioural pharmacology represents a union between two scientific disciplines, psychology and pharmacology. In general, the term can refer to any instance in which some aspect of behaviour is monitored in alliance with a pharmacological manipulation, and in the study of feeding the behavioural variable most frequently chosen has been the weight of food consumed (181).

This field of study has expanded along with the increasing interest of pharmaceutical concerns in the development of anti-obesity agents. This venture has needed testing procedures to determine which of numerous new compounds produced, display clinically desirable behavioural activity. The second purpose of this field of study involves the use of detailed procedures for investigations of mechanisms of drug action, whilst the third is the use of drugs to explore the structure of complex behaviour in terms of the associations between physiological occurrences and behavioural events (181).

3.2.1 The Structure of Eating and its Relationship to Behaviour

Drugs are usually tested for their effects on appetite under restricted conditions, the most common of which involves adapting a rat to a feeding schedule. When the rat's intake has stabilised on this schedule, the drug treatment begins. The effect of the drug treatment and hence anorexia is defined objectively by measuring the inhibition of the weight of food consumed by these experimental animals in a brief time interval (usually 15 - 20 minutes) (233, 234). A similar paradigm is used for humans except that subjective reports are usually obtained in addition to changes in food intake. These methods are used to evaluate the acute effect of drugs on meals or short-term food intake and the drug effect is understood in terms of feeding as an episodic behaviour. Drugs are also administered daily for weeks to determine their therapeutic effect on body weight (234).

Mammalian food intake comprises complex behaviour patterns and constitutes a discontinuous process in which periods of eating alternate with non-feeding bouts. Accordingly, it is possible to measure feeding by assessing various parameters of meal patterns such as number of meals taken over a given period, meal sizes, meal duration, inter-meal intervals and certain relationships between these variables such as the ratio of meal size to the pre- or post-meal interval. These techniques draw attention to the distinction between food intake and feeding behaviour which can only be understood through a detailed analysis of the topography of the eating response (181).

The simplicity of the notion of giving the unit of anorexia a fundamental and unequivocal identity may be contrasted with the complex interaction of processes which actually regulate feeding activities. These processes control the onset, maintenance and termination of eating episodes, the selection of particular nutrients and food items, the expression of preferences and dislikes, the long-term temporal patterns of feeding and the relationship between feeding and other pertinent behaviours. In addition, in humans the act of eating is enveloped by economic variables and social influences pandered by beliefs, attributions and cognitions (233).

An examination of the structure of feeding activities reveals a highly organised sequence of actions which have a clearly defined beginning and end. There is a strong possibility that mechanisms responsible for the initiation of a feeding occasion (appetitive phase) may differ from the mechanisms which maintain the behaviour (consummatory phase) (181, 182).

3.2.2 Hunger and Appetite - Constructs in Search of Identities

Hunger and appetite are considered to be two distinct physiological phenomena and the differences between them are important when designing and evaluating clinical studies. Hunger is defined as the physiological need for food occasioned by food deprivation (bodily sensations) and appetite is defined as the psychological motivation for food which is independent of the nutritional state of the individual (mental signals) (235, 239, 243).

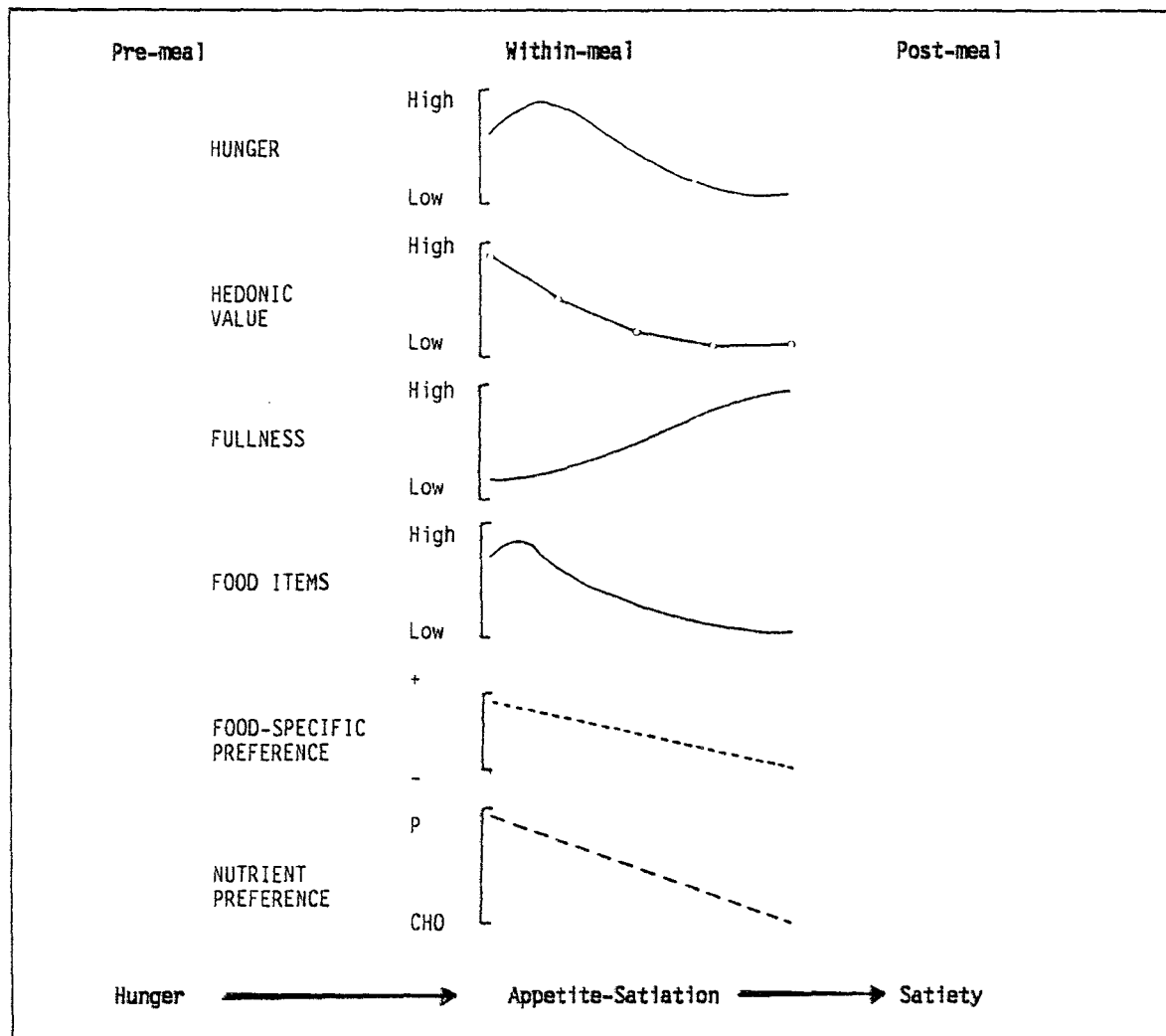
Like many other behaviour sequences, feeding is a periodic series of discrete events with a definite temporal structure. Human feeding is distributed in episodes which can be regarded as discrete meals. Consequently, the meal can be regarded as one basic unit of analysis of feeding behaviour. Although there is a great deal of controversy over the definition of a meal, meal pattern analysis provides one way of isolating events that occur at the initiation of an eating episode; during the maintenance of eating behaviour, toward the close of a feeding period and which inhibit further eating following ingestion. The partitioning of eating into three basic phases - initiation, maintenance and termination - suggests one way in which hunger, appetite and satiety may be related to observed behaviour (182).

Figure 3.1 represents the most significant motivational criteria which are likely to alter during the ingestion of food. At the initiation of a meal, hunger is characterised by strong hunger sensations and a low fullness value, a high hedonic rating, a large score on the food preference checklist and a relative preference for protein. At the close of the meal, satiation is characterised by low hunger but high fullness ratings, a low checklist score indicating sensory-specific satiety and a relative preference for carbohydrate (*vide infra* 3.3.2 for discussion of terminology).

FIGURE 3.1

Fluctuations in aspects of appetite which accompany ingestion during the course of a meal

Reproduced from Blundell and Hill (236)



When used in coalition with the technique of temporal tracking (*vide infra* 3.3.2.1.2), the use of this system provides information that concerns the psychological state preceding the meal, accompanying eating and following consumption (199, 236).

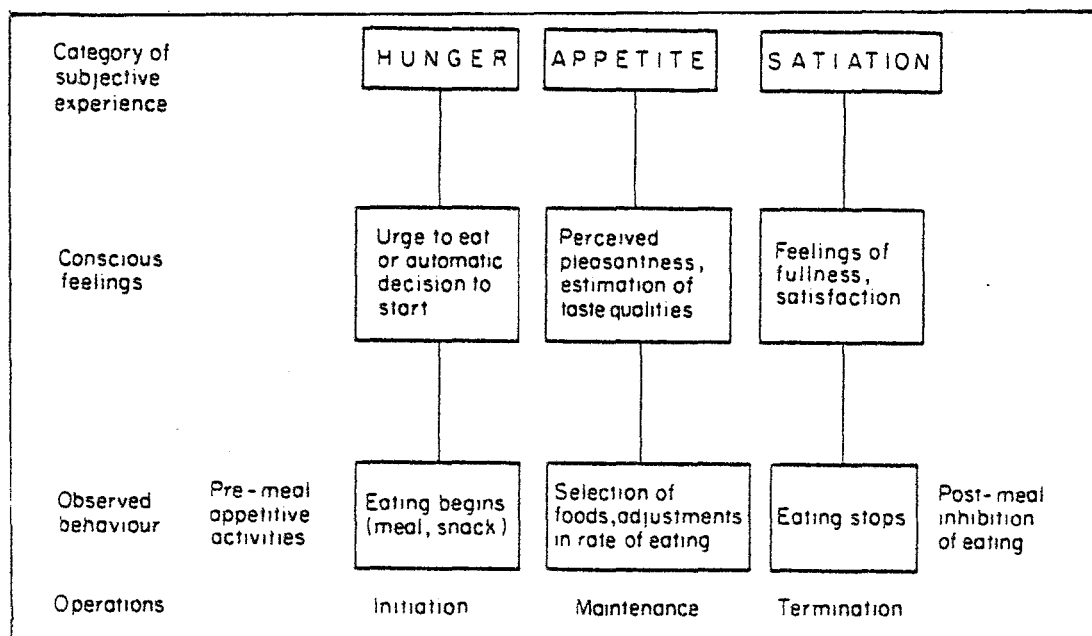
Hunger can be regarded as a process which indicates that eating is imminent and primarily determines the onset of eating while exerting a very small effect on the amount eaten (181). Appetite is intimately linked to the sensory qualities of food such as taste, texture and temperature, features which are commonly referred to as palatability. Appetite exerts a primary effect on the commodities selected, the rate of ingestion and the amount

consumed (181, 182). Food selection is a function of the appetite mechanism and this proposal is consistent with the concept of specific appetites for particular nutrients and food commodities (182).

A further distinction that must be made for technical precision is that of satiation and satiety. Satiation refers to the process of bringing the meal to a close while satiety connotes the state of inhibition over further eating. Satiety is defined by feelings of disgust or surfeit caused by excess food, gratification beyond one's natural desire or by lassitude due to repletion (181, 182).

The conceptualisation in Figure 3.2 represents a distinction between hunger and appetite and relates these terms to the structure of eating behaviour. One particular advantage of this scheme is the separation of the urge to eat from the amount of food consumed and more accurately suggests a dissension between those factors which influence the urge to begin eating and those which promote consumption once eating has begun. This model suggests a disengagement between hunger and appetite based on a distinction between willingness to obtain food and willingness to eat food once it has been obtained. This idea is consistent with the observation that the amount of food consumed frequently fails to correlate with the degree of experienced hunger, particularly if the food tastes bad (182).

FIGURE 3.2 Postulated relationship between formal eating operations and the accompanying subjective experiences
Reproduced from Blundell (182).



It is generally understood that states such as hunger and satiety bear some relation to food consumption. However, the terms cannot be defined by reference only to the bulk of food consumed. In an attempt to find identities for hunger and satiety it may be questioned whether an organism observed to be eating does so in response to the presence of hunger, or to the absence of satiety (181, 182).

In studies on human feeding, the identification of hunger and satiety is sought in correlated sensations or physiological events. Initially it would be unwise to assume the source of information of verbal reports of an experience such as hunger, as the person may be commenting on (181):

- (1) the presence of a true physiological need
- (2) the existence of physiological events or physical stimuli unrelated to bodily needs
- (3) the observation that other people have initiated consumption
- (4) stimulating effects of the presence of attractive foods
- (5) deprivation state since the previous meal, or
- (6) the appropriateness of remarks preceding the start of eating.

3.3 EVALUATION OF ASPECTS OF EFFICACY

There are three measurement criteria considered important when assessing the efficacy of an anorectic agent in humans. Anorectic efficacy is objectively measured in terms of (1) the amount of weight lost, (2) the extent of overall food intake reduction and (3) the degree of hunger/appetite suppression experienced.

In the present context, it is important to measure the effect of a drug on subjective hunger, appetite, satiety and food consumption since these factors largely, if not entirely, determine how the drug in question influences body weight, and it is this drug-induced weight change which is generally the most clinically significant effect (239, 240).

3.3.1 Measurement of Body Composition

There are numerous methods available for the measurement of body fat or composition. A variety of sophisticated laboratory methods exist for obtaining direct and reliable estimates of body fat and include underwater

weighing, volume displacement, radiographic analysis, analysis of potassium-40, isotropic dilution and ultrasound techniques. While these techniques are certainly valid, they are time-consuming and costly in terms of equipment and trained technicians, and are therefore impractical (178, 237).

The most widely used indirect technique is to check an individual's weight for their given height, frame size, age and sex against published desirable or ideal weight tables which are based on population averages, such as those prepared by the Metropolitan Life Insurance Company of America (255), for example.

Percentage overweight is then obtained from the following equation (Equ.3.1):

$$\% \text{ Overweight} = \frac{\text{Initial Body Weight} - \text{Ideal Body Weight}}{\text{Ideal Body Weight}} \times 100$$

Eqn 3.1

Height-weight indices comprise essential baseline data, but may be poor indicators of obesity. The major deficiency of standard height and weight tables is the inability to differentiate lean body mass from fat weight, thus limiting their use for estimating fat proportions (175, 178).

As opposed to reliance on these height-weight tables, the Quetelet Index or Body Mass Index (BMI) has been recommended (175). BMI is calculated using the following formula (Equ. 3.2):

$$\text{BMI} = \frac{\text{Body Weight (kg)}}{[\text{Height (m)}]^2}$$

Eqn 3.2

An individual with a BMI of 27 kg/m² is roughly 20% overweight (228). An important distinction that must be made is that the term overweight refers to deviations in body weight from some standard weight related to height and may not necessarily mean obese (175). The definitions of these terms are as follows:

Overweight:

1. BMI of 25 to 30 kg/m².
2. Body weight between the upper limit of acceptable and 20% above that limit.

Obese:

1. BMI greater than 30 kg/m².
2. Body weight more than 20% above the upper limit for height.
3. Body fat 25% of body weight in males or 30% in females.

Skinfold fat and body circumference are the two anthropometric variables most commonly used in body density predictions. Using sound techniques, skinfold thickness measurements can be reliable predictors of percentage body fat if they are not used inter- racially or in the grossly obese. However, skinfold measurements are not useful to assess slow, gradual weight loss and accurate measures are needed by trained personnel (175, 237).

Usually the sum of the skinfolds taken at seven anatomical locations are used as reliable measures of subcutaneous fat. Figure 3.3 is a diagrammatical representation of the location of these sites on the human body.

However, it has been suggested that the age of the individual and sum of three skinfolds can be used to evaluate adult body composition and % body fat. These sums provide a good representation of the total body with regard to gender and are highly correlated ($r > 0.97$) with the sum of seven skinfolds. Percentage fat is estimated from the age of the subject and sum of their skinfolds using standard tables (237).

The preferred sum of three skinfolds are different for men and women and include:

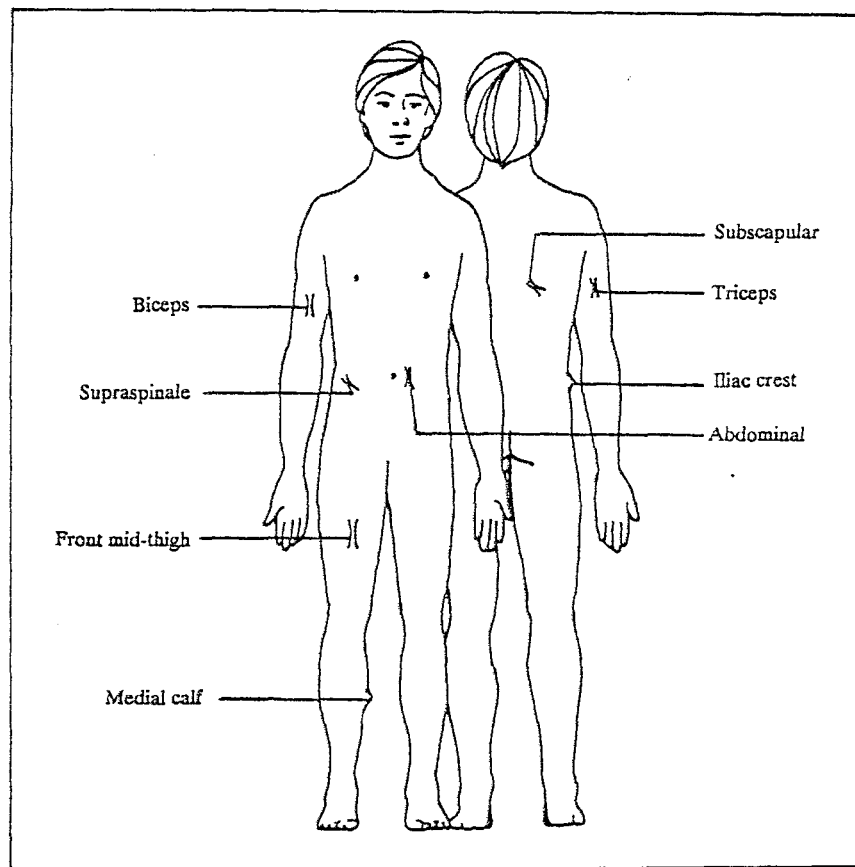
MEN: Sum of chest, abdomen and thigh skinfolds

WOMEN: Sum of triceps, suprailiac (iliac crest) and thigh skinfolds

FIGURE 3.3

Skinfold sites on the human body

Reproduced from Ross and Marfell-Jones (238)



Anthropometric measurements and somatotyping may be useful in assessing the degree of obesity and identifying other characteristics, such as peripheral or central fat distribution, which can infer expected morbidity and prognosis (218).

3.3.2 Measurement of Hunger, Appetite and Satiety

Before a quantitative determination concerning the effects of drugs on subjective hunger can be made, a "measuring" instrument that is both valid and reliable is required, to allow the subjective sensations underlying hunger to be translated into objective data (239, 240). However, the

measurement of hunger and appetite in man, critical in the objective study of food regulation and obesity presents conceptual and methodological problems and is not a simple issue, as often presumed (245).

The only means of "measuring" hunger and appetite is to ask a subject to compare one experience with another using a ranking procedure : that is, to ask the subject whether he or she was more or less hungry than on a previous occasion, and to assign numerical scores to these rankings. These numbers can then be manipulated using various statistical techniques (239).

3.3.2.1 Ratings of Hunger Appetite and Satiety

The two most common rating methods used are fixed-point scales and visual analogue scales.

3.3.2.1.1 Fixed-Point Scales

Fixed-point scales, also known as multi-stem scales (241) are quick and simple to use, and the data that they provide are easy to analyze. Viewed simplistically, these scales are numerical indications of the absence or presence of hunger. However, the scales can vary greatly in complexity. Different research groups have tended to construct their own scales, which vary not only in the number of points used but also in the definition of the measured variable (242). Thus some researchers have used five-point (63, 243) and others seven-point scales (244, 245). For example, a seven-point scale would contain the numbers 1 through to 7 and text assignment in terms of hunger would be of a similar order to 1 = not at all, 2 = a little, 3 = somewhat, 4 = moderately, 5 = quite a bit, 6 = very and 7 = extremely.

3.3.2.1.2 Visual Analogue Scales

One way of overcoming some of the disadvantages of fixed point scales is to abolish the points and bypass the numbering system completely. Visual-analogue scales (VAS) are horizontal lines, usually 100 mm long, unbroken and unmarked except for word anchors at each end of the extremes of the subjective feelings to be quantified. For use in experiments involving hunger and food intake, a hunger VAS, one end of which is labelled "NOT AT ALL HUNGRY" and the other end "AS HUNGRY AS YOU HAVE EVER FELT" is used (246, 247). The user of the scale is instructed to mark the line at a point

that most accurately represents the intensity of the subjective feeling at that time (242, 239, 240).

For analysis of the results, the answer mark on the line of the scale is measured to the nearest millimetre, producing a score of between 0 and 100 for each determination (246, 247). When subjects are presented with a succession of hunger VAS at fixed intervals, the pattern of their hunger response to a drug or other experimental variable can be evaluated (246). Silverstone *et al* have found VAS to be both valid (239, 246) and reliable (239) in terms of between-subject reliability ((276) and test-retest reliability (239).

The benefits of fixed-point scales have been retained by visual-analogue scales whilst the problematic effects associated with either comprehension of descriptive terms or number preference, have been avoided. In a direct comparison of the two methods, it was found that VAS were as accurate and reliable as a fixed-point scale but more sensitive in studies registering the effects (242). However, it was demonstrated in a recent study (241), that these two methods of presenting response options show comparable responsiveness and validity. Moreover, it was concluded that the ease of administration and interpretation of the seven-point scale recommended its use.

Visual-analogue scales do, however, contain some anomalies in their distribution of responses. Much of this deflection from a normal distribution is a consequence of using bipolar scales (eg. tired/alert, hungry/satiated) rather than using unipolar scales (eg. very tired/not at all tired, hungry/not at all hungry) (242).

In studies of subjective experiences accompanying eating, VAS have been used to monitor changes in hunger ratings before, during and after ingestion of a meal. This method of "temporal tracking" has revealed hitherto unpredicted effects of physiological and sensory manipulations. In addition, this technique allows changes in subjective ratings to be related to different sections of the behavioural sequence (242, 250). It has been observed by Blundell *et al* (278) that although anorexic drugs suppress ratings of hunger prior to a meal, once eating begins these levels

are reinstated to control levels.

The psychophysical technique of cross-modal matching has been used to scale perceived satiety (248). The technique requires a subject to adjust the length of a metal tape whose graduations are visible to the experimenter only, at two minute intervals while eating a fixed-amount meal. Although the validity of using the magnitude estimation method was confirmed, reliability of the technique was judged to be uncertain.

Subjective ratings made on visual-analogue scales, fixed-point scales or by psychophysical techniques such as magnitude estimation, show subjective hunger to increase steadily as mealtime approaches and to decrease sharply after eating. Perceived satiety rises steadily during the course of the meal and decreases steadily afterwards (199, 236). It is generally believed that the higher the hunger ratings, the more food will be consumed. However, the correlation between pre-meal hunger ratings and the actual amount of food consumed varies from moderate (246) to weak (249). Also in pathological conditions such as anorexia nervosa or bulimia, ratings of hunger and satiety may not be correlated with consumption (250).

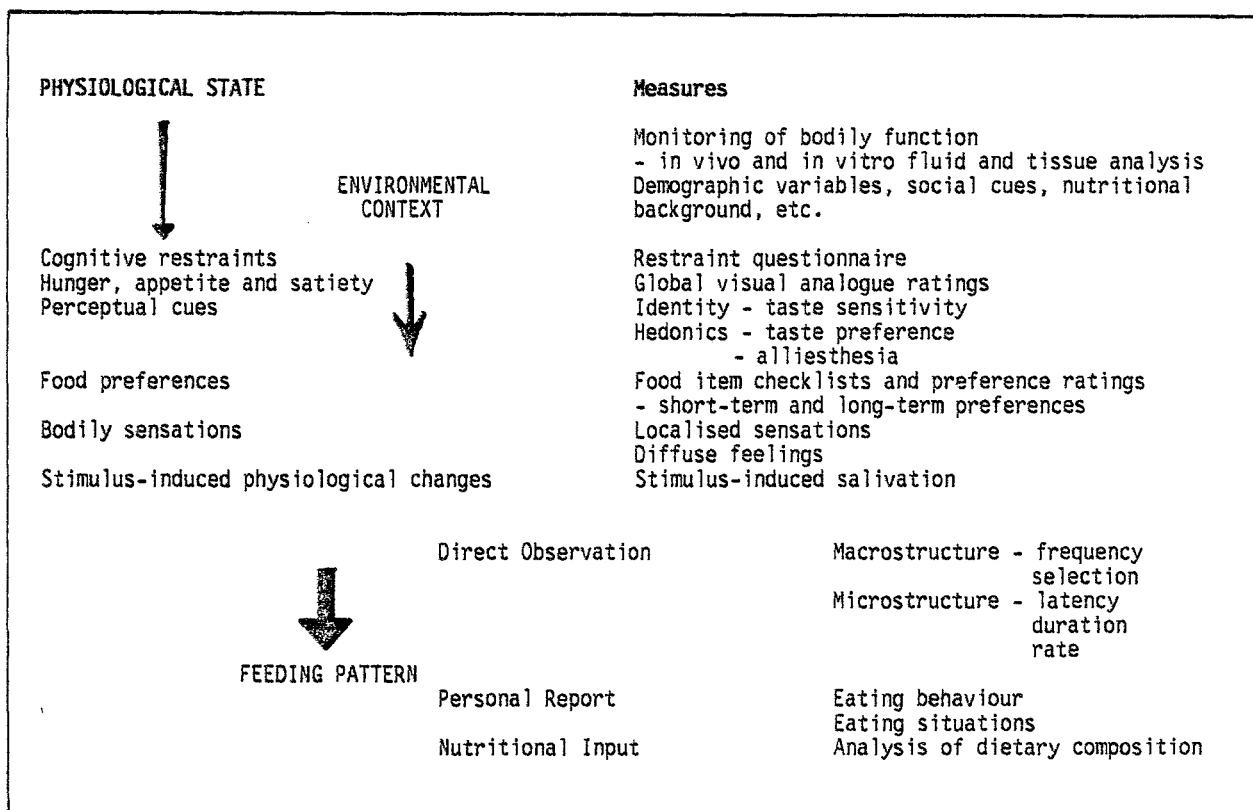
One reason that ratings of conscious experiences of hunger and satiety may not successfully predict behaviour, is because they require each volunteer to describe all their experiences in a single continuum, or to select one sensation which is assumed to correlate highly with that category of subjective experience, to the exclusion of other sensations (250).

The weaknesses associated with simple numerical rating scales have led to the development of a more complex formulation in which subjects can partition their subjective experiences into physical, emotional and cognitive aspects. Hill and Blundell (250) propose a multidimensional approach to hunger, which is founded upon an analysis of changes in bodily sensations and feelings which incorporates aspects of taste hedonics, food preference, stimulus-induced-salivation and patterns of eating. Figure 3.4 outlines this strategy and depicts procedures for sequential monitoring of causal factors such as physiological state and environmental cues, which dictate factors such as food preferences and salivation to a stimulus (conceptualized as mediating mechanisms) which relate directly to the

observed outcome in terms of the behavioural feeding pattern. The authors postulate that this approach could make categorisation of hunger much more sensitive as an indicator of nutritional adjustments (250).

FIGURE 3.4 Conceptualization of the procedure for measuring and monitoring hunger

Reproduced from Hill and Blundell (250)



3.3.2.2 Bodily Sensations

One technique widely employed to identify hunger and satiety experiences is a checklist of physical sensations, coupled with checks upon the intensity and duration of thoughts of food and the urge to begin eating or the resistance to stopping (182).

In the study of feeding, subjective experiences are usually derived from certain physical sensations of which, the most widely acknowledged, occur in the stomach. Many people perceive that hunger is signalled by an empty or rumbling stomach sensation and interpret gastric fullness as satiation. There are however, other easily identifiable sensations associated with

eating whose location is in the head, mouth or throat, as well as less easily defined bodily feelings (242).

Studies of bodily sensations often list the individual items in the form of a checklist. The subject's place a mark next to any of the sensations or feelings that are being experienced at that time (251,252). The checklist may be scored as the total number of items checked or may be categorised according to location. The number of times a group of subjects mark any item may be compared before and after various treatments to indicate treatment-induced changes in subjective sensations. Factor analysis of the data may then be performed to demonstrate the most significant effects (250).

Clear differences in sensations have been detected between pre- and post prandial ratings (251) and between normal subjects and individual's suffering from anorexia nervosa (252) thereby giving credence to the belief that these sensations do provide a source of information which is used during reports of hunger and satiety. The administration of drugs with markedly differing pharmacological profiles have been shown to adjust bodily sensations in a manner consistent with their neurochemical actions (247). This data shows that bodily sensations could provide a sensitive indicator of nutritional manipulations.

3.3.2.3 Taste Hedonics

Taste stimuli, like bodily sensations, have clearly distinguishable properties. A taste stimulus may be judged according to its intensity (strength) and to its hedonic (pleasantness) properties. It is known that people vary in their ability to perceive particular tastes. The reasons for this are varied and include adrenal cortical insufficiency, diabetes, cancer, taste bud pathology, nutrition, and age (242).

The usual way of evoking hedonic responses to a taste is to offer a range of concentrations of the taste stimulus and to plot hedonic appreciation as a function of increasing concentration. The concomitant measurement of intensity enables computation of detection and recognition limits and has shown taste stimuli to have unforeseen hedonic properties even when they are apparently undetectable. Moreover these "expectancy ratings" differ

according to weight status (242).

Using this method of data collection, three important properties of taste hedonics have been observed, as summarised by Blundell (242). Firstly, the relationship between pleasantness and the concentration of a solution is different to that of intensity. Secondly, inter-subject variability exists in this relationship, with two characteristic pleasantness-concentration profiles emerging. Type-I responders show a decrease in preference for sweet stimuli, while Type-II responders show a monotonic rise in pleasantness as sweetness increases. Both types of responders are found in all weight categories. However, there is evidence that a greater proportion of the obese are type-I responders (242, 250).

Thirdly, subjects' hedonic response to a sweet stimulus depends in part on their physiological or nutritional state. Alliesthesia, a word coined by Cabanac (213) and meaning "changed sensation", describes the dependence of hedonic experience on the internal environment. It is best shown by the decrease in pleasantness of a sweet solution after ingestion of a nutritive glucose meal (242).

The real importance of alliesthesia is likely its functional properties; that is, the decline in preference for a sweet taste leading to decreased food intake and so being part of the process of satiation (242, 250, 258).

3.3.2.4 Food Preferences

Apart from the total amount of food eaten, food preferences occupy an important position in the causal chain of mediating mechanisms underlying the consumption of food. A basic assumption is that food preferences determine food intake. The preference for one food is not simply the sum of preferences for that food's associated tastes; other qualities may be important such as odour, texture, temperature, socio-cultural influences and metabolic and neuro-chemical effects. As summarised by Hill and Blundell (250) "food preference is thus a multidimensional composite of all these factors, which may differ in their relative output" .

The most simple technique to assess changes in food preferences, is to construct a short checklist of food items. The subjects' task is to check the items that they would like to eat, considering each one independently of the others. The overall score constitutes a range of food preferences. Priority preference may be demonstrated by asking the subjects to rank the food items in order of preference. Alternatively, the frequency of checking food items may be compared between two or more predetermined categories such as high calorie-low calorie or high protein-high carbohydrate to reveal changes in macro-nutrient preference. Variants of this checklist method often include hedonic scales or visual-analogue scales associated with each item (242).

Blundell and Rogers (247) used a food preference check-list consisting of a "menu" of 30 basic food commodities whose nutritional composition could be readily identified by the subjects, on which the subjects' indicated their preference at that moment. The list was divided into high-protein and high-carbohydrate items for the purpose of analysis. A relationship was found between the presumed neurotransmitter effects of various drugs and their effects on preferences for foods rich in proteins and carbohydrates. This type of checklist does not lack sensitivity as a low dose of fenfluramine did not effect food intake or hunger ratings, but selectively reduced preferences for carbohydrate-rich items (247, 250).

An alternate approach to quantifying food preference other than the checklist or eating scale methods is the forced-choice procedure. Using this technique, the subjects are presented with the names of two food items on printed cards and are required to express a preference for one, allowing both relevant preference scores and individual hierarchies of individual preferences to be assessed (242, 250). This procedure has provided unambiguous measures of individual food preferences in a study of anorexia nervosa patients (250).

3.3.2.5 Salivation

Pavlov (240) in his experiments on conditioned reflexes, used the salivary response to the sight of food as a measure of an animals' desire to eat. He noted that such salivation could be affected by the nature of the food present, and how long it had been since the dog had last eaten; the longer

the period of deprivation, the greater the salivary response. On the basis of this and other reports, Wooley and Wooley (245) suggested that salivation in response to the sight of food may be used to objectively measure appetite in man.

The secretion of saliva is an involuntary accompaniment to eating and the salivatory response has the capacity to be conditioned to the arrival of food and to anticipate eating. These anticipatory responses are known as cephalic reflexes and are sensitive to the sight and smell of food. Functionally they act to prepare the digestive system to receive food (242).

A number of findings have motivated salivation to be envisaged as a reliable index of the quantitative measurement of appetite. Firstly, it is apparently uncontaminated by the cognitive and methodological variables that influence pen-and-paper ratings (242). Secondly, it has been shown by Wooley and Wooley (245) that anticipatory salivation is modulated by palatability and deprivation and correlates significantly with ratings of hunger and food appeal. In addition, salivation is easily measured (242).

There are three basic measurement techniques. The most widely used is the Strongin, Hinsie and Peck (SHP) method. This method consists of placing three preweighed 38 cm cotton dental rolls in the subjects' mouth (one sublingually and two buccally), leaving them in place for a two-minute collection period, removing and reweighing them. The average weight of saliva collected in grams in the three 2-minute collection periods separated by a 2-minute rest period constitutes a single measure for a single subject. The dental rolls are packaged in polyethylene bags with twister seals and are weighed to the nearest milligram before and within one hour of use (245).

An alternative to this procedure which requires very little specialized equipment, is the Lashley suction cup which monitors saliva flow rate from a single group of salivary glands. This device takes the form of a plastic cup positioned unilaterally or bilaterally over Stensen's duct and held to the inside of the cheek by negative pressure, which draws the saliva to the recording device (242, 256). This method is very accurate and may be

used to provide continuous records of saliva flow over relatively long periods of time, such as an hour.

In contrast to both of these methods, which are intrusive and somewhat uncomfortable, the total salivary output can be collected from the mouth. This may be done by suction using a dental fluid ejector continuously or at the end of a timed period, or by simply voiding the accumulated secretions into a pre-weighed container (242, 254).

Comparisons of these methods have shown them to be significantly intercorrelated. An important consideration is the design of the experiment. There are two basic ways in which salivation is studied. The one way is to measure salivation in a range of subjects and to correlate it with another variable such as weight or dieting status (242). The other method which is used more frequently is to establish a baseline of salivatory response and to compare this with the level of salivation evoked by a food-related stimulus. The stimulus used in "stimulus-induced salivation" may be the sight or smell of real food, a food word or thinking about food (242, 245).

Stimulus-induced salivation (SIS) has been shown to be a sensitive measure as a low dose (10 mg) of amphetamine reduced SIS before any effect could be seen on hunger ratings (257). In addition to deprivation and palatability (245), SIS has also been shown to be influenced by body weight, by dieting to lose weight and is even dependent on the time of day and it appears that salivation is a supersensitive response (242). These factors may account for the inconsistent relationship found between salivation and hunger ratings in studies varying in methodology and experimental design. Blundell and Rogers (247) observed pronounced decreases in baseline salivation following anorexic drug administration. The authors suggested that the timing of the salivation tests was most likely to have been the cause of this reduced salivatory response, as a sufficient interval was allowed to elapse enabling peak drug concentrations to be reached.

It has been suggested by Sahakian (254) that more attention to the cognitive and sensory processes involved in both salivation and appetite ratings is needed to clarify the conditions under which ratings of hunger and food appeal are correlated with the size of the salivation response induced by food. He mentioned, in particular, that the effect of palatability on salivation will depend on the dieting status of the individual.

However, Blundell (242) states, that "it remains to be confirmed whether salivation represents a global index of hunger or appetite". He also suggested that, on the basis of findings in other studies, SIS may be used as a measure of alliesthesia and of sensory-specific satiety.

3.3.3 The Measurement of Food Intake

From the dawn of time it has been evident that the acquisition and consumption of food is an essential factor, not only of health and welfare, but also of social life (259, 260). Due to recent interest in possible associations between diet and health, clinicians and nutritionists have realized a need for dietary methods to reliably assess the nutritional intake and status of individuals and population groups. These methods should be simple, accurate, cost-effective and above all, readily applicable in epidemiological investigations (259, 261).

There are two approaches to measuring food intake in man, the indirect and the direct.

3.3.3.1 Indirect Measures

The methods used to indirectly survey individual and group dietary intake and practices are varied and include numerous forms of diet history questionnaires and recall techniques, which are used to obtain data on habitual quantitative intake of food items, and diet diaries which are used more frequently (259, 260, 262). Diet diaries are detailed records, kept by the subject, of foods consumed over a period of time and are particularly useful in the longer-term assessment of the effects of drugs on food intake, especially if such observations are extended over days or weeks (239, 240).

Individual dietary studies fall into two basic categories, that is, recording present intake and past intake.

3.3.3.1.1 Recording Present Intake

This method, used on an individual basis, requires the subject to maintain detailed dietary records of all foods and beverages ingested over a period of time. Portion sizes may be estimated using food models or photographs (262) and/or standard household measures, or alternatively, all ingredients used in the preparation of the food may be precisely weighed (263), together with the wastage at the end of the meal (259, 261, 264).

Obviously, while the latter is a more precise method, it requires frequent supervision by the clinician and a great deal of participant effort, motivation and cooperation. A problem indigenous to both methods is the constant focus of attention on food selection and consumption. Thus, high-level self-monitoring procedures may exert their own influence on the behaviour under investigation and alter normal eating habits (242).

3.3.3.1.2 Recording Past Intake

The methods used to aid the subjects to remember and describe their retrospective intake differ largely in the duration of the recall period. The method of choice for collecting dietary data has been the 24-hour recall, which elicits an inventory of the food intake for the previous day. The subjects are asked by the interviewer to note the foods eaten on a checklist or short questionnaire (262) or to detail their meals using estimated amounts of food. Alternately, a diet history of usual dietary intake may be obtained and supplemented by the 24-hour recall (242).

A major drawback of 24-hour recall techniques is the questionable reliability of using a single days' intake as a measure of habitual consumption (259). However, on the whole, recall procedures are quick and relatively inexpensive and require little specialist supervision. An added advantage of this technique is that limited time and effort is required on behalf of the participant (242).

Following its collection, dietary data are converted into caloric or nutritional information using standard tables of food composition. These tables contain lists of single food items and food dishes, both raw and cooked, describing the method of preparation. Details of caloric values (calories and kJ) and nutritional content (g, mg) per 100 g of edible food are given. Physiological values for the energy content of macronutrients are calculated using the Atwater factors, that is 4, 9, 4 cal/g for the energy available from protein, fat and carbohydrate respectively (265).

However, there is some controversy about the accuracy of this procedure. Paul and Southgate (266) say of their own revision of McCance and Widdowson's, "The Composition of Foods", the values are of "representative samples" of the foods and as such may reflect the "average composition" of the food. Data from large population groups should exhibit intrinsic accuracy and the accuracy of studies on individuals may be improved by extending the size of the sample (242).

3.3.3.1.3 Observational Studies

The quantity of food consumed during a meal has been used as the dependent variable in many studies to determine human eating behaviour. However, careful observation of an individual while he is eating may permit the detection of certain subtle differences between drug actions that are not revealed by a simple measure of the amount of food consumed (181, 249). The classification and subsequent quantitation of the entire micro-structural sequence of eating behaviour is enabled by using data obtained from observational techniques.

Behaviour may be monitored in naturalistic settings (cafeterias, restaurants or homes) or in the laboratory under controlled conditions. Analysis may be performed on "live" behaviour or carried out from video recordings. Generally, the observational method frequently employs some form of sampling. Event sampling requires that every occurrence of a specific event is recorded, and time sampling indicates monitoring of events occurring at specific intervals during the observational period (216, 240, 242).

For eating behaviour, which normally spans duration of a meal, a significant number of events (taking a bite, swallowing, etc.) are continuously recorded by an observer. In studies of eating behaviour, the main variables are extracted and calculated from various combinations of the rate and frequency of chews, mouthfuls and pauses between eating bouts, and are listed in Table 3.1.

TABLE 3.1 Parameters of eating derived from the analysis of the micro-structure of behaviour

Reproduced from Blundell and Latham (181)

1. Total food intake (g)
2. Duration of time spent eating (minutes)
3. Latency (time elapsed before onset of eating) (minutes)
4. Number of eating bouts
5. Size of bouts (g)
6. Duration of bouts (minutes)
7. Local rate of eating (g/minute)

Observational techniques are time-consuming as close scrutiny of the videotapes is required by an independent observer to ensure that the data obtained is both accurate and reliable (239, 240, 242).

Alterations in these variables have been used in attempts to detect differences between drugs with different neurochemical profiles (267), between foods of various preference values (216), between obese and normal weight individuals (268) and to assess the development of satiation during the course of a meal (249).

3.3.3.2 Direct Measures

Methods used to quantitate human food intake directly include various techniques of measuring the amount of a standardised liquid or solid meal consumed during an experimental test session. Over the past 20 years, numerous specialized devices have been developed and existing tools adapted to improve the sensitivity, accuracy and reliability of the measurement of food intake in humans. Most provide continuous intake monitoring, some are

designed for liquid nutrient rather than solid food, whilst others allow a degree of food choice. Some attempt to allow unobstructed eating to occur, while others demand an unnatural eating response.

3.3.3.2.1 Liquid Nutrients

Hashim and Van Itallie (269) developed a technique to ensure accurate and continuous measures of caloric intake in man. The apparatus consisted of a mouthpiece connected, by means of flexible tubing, to a concealed reservoir containing liquid nutrient. The circuit was completed by the insertion of a valve and pump. As the subject depressed a button, the pump was activated and a measured quantity of liquid of pre-determined caloric content was delivered to the mouthpiece. It proved possible to monitor the intake of a subject per minute over several days by incorporating a timing device into the experimental apparatus (239, 240).

Modifying this technique for experiments of 20 minute duration, Jordan *et al* (270). made use of a container of liquid nutrient, hidden from view, from which the subjects sucked *ad libitum* through a steel straw, under constant conditions. The volume of nutrient ingested was measured by the investigator who took readings from a graduated cylinder at fixed intervals. The device was modified in one experiment, so that the liquid was pumped into the subject's mouth (271). Using similar methodological approaches, numerous researchers were able to show that the ingestion of a liquid diet was sensitive to drug effects (63, 180, 272).

Although the consumption of liquid foods can be recorded precisely and measured with ease, the use of such techniques to measure food intake is subject to significant limitations and hence far from optimal. In substituting liquid nutrient for solid food as the sole source of energy, one is effectively measuring drinking and not eating. It is clear that these methods do not emulate normal behaviour as the nutrient provided is monotonous and unusual, as no element of choice, nor opportunity to savour the various tastes and textures is possible (239, 240, 273).

3.3.3.2.2 Solid Food

A number of techniques have been devised to overcome the problem of direct measurement of the quantity of solid food eaten over a given period of time, in terms of actual caloric intake and mass of food consumed. As with many forms of clinical measurement, proposed methods are a compromise between measurement accuracy and ease of application.

3.3.3.2.2.1 Bomb Calorimetry of Duplicate Meals

Two identical duplicate meals are prepared with weighed and measured food constituents. The subject is requested to eat his fill from one of the two meals. The remaining food is placed in a bomb calorimeter, ignited by means of a small electric current and the heat of combustion calculated from the rise in temperature in the calorimeter. From these physical measurements the calorie content of the meal can be determined. The calorie content of the untouched duplicate is similarly measured, the difference between the two being equivalent to the calories consumed by the subject (274).

This is the most accurate of all the available methods to determine calorie consumption at a given meal but it is limited to studies involving a small population of only one or two subjects at a time. The method requires detailed analysis by an expert dietician and is thus both time-consuming and expensive (239, 240, 242).

3.3.3.2.2.2 Standardised Foods and Sandwich Meals

A standardised sandwich meal was developed in an attempt to combine ease of measurement with a certain amount of variety in as naturalistic setting as possible (239, 240). At each meal subjects received a predetermined number of quartered crustless sandwiches. Each constituent was accurately weighed and the calorie content determined from standard food composition tables. Following meal cessation, the number of each sandwich variety and mass of constituent was recorded and the total calorie consumption calculated. This approach has been successfully applied in a study of the effects of dextro-amphetamine (242).

More recently, methods have been developed and used whereby the intake of certain standard foods such as nuts, crackers and sausages of known calorie content is measured (240). However, while it is a relatively simple

procedure to count the number of crackers, nuts, sausages and sandwiches consumed, the foods themselves lack variety and are more in the nature of snacks than complete meals.

3.3.3.2.2.3 Automatic Monitoring via Eating Utensils (BITE)

In order to gain more insight into the mechanisms controlling food intake, it is necessary to observe and measure eating parameters and to establish human eating patterns in the presence and absence of disease states. The Bite-Indicating Telemetering Eatometer (BITE) was developed by Moon (275) to continuously monitor the consumption of solid and semi-solid foods. The technique is based on the recognition that human eating is composed of a sequence of contacts between the mouth and the eating utensil and that the number of contacts is proportional to the amount of food consumed. Therefore, by continuously monitoring these utensil-to-mouth contacts, it becomes possible to track the temporal course of food consumption.

The BITE apparatus records the rate and frequency at which a subject deposits food orally using specially constructed spoons and forks with handles containing telemetering equipment (275). Mouth contact permits the passage of current from the utensil to the handle, which constitutes a signal that is telemetered to recording devices by a battery-powered transmitter within the utensil handle.

Studies using the BITE apparatus have shown that a continuous record of all utensil-to-mouth contacts can be obtained over a set period of time. The value of such measures may be augmented with the addition of a weighing cell, which would provide a continuous measure of total food and calorie intake over the same time period (239, 242, 275).

At the moment, the full potential of this system is unknown, as to date no drug studies have been undertaken using these novel electro-mechanical methods. While they might allow an accurate representation to be made of the detailed micro-structure of eating, they do not allow more extended observations, nor can they furnish information about food choice (242).

3.3.3.2.2.4 Monitoring Intake via the Plate (UEM)

Whilst the BITE procedure attempts to analyze the structure of eating behaviour by monitoring intra-meal events such as mouthfuls and intervals, it falls short of the requirement to monitor changes in the actual weight of food consumed without the addition of a weighing cell. A device called the "Universal Eating Monitor" (UEM) was developed to continuously measure alterations in the amount of normal chewable solid foods or liquids ingested (273). However, the disadvantage of this technique is that no measure is made of the physical elements of eating.

A concealed electronic balance on which a plate containing the food rests, is connected to a specialized digital computer which automatically monitors the weight of food on the plate, producing a cumulative intake curve for the entire period of study. A pilot study utilizing this technique demonstrated that it could accurately and precisely temporally track the intake of liquid and solid foods, and that the device is sensitive to some of the factors influencing overall food consumption (273). The results obtained in a recent study to evaluate the effect of the gut hormone cholecystokinin (CCK-8) on eating illustrates the potential of the method for use in investigations of the effects of anorectic drugs on food intake (242).

3.3.3.2.2.5 Food Dispensing Machines

Many of the techniques used to study human eating behaviour have been improvised from tactics used to monitor animal feeding patterns. The principle of using pellet dispensers and eatometers to measure the effects of pharmacological manipulations on animal feeding patterns has recently been extended for studies of anorectic drug effects on human food intake patterns (276).

The solid-food dispenser is a modified commercial food vending machine which provides quartered sandwiches as food units that are accurately controlled with regard to weight, nutrient content and calorific value. The removal of each food unit from the apparatus is monitored and a cumulative record of the caloric intake and behaviour of the subject is obtained. The use of this technique has been shown to detect alterations in eating profiles induced by anorectic drugs and to compare temporal patterns of

hunger ratings and food intake (242, 276).

An advantage of this type of device is that by stocking it with food items of different macro-nutrient composition, it is possible to measure protein and carbohydrate intakes separately and to assess particular nutrient or taste preferences (276).

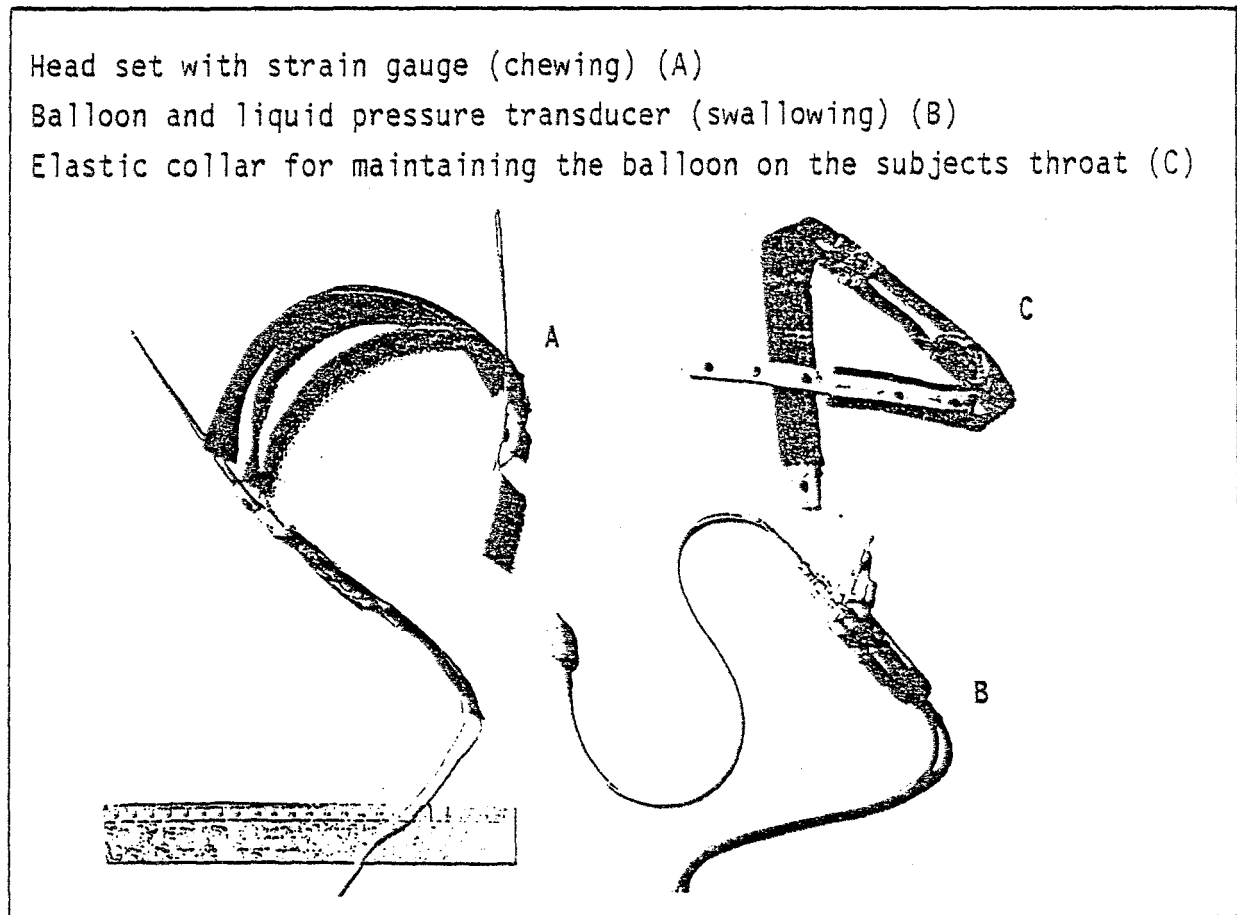
3.3.3.2.2.6 Monitoring of Chewing and Swallowing - The Edogram

The methods described thus far have attempted to trace human eating in two ways, either by monitoring the volume or weight of food consumed or by recording the behaviour of the subjects as they eat. Observational methods have been used to record and analyse the structure of eating behaviour (216) and finer units of behaviour such as salivation (245) have been used as objective measures to quantitate both the internal state of depletion and the sensory qualities of foods.

Pierson and Le Magnen (222, 277) initiated an automated and objective method for describing the micro-structure of eating and established the edogram. The edogram was composed from precise oscillating eletromyographic recordings of the fine motor sequences of the masseter muscles during the masticatory movements known as chewing, in conjunction with parallel records of deglutition or swallowing movements.

More recently chewing has been measured by a strain gauge that monitors jaw movements while swallowing has been measured by pressure changes in a balloon resting on the Adam's apple and kept in place by an elastic collar (222, 277). Figure 3.5 depicts a photograph of the equipment used for the recording of chewing and swallowing activity, where A is the head set with strain gauge, B is the balloon and liquid pressure transducer and C is the elastic collar.

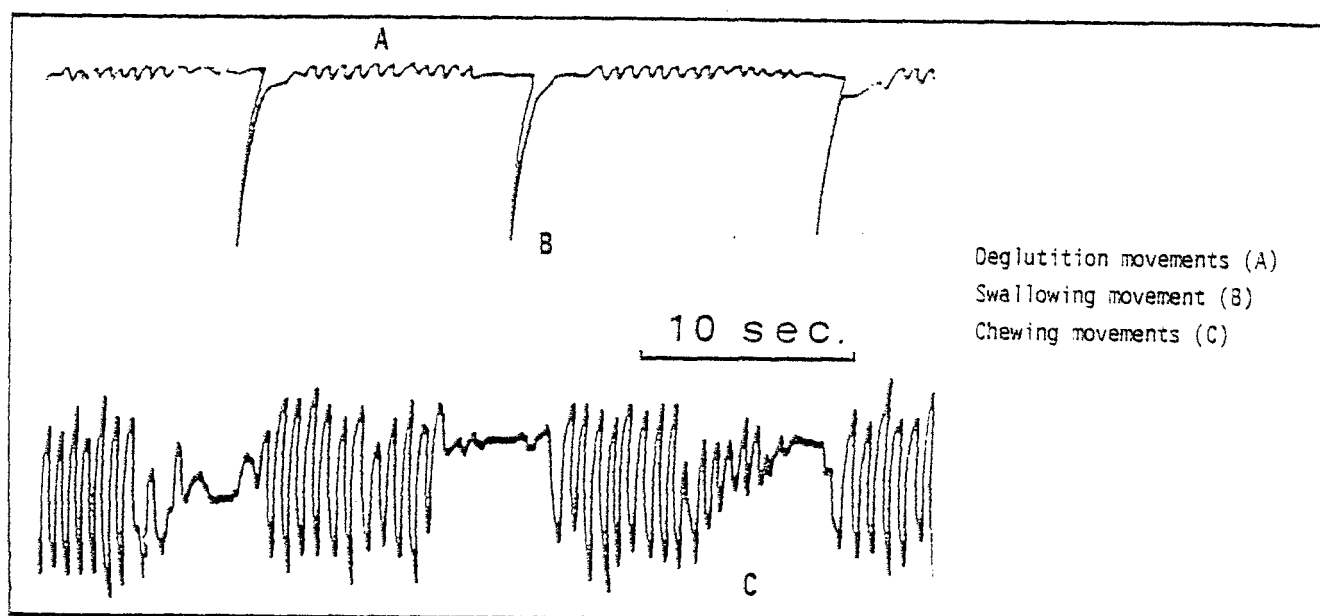
FIGURE 3.5 Equipment for the monitoring of chewing and swallowing activity
Reproduced from Bellisle and Le Magnen (222)



The edogram represented in Figure 3.6 allows a fine temporal analysis of the chewing time per food unit, the number and frequency of chewing movements, the swallowing interval and the number and distribution of deglutitions per food unit (222, 277). This procedure provides a sensitive technique for the continuous tracking of calorie intake and for the detection of changes in important eating parameters affecting eating behaviour, as the standardised test foods used in these studies are normally a number of small distinctly flavoured sandwiches of known calorie content. With this device, it becomes possible to describe how eating behaviour and food intake is influenced by variables such as palatability of the food, level of deprivation and body weight of the subjects (242, 277).

FIGURE 3.6 The edogram

Reproduced from Bellisle and Le Magnen (222)



3.4 EVALUATION OF ASPECTS OF SAFETY

As already mentioned in section 3.1, most of the appetite suppressant drugs on the market, due to their structural similarity to norepinephrine and their mechanisms of action, may cause adverse cardiovascular reactions manifest as increased blood pressure and heart rate, which may lead to hypertensive crisis. In addition, these compounds may show abuse liability and dependence potential as a direct consequence of CNS stimulation. Although appetite suppressants differ in their relative potencies for these effects, it must be established to what degree, if any, these agents can cause adverse effects.

Abused substances share two primary measurable properties. Firstly they serve as reinforcers ("rewards" that contribute to compulsive drug-seeking behaviour), as determined from animal and human studies of drug administration and secondly they serve as euphrogenics that produce subjective feelings of euphoria and well-being, as determined from human self-report data. Additionally, abused drugs may be categorized on the basis of their interoceptive stimulus effects, measured using psychometric instruments in humans or drug discrimination trials in animals. Methods have been developed that reliably measure these properties of various substances in both animals and humans and that allow for comparison with

the profiles of other drugs of known abuse potential (280-282).

Abused substances produce behavioural (cognitive and emotive), physiological and subjective effects, of which subjective effects are crucial to predict abuse liability. The basic technique is the single-dose drug administration procedure, which employs subjects who have previously used and abused psychoactive substances. Typically, double-blind procedures are instituted and the test compound is compared with placebo and an appropriate positive control such as amphetamine in a study of anorectic agents, for example. Following administration of the drug, a variety of signs (observer reported) and symptoms (subject reported) are assessed at periodic intervals dependent on the time action of the drug (282).

3.4.1 Measurement of Abuse Liability and Stimulant Effects

Self-report measures of subjective drug effects are collected from the volunteers using structured questionnaires. The "Single-Dose Questionnaire" is the simplest psychometric instrument and contains four scales: the first determines psychoactivity of the drug, the second permits classification, the third permits characterization and quantitation of symptoms, whilst the fourth is a measure of euphoria (280).

Another self-report measure is the Addiction Research Centre Inventory (ARCI) pioneered by Haertzen *et al* in 1963 (283). The ARCI questions were sampled from the responses made to sentence completion stems by opiate addicts while they were under no-drug or various-drug states. The items so selected were considered to be useful for the quantitation of ordinary states of being as well as for altered states of consciousness (284). The ARCI is a self-report true-false questionnaire with 550 empirically derived scales sensitive to various classes of psychoactive substances.

Martin *et al* (281) sampled various items from several of the original ARCI scales which yielded a 49 item ARCI scale. The authors concluded from their investigations using this 49 item scale "that it would appear that the constellation of subjective and physiological responses herein described provides a valid measure of the abuse potentiality of amphetamine-like drugs".

Short forms of the ARCI, of which there are many, can be administered quickly and are especially useful for demonstrating potency, time actions of drugs and whether or not a drug effect is present. However, none of the short forms contain any estimate of possible subject carelessness in form completion (280).

3.4.1.1 The Addiction Research Centre Inventory (ARCI)

The 49-item version of the ARCI commonly used for the assessment of anorectic drug effects contains subsets from 5 scales:

- (1) The Morphine-Benzedrine Group (MBG) which is a general measure of drug-induced euphoria and well-being.
- (2) Amphetamine (A) which is a measure specific for dose-related effects of *d*-amphetamine.
- (3) The Benzedrine Group (BG) which is an amphetamine scale consisting mainly of items relating to intellectual efficacy and energy.
- (4) The Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) which is a measure of sedation and intoxication.
- (5) The Lysergic Acid Diethylamide Specific Scale (LSD) which is a measure of dysphoria and somatic symptoms.

The 49 statements are presented in the form of a true-false questionnaire and the subjects are instructed to indicate whether each question is true or false as they go through the scale.

3.4.1.1.1 ARCI Item Data Capture and Analysis

The data processing program was written in Digital Equipment Corporation (DEC) BASIC and was kindly supplied by Dr L.D. Chait, Department of Psychiatry, University of Chicago, Illinois (285). This program was converted to Microsoft GW-BASIC by Mr A.G. Soper, School of Pharmaceutical Sciences, Rhodes University, Grahamstown, South Africa. In addition, Mr Soper added a data capture program.

The data capture program, ARCICAP allows the responses to the 49 statements (items) to be entered from the ARCI questionnaire. The user is prompted with the relevant statement for each response, thus permitting ARCICAP to replace the ARCI form if so desired. A "1" is recorded for a "True" response and a "0" for a "False" response. Captured data are replaced in

a file with a user selected name and the extension ".CAP". ARCICAP performs some error checking and allows the user to make corrections.

For data processing, a set of 49 responses is read from the data (.CAP) file. Eight primary scores [S(1) - S(8)] are computed from 8 subsets of the responses to the item numbers relevant to that score. These scores are allocated to the eight scales, that is, S(1) = PCAG neg, S(2) = BG pos, ..., S(8) = LSD neg., etc.

In the primary processing phase, the first 5 scores [S(1) - S(5)] receive ONE point for each TRUE response in the appropriate subset, with the remaining 3 scores [S(6) - S(8)] receiving ONE point for each FALSE response in the appropriate subset. The item number allocation relevant to the 8 primary scores and hence the 8 scales is listed below:

SCORE	ITEM NUMBER ALLOCATION (Subset)	SCALE
S(1) Items	1,2,3,4,5,6,7,8,9,10,11	PCAG pos
S(2) Items	23,26,28,30,31,32,34,36,37	BG pos
S(3) Items	34,35,41,42,43,44,45,46,47,48	LSD pos
S(4) Items	13,14,15,16,17,18,19,20,21,22,23, 24,25,26,27.....	MBG pos
S(5) Items	24,25,26,27,29,30,31,32,33,34,35 ..	A pos
S(6) Items	12,23,29,48	PCAG neg
S(7) Items	10,38,39,40	BG neg
S(8) items	11,22,33,49	LSD neg

In the secondary phase of processing, the 8 primary scores are combined as follows to yield the secondary scores which relate to the final scales:

FINAL SCALE	FINAL SCALE
S(1) becomes S(1) + S(6)	PCAG
S(2) becomes S(2) + S(7)	BG
S(3) becomes S(3) + S(8)	LSD
S(4) remains S(4)	MBG
S(5) remains S(5)	A
S(6) becomes S(1) + S(2) + S(3) + S(4) + S(5)	

As a check, if S(6) now equals zero, scores S(1) to S(5) are each set to 99 to indicate a condition of error. S(6) is not used in the final result set. The final result set pertaining to the 5 ARCI scales is scores S(1) to S(5).

Figure 3.7 shows a typically completed ARCI questionnaire.

FIGURE 3.7 Typical Completed ARCI Questionnaire

THE ADDICTION CENTRE RESEARCH INVENTORY	
INSTRUCTIONS	
These 49 items may or may not describe how you feel. Circle the T next to each item number that does describe how you feel, and circle the F next to each item that does not describe how you feel.	
T	1. My speech is slurred.
T	2. I am not as active as usual.
T	3. I have a feeling of just dragging along rather than coasting.
T	4. I feel sluggish.
T	5. My head feels heavy.
T	6. I feel like avoiding people although I usually do not feel this way.
T	7. I feel dizzy.
T	8. It seems harder than usual to move around.
T	9. I am moody.
T	10. People might say I am a little moody today.
T	11. I feel drowsy.
T	12. I am full of energy.
T	13. Today I say things in the easiest possible way.
T	14. Things around me seem more pleasing than usual.
T	15. I have a pleasant feeling in my stomach.
T	16. I feel I will lose the contentment that I have now.
T	17. I feel in complete harmony with the world and those around me.
T	18. I can completely appreciate what others are saying when I am in this mood.
T	19. I would be happy all the time if I felt as good as I feel now.
T	20. I feel so good that I know other people can tell it.
T	21. I feel as if something pleasant had just happened to me.
T	22. I would be happy all the time if I felt as I do now.
T	23. I feel more clear headed than dreamy.
T	24. I feel as if I would be more popular with people today.
T	25. I feel a very pleasant emptiness.
T	26. My thoughts come more easily than usual.
T	27. I feel less discouraged than usual.
T	28. I am in the mood to talk about the feelings I have.
T	29. I feel more excited than dreamy.
T	30. Answering these questions was very easy today.
T	31. My memory seems sharper to me than usual.
T	32. I feel as if I could write for hours.
T	33. I feel very patient.
T	34. Some parts of my body are tingling.
T	35. I have a weird feeling.
T	36. My movements seem faster than usual.
T	37. I have better control over myself than usual.
T	38. My movements seem slower than usual.
T	39. I find it hard to keep my mind on a task or job.
T	40. I don't feel like reading anything right now.
T	41. It seems I am spending longer than I should on each of these questions.
T	42. My hand feels clumsy.
T	43. I notice my hand shakes when I write.
T	44. I have a disturbance in my stomach.
T	45. I have an increasing awareness of bodily sensations.
T	46. I feel anxious and upset.
T	47. I have unusual weakness of my muscles.
T	48. A thrill has gone through me one or more times since I started this test.
T	49. My movements are free, relaxed, and pleasurable.

Name Eleanor Week 2 Day 7 Time pm

The response data obtained from this questionnaire was subjected to the ARCI computer data capture program ARCICAP to yield the following data file:

0,0,0,0,0,0,0,0,0,0,0,0,1,1,1,1,0,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,0,0,0,
1,0,0,0,0,0,0,0,0,0,0,0,1,1, Date:wk2dy7, Time:pm, User:Lauri,
Volunteer:Eleanor

The text footer is self-explanatory with the user being the person who entered the data into the computer program.

This file was processed using the computer program to yield the following results:

Date: wk2dy7, Time: pm, User: Lauri, Volunteer: Eleanor

Final Score	Final Scale
S(1) = 0	PCAG
S(2) = 11	BG
S(3) = 2	LSD
S(4) = 14	MBG
S(5) = 9	A

This set of results (scores) was manually checked against the software supplied by Dr Chait and Mr Soper, and was found to be identical, as follows:

Number of Items	Phase One Score	Phase One Score		Phase Two Score	Phase Two Score		Final Score	Final Scale
		1's	0's		1's	0's		
11	S(1)	0	11	S(1)=S(1)+S(6)	0	11	0	PCAG
9	S(2)	7	2	S(2)=S(2)+S(7)	11	2	11	BG
10	S(3)	1	9	S(3)=S(3)+S(8)	2	12	2	LSD
15	S(4)	14	1	S(4)=S(4)	14	0	14	MBG
11	S(5)	9	2	S(5)=S(5)	9	0	9	A
4	S(6)	0	4					
4	S(7)	4	0					
4	S(8)	1	3					

3.4.1.2 The Profile of Mood States (POMS)

An experimental version of the POMS described by McNair *et al* in 1971 (133-137, 285, 286) is used, which consists of 72 adjectives commonly used to describe momentary mood states. Subjects indicate how they feel at the moment in relation to each of the adjectives on a 5-point scale ranging from "NOT AT ALL" (0) to "EXTREMELY" (4). There are eight clusters or scales of items (anxiety, depression, anger, vigour, fatigue, confusion, friendliness and elation) that have been separated empirically using factor analysis. The value of each scale is determined by adding the numbers checked for each adjective in the cluster and dividing the total by the number of adjectives in that cluster.

Two additional, unvalidated scales (arousal and positive mood) that are derived from the other scales are commonly used. The two additional scales are calculated as follows:

$$\text{Arousal} = (\text{Anxiety} + \text{Vigour}) - (\text{Fatigue} + \text{Confusion})$$

$$\text{Positive Mood} = \text{Elation} - \text{Depression}$$

3.4.1.2.1 POMS Item Data Capture and Analysis

The data processing program was written in Digital Equipment Corporation (DEC) BASIC and was supplied by Dr L.D. Chait, Department of Psychiatry, University of Chicago, Illinois (285). Dr Chait also supplied a copy of the POMS questionnaire. This program was converted to Microsoft GW-BASIC by Mr A.G. Soper, School of Pharmaceutical Sciences, Rhodes University, Grahamstown, South Africa. In addition, Mr Soper added a data capture program.

The data capture program (POMSCAP) allows the answers to the 72 adjectives and the date/time/name data to be entered from the POMS questionnaire, edited and written to disk in the format required by the data processing program, POMS. Seventy two answers plus the date/time/name comprise a single record.

POMS reads one complete record from the input file and some error checking is performed. Two answers receive extra processing, thus:

If the response value is $<$ or $= 4$ then the value becomes $4 - \text{value} \dots (i)$

The values which are treated in this manner are:

Response 36 "Relaxed" (used in score 1)

Response 43 "Efficient" (used in score 6)

Eight scores [S(1) - S(8)] which relate to the 8 scales are then computed by averaging the elements of each subset (item number) of the 72 answers, as follows:

$$\text{Score} = \frac{\sum_{i=1}^{i=n} (A_i)}{n} \dots\dots\dots(ii)$$

Where : A_i = responses (i.e. a value of either 0, 1, 2, 3, or 4) allocated to each item in that subset
 n = number of items in that subset

Each item expressed as an adjective is allocated to the eight clusters (scales) as follows (285):

SCORES	ITEM NUMBER ALLOCATION (Subsets)	SCALE
S(1):	Items 2,11,18,27,36,39,48,53,65	(3a) Anxiety
S(2):	Items 6,10,16,22,25,29,35,41,42,50,51,54,64,67,69	(3b) Depression
S(3):	Items 4,14,19,24,30,33,44,47,52,58,62,71	(3c) Anger
S(4):	Items 8,17,23,31,46,59,61,66	(3d) Vigour
S(5):	Items 5,12,20,32,38,55,70	(3e) Fatigue
S(6):	Items 7,9,21,37,43,57,63	(3f) Confusion
S(7):	Items 1,15,28,34,40,49,60,68	(3g) Friendliness
S(8):	Items 3,13,26,45,56,72	(3h) Elation

Two further scores are computed from the previous 8 scores.

S(9) = [S(1) + S(4)] - [S(5) + S(6)].....(9) Arousal

S(10) = S(8) - S(2)(10) Positive Mood

Figure 3.8 shows a typically completed POMS questionnaire. The response data obtained from this questionnaire was subjected to the POMS computer data capture program to yield the following data file:

3,0,3,0,1,0,0,2,0,0,0,0,1,0,3,0,2,0,0,0,0,0,3,0,0,2,0,3,0,0,3,0,0,2,0,3,
 0,0,0,2,0,0,2,0,3,2,0,0,2,0,0,1,0,0,0,1,0,0,1,3,1,0,1,0,0,0,0,3,0,0,0,1,
 Date:wk2dy7, Time:pm, User:Lauri, Volunteer:Eleanor

FIGURE 3.8 Typical Completed POMS Questionnaire

THE PROFILE OF MOOD STATES

INSTRUCTIONS

Here is a list of words and phrases that describe different feelings people have. Please read each word and decide how much you are feeling that way right now: not at all, a little, moderately, quite a bit, or extremely. Circle a number next to the word to show your answer.

Please be sure to circle ONE number - and ONLY ONE number - next to every word on the sheet. Example: The first word is "Friendly". Consider how friendly you have been feeling. If you have not been feeling friendly at all, circle the number "0" to the left of the word "Friendly":

0 1 2 3 4 Friendly

0 for "not at all"
1 for "a little"
2 for "moderately"
3 for "quite a bit"
4 for "extremely"

0	1	2	3	4	Friendly
0	1	2	3	4	Tense
0	1	2	3	4	Happy
0	1	2	3	4	Angry
0	1	2	3	4	Worn out
0	1	2	3	4	Unhappy
0	1	2	3	4	Confused
0	1	2	3	4	Lively
0	1	2	3	4	Unable to concentrate
0	1	2	3	4	Sorry for things done
0	1	2	3	4	Shaky
0	1	2	3	4	Listless
0	1	2	3	4	Overjoyed
0	1	2	3	4	Peeved
0	1	2	3	4	Agreeable
0	1	2	3	4	Sad
0	1	2	3	4	Active
0	1	2	3	4	On edge
0	1	2	3	4	Grouchy
0	1	2	3	4	Fatigued
0	1	2	3	4	Muddled
0	1	2	3	4	Blue
0	1	2	3	4	Energetic
0	1	2	3	4	Spiteful
0	1	2	3	4	Hopeless
0	1	2	3	4	Satisfied
0	1	2	3	4	Panicky
0	1	2	3	4	Helpful
0	1	2	3	4	Unworthy
0	1	2	3	4	Annoyed
0	1	2	3	4	Cheerful
0	1	2	3	4	Exhausted
0	1	2	3	4	Resentful
0	1	2	3	4	Forgiving
0	1	2	3	4	Discouraged

0 for "not at all"
1 for "a little"
2 for "moderately"
3 for "quite a bit"
4 for "extremely"

0	1	2	3	4	Relaxed
0	1	2	3	4	Bewildered
0	1	2	3	4	Sluggish
0	1	2	3	4	Uneasy
0	1	2	3	4	Kindly
0	1	2	3	4	Lonely
0	1	2	3	4	Miserable
0	1	2	3	4	Efficient
0	1	2	3	4	Bitter
0	1	2	3	4	Pleased
0	1	2	3	4	Alert
0	1	2	3	4	Ready to fight
0	1	2	3	4	Restless
0	1	2	3	4	Good-natured
0	1	2	3	4	Gloomy
0	1	2	3	4	Desperate
0	1	2	3	4	Rebellious
0	1	2	3	4	Nervous
0	1	2	3	4	Helpless
0	1	2	3	4	Weary
0	1	2	3	4	Elated
0	1	2	3	4	Forgetful
0	1	2	3	4	Deceived
0	1	2	3	4	Full of pep
0	1	2	3	4	Warm-hearted
0	1	2	3	4	Carefree
0	1	2	3	4	Furious
0	1	2	3	4	Uncertain about things
0	1	2	3	4	Worthless
0	1	2	3	4	Anxious
0	1	2	3	4	Vigorous
0	1	2	3	4	Terrified
0	1	2	3	4	Good-tempered
0	1	2	3	4	Guilty
0	1	2	3	4	Bushed
0	1	2	3	4	Sad-tempered
0	1	2	3	4	Refreshed

Name EleanorWeek 2Day 7Time pm

This file was processed using the computer program producing the following results in the output file:

Date: wk2dy4, Time: pm, User: Lauri, Volunteer: Eleanor

Final Score	Final Scale
S(1) = 0.111	Anxiety -----> Note i)
S(2) = 0.000	Depression
S(3) = 0.083	Anger
S(4) = 1.750	Vigor
S(5) = 0.143	Fatigue
S(6) = 0.429	Confusion -----> Note ii)
S(7) = 2.625	Friendliness
S(8) = 1.833	Elation
S(9) = 1.290	Arousal -----> Note iii)
S(10) = 1.833	Positive Mood -----> Note iv)

Note i) Computed using subset (3a). Since response 36 is an element of this set and since response 36 is processed by (1), response 36 becomes $4-3=1$ and the average becomes:

$$(0 + 0 + 0 + 0 + 1 + 0 + 0 + 0 + 0) / 9 = 0.000$$

Note ii) As for Note i) above except this value is computed using (3f). In this case response 43 is present resulting in an average of $3 / 7 = 0.429$

Note iii) Score 9 computed using (4)

Note iv) Score 10 computed using (5)

This set of results was manually checked against the software supplied by Dr Chait and Mr Soper and was found to be identical, as follows.

	Response / Value	Number of Items	Final Score	Final Scale
S(1) =	1 /	9 =	0.111	Anxiety
(Note: response 36 is present, thus value = $4 - 3 = 1$)				
S(2) =	0 /	15 =	0.000	Depression
S(3) =	1 /	12 =	0.083	Anger
S(4) =	14 /	8 =	1.750	Vigor
S(5) =	1 /	7 =	0.143	Fatigue
S(6) =	3 /	7 =	0.429	Confusion
(Note: response 43 is present, thus value = $4 - 2 = 2$)				
S(7) =	21 /	8 =	2.625	Friendliness
S(8) =	11 /	6 =	1.833	Elation
S(9) =	1.861-0.572	=	1.290	Arousal
(Note: $S(9) = [S(1)+S(4)] - [S(5)+S(6)]$)				
S(10) =	1.833-0.000	=	1.833	Positive Mood
(Note: $S(10) = [S(8) - S(2)]$)				

3.4.1.3 Visual Analogue Scales (VAS)

The VAS form consists of six horizontal 100 mm line, each labelled with an adjective ("stimulated", "high", "anxious", "sedated", "down" and "hungry"). The left ends are labelled "NOT AT ALL" and the right ends "EXTREMELY". Subjects place a mark on each line to indicate how they feel at the moment they are completing the scale (133-137, 285).

The 49-item ARCI, 72-item POMS and 6-item VAS have been used in studies to determine whether PPA, in various dosages exhibits abuse liability and/or dependence potential (133-137).

3.4.2 Cardiovascular Measurements

Systemic arterial blood pressure is a physiologic variable which reflects the effects of cardiac output, peripheral vascular resistance and other hemodynamic variables (287).

3.4.2.1 Equipment used for Blood Pressure Determinations

Direct intra-arterial measurements of blood pressure are more precise than indirect measures using a sphygmomanometer. Nevertheless, properly measured, elevated indirect blood pressure readings are an important sign of vascular disease. Manual and automated mechanical devices are used for the indirect measurement of blood pressure (287).

3.4.2.1.1 Manual Mechanical Devices

The sphygmomanometer consists of a compression bladder of rubber enclosed in an unyielding cuff covered with nondistensible material of the contact closure (velcro), hook or bandage type. The bladder is connected by tubing to an inflating bulb or pump by which the pressure is increased, a manometer from which the applied pressure is read and a controlled exhaust valve to deflate the system.

The inflatable bladders and cuff are usually standardised with regard to length and width. The correct bladder size must be chosen in relation to the arm circumference to ensure measurement accuracy. The manometers used may be of two types, that is a mercury manometer or a manual aneroid consisting of a rotating needle to indicate blood pressure changes. When used with a stethoscope of standard variety, this technique is known as the

auscultatory method of blood pressure determination (287).

3.4.2.1.2 Automated Devices

The term automated can refer to various characteristics of the device. Most types of automated equipment have (288):

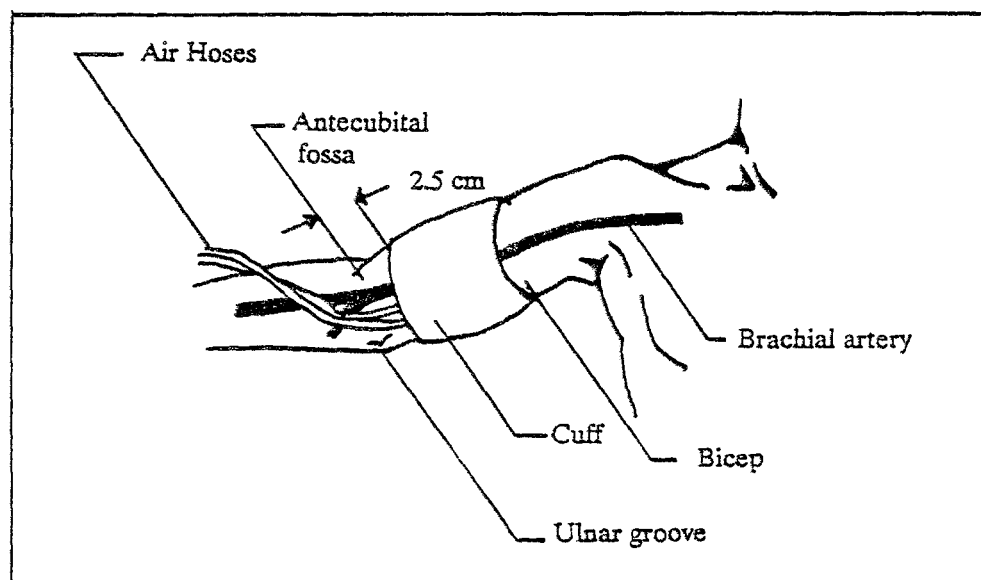
- 1) an electronic aneroid containing a microphone in the cuff for the detection of the Korotkoff sounds
- 2) digital or automatic displays for the blood pressure readings
- 3) a push-button feature for the automatic inflation or deflation of the cuff.

3.4.2.2 The Determination of Blood Pressure

The deflated cuff is attached to the sphygmomanometer around the subject's right or left arm at the level of the heart or phlebostatic axis, as it is medically known. The cuff bladder is positioned over the brachial artery, with the lower margin about 2.5 cm above the antecubital fossa which lies medially in front of the elbow. A preliminary palpatory determination of the systolic blood pressure should be performed to enable the investigator to estimate the maximal pressure to which the system needs to be elevated in subsequent determinations (287). Figure 3.9 is a graphic representation of the anatomical positioning of the cuff for blood pressure measurements.

FIGURE 3.9 The placement of the cuff bladder on the arm for blood pressure determinations

Reproduced from Schmidt *et al* (290)



A bell stethoscope is firmly applied to the antecubital space over the brachial artery, and the cuff inflated with the bulb, to occlude the artery and raise the pressure to approximately 30 mmHg above the point at which the radial pulse disappears. Thereafter, the pressure should be released at a rate of 2 to 3 mmHg/second to exclude the possibility of systematic error (287).

As the pressure declines, the Korotkoff sounds become audible over the artery below the cuff and pass through five phases as the pressure decreases and the sounds disappear (289).

- | | |
|------------|--|
| Phase I: | The period marked by the first appearance of faint clear tapping sounds which gradually diminish in intensity, which corresponds to the systolic pressure . |
| Phase II: | The period during which a murmur or swishing quality is heard. |
| Phase III: | The period during which the sounds are crisper and increase in intensity. |
| Phase IV: | The period marked by the distinct, abrupt muffling sound so that a soft, blowing quality is heard. |
| Phase V: | The point at which the sounds disappear, which corresponds with the diastolic pressure . |

When all sounds have disappeared, the cuff should be deflated rapidly and completely. One to two minutes should be allowed to elapse for the release of blood trapped in the veins before further determinations are made. Blood pressure determinations can be performed with the subject seated, standing or supine.

The American Heart Association recommends the use of the following guidelines to ensure accurate blood pressure readings (287, 290):

- 1) The observer should be trained in performing blood pressure measurements and be uninhibited by sensory impairment.
- 2) During the pressure observation, the eyes should be level with the meniscus of the mercury column or centred on the gauge.
- 3) All observations should be performed by the same independent observer.
- 4) The subject should be accommodated in a quiet room at a comfortable temperature with the arm unrestricted by clothing or other material.

- 5) The subject should avoid exertion, exposure to cold, eating or smoking for half an hour prior to the measurements.
- 6) There should be no postural change in the subject for 5 minutes before the recording of blood pressure.

CHAPTER 4CLINICAL STUDY - EVALUATION OF SAFETY AND EFFICACY

A clinical trial was performed in order to supplement the vast amount of data available concerning the safety and efficacy of PPA. Whilst much research has been carried out to assess the central and cardiovascular safety of PPA (with the majority of these studies being carried out over short periods of time) and numerous reports attest to the efficacy of PPA in causing weight loss in humans, there is a paucity of information regarding its effects on appetite and food intake.

As mentioned in section 1.5, some researchers (56,57) have reported that PPA causes appetite suppression. However, only in one study by Hoebel *et al* (62) were the effects of PPA on hunger/appetite emphasized. Following on from the discussion in section 3.2.2 and 3.3.2.5, respectively, it would be of interest to determine the effect of PPA on the satiety sequence and on salivation (a putative measure of appetite), as no published data are available in this regard.

Only two reports, in which the subjects were not placed on a caloric-restricted diet, of the effects of PPA on food intake have appeared in the literature, one in which the intake of a liquid lunch was measured (63), and the other which employed diet diaries to indirectly monitor overall food intake and the elective consumption of macro-nutrients (98).

It is clear that more research is needed to extend the available data concerning the effects of PPA on overall food intake, the elective consumption of macro-nutrients and on the 3 basic phases of eating i.e. initiation (hunger), maintenance (appetite) and termination (satiety).

The primary objective of the clinical study was to initialise a multidimensional approach to evaluate the efficacy and safety of PPA as an appetite suppressant in humans, using standardised methods and procedures. Aspects of efficacy assessed were broad and included the effects of PPA on subjective hunger, appetite and satiety, salivation, body weight, food intake and the elective consumption of macro-nutrients. In addition, the

safety of PPA was evaluated in terms of blood pressure influences, changes in subjective mood and abuse potential. The subjects were dosed to steady-state for 4 weeks and peak and trough serum levels were analysed to enable possible correlations of these variables with serum levels of PPA.

A pilot feasibility trial was conducted to determine whether such an approach was possible. Because of the extremely subjective nature of such an approach and hence the reality of large inter-subject variability, a crossover design was implemented to enable each subject to serve as his/her own control.

In a cross-over design, typically, two treatments are compared, with each subject or patient taking each treatment in turn. The patients are allocated to two groups and receive treatments on two different occasions called periods or legs. The order of treatment is randomised, with the first group receiving the treatments in the order AB and the second group in the order BA, where A and B are the two treatments. The balancing of order (AB or BA) takes care of time trends or other "period" effects, if present. A period effect is defined as a difference in response due to the occasion on which the treatment is given, independent of the effect of the treatment (291, 292).

One of the most appealing factors associated with the crossover design, is that each subject acts as his or her own control. This feature enables direct comparison of drug treatments and is particularly efficient in the presence of large inter-subject variation. Since each subject takes both of the treatments, the comparison is based on the relative magnitude of the within-subject variation to between-subject variation. Thus, given an equal number of observations, crossover experiments are more powerful and usually result in greater precision than the parallel-groups design, where different subjects comprise the two groups (291).

However, there are some problems associated with crossover designs (291). A crossover study may take longer to complete than a parallel study because of the additional testing period required. In the crossover design, missing data pose a more serious problem than in a parallel design. Since each subject must supply data on two occasions, the chances of observations

being lost are greater in the crossover design. In addition, if one subject defaults from a study phase, not only their data but data from another subject being administered the opposite sequence, is lost.

Perhaps the most serious problem associated with the use of crossover designs is the possibility of interactions (292). The most common interaction that may be present in crossover studies is a differential carryover or sequential effect. This effect occurs when the response during the second period is dependent on the response in the first period, and this dependency differs depending on which of the two treatments is given during the first period. In bioequivalence studies, differential carryover usually occurs if the washout period between administration of dosage forms is of insufficient duration to allow the body to eliminate the first dosage form completely.

However, this example only illustrates the problem; often carryover effects are not as obvious. The effects can be caused by uncontrolled factors such as psychological or physiological states of the subjects, or by external factors such as the weather, clinical setting, and so on. When carryover effects are present, the usual interpretation and statistical analysis of crossover studies are invalid. Only the first period results can be used, resulting in a smaller, less sensitive experiment (292).

4.1 PILOT STEADY-STATE TRIAL

A pilot steady-state trial was conducted using one female volunteer to establish various conditions such as frequency and times of blood sampling as well as the PPA concentrations which could be expected in serum after the ingestion of seven doses of a sustained release capsule containing 75 mg of PPA.HCl, administered at 12 hourly intervals.

The volunteer was a smoker and had no previous history of hypertension. Blood and urine samples collected prior to the trial were subjected to clinical chemistry tests and were found to be normal. The volunteer received a copy of the trial protocol and signed a consent form (Appendix 1). She received an honorarium for participating in the trial and practised similar standardisation procedures as described in section 4.2.4.

The subject ingested one capsule of PPA.HCl with 200 ml of tap water at 08h00 and 20h00 each day for three days prior to the trial day (day 4). A 10 ml blood sample was withdrawn 5 minutes prior to the first (blank 0.0 hr sample) and subsequent doses. The subject began fasting at 22h00 on day 3 and a blood sample was withdrawn prior to the 7th and final dose at 08h00 on day 4. Thereafter, the subject was given a standardised breakfast consisting of 2 slices of toast with margarine and jam and 250 ml orange juice. Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 6, 8, 9, 10, and 12 hours after ingestion of the 7th dose of the drug. The subject received a low fat standardised lunch at 13h00 and a standardised snack at 17h00.

4.2 CLINICAL EFFICACY AND SAFETY TRIAL: METHOD AND DESIGN

4.2.1 Study Population

Subjects were volunteers from the Grahamstown area who answered an advertisement placed in the local newspaper regarding people who wanted to lose weight. Prospective subjects were screened for their ability to participate in the study. At the initial visit, the investigator recorded the following variables:

- (a) Age in years, sex and race.
- (b) Occupation.
- (c) Height in metres and weight in kilograms.
- (d) Ideal body weight and % overweight according to the Metropolitan Life Insurance Company Tables of 1983 (255).
- (e) Body Mass Index described in section 3.3.1.

The subjects then reported to the attending physician who performed the following examinations:

- (a) Body frame assessment as small, medium or large.
- (b) Medical history and vital signs physical examination.
- (c) Obtained sufficient blood and urine samples to allow for the determination of the following clinical laboratory values:

Haematological status: Haemoglobin, haematocrit, leucocytes, red blood cell count, platelet and differential counts and sedimentation rates

Clinical chemistry: SGOT (serum glutamic oxalacetic transaminase), SGPT (serum glutamic pyruvic transaminase), serum creatinine and urea, serum bilirubin and alkaline phosphatase, glucose, cholesterol, triglycerides, sodium and potassium chlorides and total protein

Urinalysis: Specific gravity, pH, bile, protein, glucose, ketones, blood and bilirubin

Subjects were eligible for inclusion into the study programme if they were:

- (a) Male or female caucasians between 18 and 45 years old ;
- (b) Normotensive individuals in general good health;
- (c) Approximately 10 % above normal weight for their height and age;
- (d) Highly motivated to lose weight;
- (e) Normal in terms of medical history, physical examination and if they presented normal clinical laboratory values.

Prospective subjects were excluded from participating in the study programme if:

- (1) they had any significant clinical disease, overt illness or surgical condition such as cardiovascular or gastro-intestinal disease, hepatic or renal dysfunction, endocrine disorders, hypertension, asthma or diabetes mellitus;
- (2) they had a positive past history of psychiatric or affective disorders;
- (3) they were female who were, or were apt to become pregnant, or if they were lactating or in the postpartum stage of motherhood;
- (4) they had an inability to communicate with the investigator;
- (5) they had any known or pre-existent sensitivity or intolerance to PPA;
- (6) they had been on any weight reduction programme for three weeks prior to the study;
- (7) they abused alcoholic beverages or had participated in another trial within 60 days preceding the study;

- (8) they had a major illness during the 3 months preceding the study;
- (9) they had undergone treatment within the previous 3 months with any drug known to have a well-defined potential for toxicity to one of the major organs;
- (10) they required any concomitant medication (prescription legend or OTC preparation) such as tricyclic antidepressants, MAO-inhibitors, antihypertensives, other sympathomimetic agents, sodium bicarbonate or other antacids, aspirin, indomethacin or anticholinergic agents;
- (11) during the course of the trial, their blood pressure rose above 10 mm Hg (diastolic) or above 30 mm Hg (systolic) and was sustained over three consecutive measurements of 30 minutes duration (10 mg Nifedipine was kept on hand for any hypertensive emergencies).

Eight normal, healthy, caucasian women who conformed to the criteria set out above, were selected to participate in this trial. Individual details of these volunteers are depicted in Table 4.1.

Subject	Age	Initial Weight (kg)	Height (cm)	Body Mass Index	Frame Size	Ideal Weight (kg)	% Over-weight
SS (1)	38	70.67	175	23.08	M	66.00	7.08
CA (2)	22	61.80	153	26.57	M	54.50	13.39
LE (3)	36	77.00	169	26.96	L	68.70	12.08
EA (4)	37	65.73	160	25.68	S	58.05	13.23
VW (5)	20	72.80	169	25.49	M	68.70	5.97
LI (6)	32	81.20	168	28.94	L	68.05	19.32
EG (7)	42	62.40	161	23.95	M	58.55	6.01
CV (8)	32	66.60	165	24.46	M	60.70	9.72
Mean ± SD	32.38 ± 7.70	69.78 ± 6.94	165 ± 6.82	25.64 ± 1.86		62.91 ± 5.62	10.85 ± 4.60

TABLE 4.1 Demographic Details of Subject Population

Each volunteer received a copy of the trial protocol and written informed consent (Appendix 2) was obtained. The selected volunteers indicated a willingness and good motivation to co-operate and were paid an honorarium for participating in the study.

4.2.2 Test Medication Dosage Forms

The study compared the effects of PPA with a placebo control and identification parameters for both dosage forms are listed below:

1) Test Medication A (TM A)

Name: Phenylpropanolamine Hydrochloride.
 Dosage and Dosage Form: 75 mg Sustained Release (SR) capsule.
 Identification: Size 2 capsule (white body, green cap) containing white micro-encapsulated beads.
 Manufacturer: Euderma, Italy.
 Batch Number: Lot S129/1
 Date of Manufacture: 19-09-1989
 Supplier: Lennon Ltd, South Africa.

2) Test Medication B (TM B)

Name: Pharmacologically Inert Placebo.
 Identification: Size 2 capsule (white body, green cap) containing white micro-encapsulated beads.
 Manufacturer: Euderma, Italy.
 Batch Number: Lot S209/1
 Date of Manufacture: 20-09-1989
 Supplier: Lennon Ltd, South Africa.

Both test medications were formulated in identically appearing capsules and packaged in individual bottles. Each bottle of medication was labelled with the subject's name and phase and contained 56 capsules, sufficient for each subject, for each phase of the trial.

4.2.3 Experimental Design

The study was carried out for a period of eleven weeks in a double-blind, randomised, placebo-controlled cross-over manner. Table 4.2 depicts the sequence of events for the trial.

WEEK ONE	: Baseline evaluation period
WEEK TWO - FIVE	: First phase of the study
WEEK SIX ¹	: Wash-out period
WEEK SEVEN	: Re-establishment of baseline conditions
WEEK EIGHT - ELEVEN ²	: Second phase of cross-over study

¹ The seventh week of the trial corresponds to the first week of the second phase.

² Weeks 8 - 11 of the trial correspond to weeks 2 - 5 of the second phase.

TABLE 4.2 Study Plan for the Trial Summarising Weekly Events

As the cross-over design requires that equal numbers of subjects are allocated to each sequence or order of treatment, 4 subjects were allocated to the treatment in the order A (PPA) followed by B (placebo) and 4 subjects in the order B followed by A using a randomisation schedule established by an independent colleague. Random assignment of subjects to PPA or placebo not only ensures complete double-blinding, but also eliminates a potential source of bias in comparison of treatment groups in baseline characteristics. Double-blind procedures infer that neither the subject nor the investigator knew which test medication was being administered during each phase.

Each subject received one test medication for phase 1 (week 2-5) and was crossed over for phase 2 (week 8-11) receiving the test medication that was not used during the first phase. The subjects ingested the respective test medications twice daily on a 12-hour fixed-dose schedule, at 08h00 and 20h00 hours for eight weeks according to the study design. Table 4.3 depicts the random allocation of test medication to subjects per phase.

Subject	Test Medication	
	Phase 1	Phase 2
SS (1)	PPA	Placebo
CA (2)	PPA	Placebo
LE (3)	Placebo	PPA
EA (4)	Placebo	PPA
VW (5)	Placebo	PPA
LI (6)	Placebo	PPA
EG (7)	PPA	Placebo
CV (8)	PPA	Placebo

TABLE 4.3 **Test Medication Allocation**

In an attempt to ensure patient compliance, the bottles containing the test medications, labelled with subject's name and phase were stored by the trial co-ordinator. The subjects were required to report each day during the week just prior to 08h00 and 20h00 to receive their medication. The weekend dose(s) were given to each subject in a bottle containing 4 doses of medication with instructions to ingest the doses at the specified times. It was hoped that the serum data obtained on the seventh day of every week

at 20h00 would indicate whether the subject's had conformed to the weekend ingestion schedule instructions.

During the first and seventh weeks of the trial the subjects did not receive any medication and baseline variables were established as detailed in the daily experimental schedule (Table 4.4). To facilitate subject handling, 4 women started the trial on a Monday and the other four on a Tuesday. Two women of the latter group began the trial two weeks later than the other six.

4.2.4 Standardisation Procedure

Identical test conditions were used for both treatments in order to prevent fluctuations in variables such as meal times, physical activity and caffeine and tyramine consumption across phases.

1. The subjects were requested to fulfill the following requirements:
 - (a) To refrain from ingesting alcohol, caffeine or xanthine containing beverages and food such as tea, coffee, chocolate and all cola-flavoured soft drinks for 48 hours prior to and during both phases of the trial including the baseline weeks.
 - (b) Subjects were allowed to consume caffeine-free coffee and tea.
 - (c) To refrain from ingesting foods containing tyramine i.e. mature cheese, marmite, bovril, yeast, broad beans, beer, pickled herrings, hung game and foods containing the yellow food colour, tartrazine for 14 days prior to the onset until study completion.
 - (d) Not to take medications, including over-the-counter preparations for one week preceding the trial and for the duration of the trial and, if they needed concomitant medication to inform the investigator accordingly.
 - (e) To maintain their usual state of physical activity across both phases.
 - (f) To standardise their meal times for both phases when blood samples were taken.
2. The subjects were encouraged to follow their usual dietary habits and not to follow any dieting practice for the duration of the trial.
3. The subjects were requested to report any unusual effects that they experienced.

4.2.5 Sampling Schedule for the Trial

The measurements, questionnaires and data collection format for the entire eleven week trial are detailed in the daily experimental schedule (Table 4.4).

<u>DAILY EXPERIMENTAL SCHEDULE</u>		
<u>WEEK ONE</u>		
DAY1	07h30	Weight BP, MQ
	12h50	BP, BS, AHQ, BSQ
	13h00	TEST MEAL PRESENTATION SIS, MQ
	13h10	TEST MEAL SQ, FPQ
DAY2	07h30	Weight, BP, MQ
	19h50	MQ
DAY3	07h30	Weight, MQ
	19h50	MQ
DAY4	07h30	Weight, BP, MQ
	12h50	BP, BS, AHQ, BSQ
	13h00	TEST MEAL PRESENTATION SIS, MQ
	13h10	Test meal SQ, FPQ
DAY5	07h30	Weight
DAY7	19h50	BP, MQ
<u>WEEK TWO</u>		
DAY1	07h30	Weight
	07h50	Blood sample, BP, MQ
	08h00	Test medication
	12h50	Blood sample, BP, BS, AHQ, BSQ
	13h00	TEST MEAL PRESENTED SIS, MQ
	13h10	TEST MEAL SQ, FPQ
	19h50	Blood sample, BP, MQ
	20h00	Test medication
DAY2 & 3	07h30	Weight, BP, MQ
	07h50	Blood sample
	08h00	Test medication
	19h50	Blood sample, BP, MQ
	20h00	Test medication
DAY4	07h30	Weight, BP, MQ
	07h50	Blood sample
	08h00	Test medication
	12h50	Blood sample, BP, BS, AHQ, BSQ
	13h00	TEST MEAL PRESENTED SIS, MQ
	13h10	TEST MEAL SQ, FPQ
	20h00	Test medication
DAY5 & 6	08h00	Test medication
	20h00	Test medication
DAY7	08h00	Test medication
	19h50	Blood sample, BP, MQ
	20h00	Test medication
<u>WEEKS THREE, FOUR AND FIVE</u>		
DAY1	07h30	Weight
	08h00	Test Medication
	20h00	Test medication
DAY2 & 3	08h00	BP, Test medication
	20h00	BP, Test medication
DAY4-7		As for WEEK TWO
<u>WEEK SIX</u>		
		Washout period
<u>WEEK SEVEN</u>		
		As for WEEK ONE
<u>WEEK EIGHT</u>		
		As for WEEK TWO
<u>WEEKS NINE, TEN & ELEVEN</u>		
		As for WEEKS THREE, FOUR & FIVE
<u>KEY TO THE ABBREVIATIONS USED</u>		
BP = Blood Pressure		
AHQ = Appetite and Hunger Questionnaire		
SQ = Satiety Questionnaire		
SIS = Stimulus-Induced-Salivation		
BS = Baseline Salivation		
MQ = Mood Questionnaire (ARCI, POMS, VAS)		
BSQ = Bodily Sensation Questionnaire		
FPQ = Food Preference Questionnaire		

TABLE 4.4 Experimental Schedule Indicating the Testing Procedures and Timing of Particular Events.

4.2.6 Collection and Storage of Blood Samples

In accordance with the experimental schedule, a total of 38 blood samples for each subject per phase were withdrawn at the specified times. Table 4.5 depicts a summary of the blood sampling times.

Week 2	Day 1	07h50, 12h50 and 19h50
Week 2	Day 2-3	07h50 and 19h50
Week 2	Day 4	07h50 and 12h50
Week 2	Day 7	19h50
Week 3,4,5	Day 4	07h50 and 12h50
Week 3,4,5	Day 7	19h50
Week 8	Day 1	07h50, 12h50 and 19h50
Week 8	Day 2-3	07h50 and 19h50
Week 8	Day 4	07h50 and 12h50
Week 8	Day 7	19h50
Week 9,10,11	Day 4	07h50 and 12h50
Week 9,10,11	Day 7	19h50

TABLE 4.5 Summarised Blood Sampling Schedule.

A sterile hypodermic needle was inserted into a suitable vein in the forearm by a qualified nurse and ten millilitres of blood was withdrawn by syringe aspiration and collected into labelled Vacutest tubes. The samples were allowed to stand at room temperature for half an hour to allow the proteins to coagulate for serum separation.

The blood samples were centrifuged at 3000 rpm for 10 minutes and serum aliquots from each sample were transferred to clean labelled tubes and stored at -20°C until analysis. In a few cases, the serum contained fibrin clots, which were squeezed with the aid of an orange stick to free serum. These samples were re-centrifuged to separate the serum.

The phenylpropanolamine concentrations in these serum samples were determined using a validated reverse-phase HPLC method of analysis, with UV detection at 210 nm (Section 5.5).

4.2.7 Physical measurements

4.2.7.1 Body mass measurements

The subjects were weighed 25 times during each phase (5 measures per week). The measurements were performed on a calibrated portable digital balance accurate to 0.2 kg (Weigh-Less, Durban, South Africa). Three consecutive measures were made and an average weight recorded. To minimize the possibility of instrumental or procedural error the subjects were weighed by the same person, at the same time each morning in their undergarments, without shoes. The weight of the undergarments was established and excluded in the subject's total weight.

4.2.7.2 Skinfold Thickness Measurements

Skinfold thickness was measured at three anatomical locations, one truncal site (supraspinale) and two extremity sites (triceps and front mid-thigh). The location of these sites on the human body is given in Figure 3.3.

The triceps skinfold was measured from the back on the unclothed posterior surface of the pendant right arm at a level midway between the tip of the acromion and the tip of the elbow. The skinfold was lifted parallel to the long axis of the arm with the subject standing.

The supraspinale skinfold was measured 3 cm from the iliac crest with the fold (taken at midline of the body) taken obliquely, descending medially and downwards at an angle of 45 degrees to the horizontal. Subject stands erect with arms pendant.

The front-thigh skinfold was measured by raising a fold parallel along the long axis of the femur with the leg flexed at an angle of 90 degrees. Mid-thigh position is estimated half-distance between the inguinal crease and the anterior patella.

A Harpenden skinfold caliper with a constant jaw pressure of ten grams per square centimetre was used for all of the above measurements. With the exception of the supraspinale measurements, all skinfolds were taken in the vertical plane. The following techniques were used:

- (a) A fold of skin and subcutaneous tissue was picked up firmly between the thumb and forefinger 1 - 2 cm above the area under consideration and pulled away from the underlying muscle.
- (b) The caliper jaws were placed 1 - 2 cm below the thumb and forefinger holding the skin and tissue, at a depth of approximately 1 cm.
- (c) The skinfold was firmly held throughout the application of the caliper and the reading was taken when the needle became steady after full pressure of the jaws had been applied to the skinfold. The measurement was recorded to the nearest 0,1 millimetre.
- (d) The surface of the caliper jaws was parallel to the skinfold plane.
- (e) The accuracy of the measurement depends on the precise location of the skinfold site and standardisation of the skinfold crest alignment.
- (f) The measurement consists of an average of three readings.

Skinfold thickness measurements were performed on the first day of week 1 for both phases, during the trial and on the final day of each phase by the same anthropometric experimenter with the subjects in their undergarments. All bilateral measurements were made on the right side of the body.

4.2.7.3 Cardiovascular measurements

Supine systolic and diastolic blood pressures were measured with a mercury manometer using the auscultatory method throughout the entire study period in accordance with the experimental schedule. These measurements were performed using the recommendations of the American Heart Association detailed in section 3.4.2.2.

Upon the initial examination, blood pressure was recorded in both arms and the arm found to have the higher pressure was used in subsequent examinations. Blood pressures were obtained 34 times during each phase (5 measures during week 1, 10 during week 2, 9 during week 3 and 5 during weeks 4 and 5).

4.2.8 Behavioural Measurements

4.2.8.1 Measurement of Subjective Mood and Stimulant Effects

A Mood Questionnaire (MQ) was used to measure the possible behavioural reinforcing and subjective effects and was completed a total of 29 times during each phase by each subject, in accordance with the times indicated in the experimental schedule (Table 4.4). The MQ (Appendix 3) consisted of three subdivisions and included the 49 item Addiction Research Centre Inventory (ARCI) (Table A3.1), the 72 item Profile of Mood States (POMS) (Table A3.2) and the 6 item Visual Analogue Scales (VAS) (Table A3.3). The ARCI, POMS and VAS item data are detailed in section 3.4.1.1-3.

4.2.8.2 Ratings of Hunger, Appetite and Satiety

Visual analogue scales as described in section 3.3.2.1.2 were used to measure subjective hunger, appetite and satiety (Appendix 4). The Appetite and Hunger Questionnaire (AHQ) was adapted from Silverstone *et al* (246) and contained 4 questions relating to hunger, appetite, preoccupation with thoughts of food and estimates of likely food consumption (Table A4.1). The Satiety Questionnaire (SQ) was adapted from Silverstone *et al* (246) and contained 6 questions relating to fullness, preoccupation with thoughts of food, food appeal, taste of the food, and estimates of consumption of a favourite food (Table A4.3). The results were analysed by measuring the answer mark on the line of the scale to the nearest millimetre.

The Bodily Sensations Questionnaire (BSQ) discussed in section 3.3.2.2 and thought to be a means to measure feelings of hunger, was adapted from a questionnaire used by Monello and Mayer (251) and Garfinkel (252), and included checklists for mouth, throat, gastric and cerebral sensations (Table A4.2). The results of the BSQ were categorised according to location and the number of subjects and the number of times each sensation was recorded was compared after treatment with PPA (TM A) and placebo (TM B).

The Food Preference Questionnaire (FPQ) discussed in section 3.3.2.4 and used to measure subjectively perceived preferences for particular foods, was in the form of a checklist and consisted of a list of 30 basic food commodities on which subjects indicated their preferences at that moment (Table A4.4). The FPQ incorporated 15 high protein and 15 high carbohydrate

items.

These questionnaires were completed on the test meal days only, a total of seven times per subject for each phase.

4.2.8.3 Measurement of Food Intake and Salivation

Solid food intake was measured directly in the form of a standardised test meal. The freshly prepared food consisted of approximately 100g roast beef with 20g gravy, 200g boiled jacketed potato, 100g mixed steamed vegetables, 2 slices of brown bread and 20g of margarine. Milk or water was also provided according to individual preference. Each food commodity was accurately weighed to 0.1 g (Sartorius 1213 MP, Optical Instruments) and placed separately in a segmented stainless steel dish (the gravy was poured over the beef). Each segmented dish was then covered with a lid and kept warm on a Bain-Marie.

On the test meal days, the subjects entered the clinic where a blood sample was withdrawn. Subjects were asked to clear their minds of thoughts of food and baseline salivation was measured. The experimenter instructed the subjects to complete a questionnaire booklet containing AHQ and BSQ before commencing their meal and the subjects were subsequently taken to the test room where the test meal was to be consumed.

The room chosen was pleasantly comfortable and sufficiently neutral to prevent subjects from being in a rush to leave or from dawdling due to the attractive atmosphere. The room was furnished with four chairs and four tables and no clock was present.

Each subject was invited to sit at an adjoining table where a second salivation test (stimulus-induced) was conducted in the presence of the food stimuli. During this time, the subjects completed the MQ. Subjects were told that they were free to eat as much or as little as they desired and that they could select freely among the food items. The subjects were also requested not to mix food items, to abstain from talking or reading during the session and to complete the SQ and FPQ after finishing their meal. The experimenter then left the room.

The subjects began eating at approximately 13h30 and left the room upon cessation of the meal, whereupon the remaining food items were re-weighed individually. From the amount of each food item eaten, total caloric (kJ), protein, carbohydrate and fat consumption was estimated using standard tables of food composition (265). In addition, protein, carbohydrate and fat energy percentages for each test meal were calculated according to the following equations:

$$\text{Protein Energy \%} = \frac{\text{Total Protein Intake (kJ)} \times 100}{\text{Total Food Intake (kJ)}} \quad \text{Eqn 4.1}$$

$$\text{Fat Energy \%} = \frac{\text{Total Fat Intake (kJ)} \times 100}{\text{Total Food Intake (kJ)}} \quad \text{Eqn 4.2}$$

$$\text{Carbohydrate Energy \%} = \frac{\text{Total Carbohydrate Intake (kJ)} \times 100}{\text{Total Food Intake (kJ)}} \quad \text{Eqn 4.3}$$

Salivation was measured using the Strongin-Hinsie-Peck (SHP) method reported in section 3.3.2.5. The average weight of saliva collected in grams in three 2-minute collection periods was taken as a single measurement.

4.2.8.4 Additional Measurements - Observational Studies and Diaries

In an attempt to gain some insight into whether or not PPA could, conceivably, affect the micro-structure of human eating behaviour, the subject's eating patterns were observed during each test meal. The test meals were recorded on videotape for subsequent analysis of the parameters mentioned in Table 3.1 and monitored by means of a television camera. The camera unfortunately had to be visible to the subjects, as it would have been impossible to relocate the subjects to another building containing an experimental room with a one-way screen behind which the camera could have been hidden.

In a further attempt to establish whether PPA exerted any effect on normal eating habits, in terms of quantities and types of food consumed, in addition to the test meals, the subjects were requested to complete a daily food intake diary (section 3.3.3.1). The diaries contained tabulated food intake columns for the three usual main meal and snack times as well as AHQ and SQ (Appendix 4, Tables A4.1 and A4.3, respectively), which the subjects were requested to complete. The diaries were kept by the subjects and were presented to the experimenter upon completion of the trial, for subsequent analysis of content.

4.3 RESULTS - EVALUATION OF CLINICAL TRIAL EFFICACY AND SAFETY DATA

4.3.1 Analysis of Serum Samples

The method and results of the analysis of all serum samples obtained from the pilot steady-state and the clinical efficacy and safety trial will be discussed in Section 5.5.

4.3.2 "Drop-outs" and Subject Compliance with the Schedule

Subject 5 developed a urinary tract infection on Day 4, week 2 of phase 2 (PPA) and took Norfloxacin, Citrosoda and Paracetamol for the following 6 days. She did not however, default from the study. Subject 7 developed a chest infection and was unable to complete weeks 4 and 5 of phase 1 (PPA) but returned after her illness to complete phase 2. Subject 8 developed measles during phase 2 (placebo) and was unable to complete weeks 2-5 of this phase. The remaining subjects completed both phases with no untoward medical complications.

4.3.3 Reports of Adverse Reactions

The incidence of side effects reported by the subjects was extremely low and sporadic. Subjects 1, 6 and 7 did not complain of any side effects during phase 1 or 2. Subject 2 reported experiencing an "awareness of self" at lunch time during the first day that she received PPA (Phase 1), and complained of diarrhoea on the second day of phase 1. Subject 3 complained of nausea in the morning and at night for the entire first week that she was taking PPA (phase 2), and had a migraine during lunch time on the fourth day (week 3) of phase 2. Subject 4 reported feeling thirsty prior to the lunch time session on the first day that she took PPA (phase 2), and

was constipated on the second day of the same phase. Subject 5 was tired in the evening of the first day of the third week that she was taking PPA (phase 2). Subject 8 complained of tiredness in the evening of the first day that she took PPA (phase 1).

Most of these reports of adverse reactions occurred during the first or second day of the PPA phase, whilst no reports of side effects occurred during the placebo phase. All subjects who complained of side effects only did so on one occasion, with the exception of subject 3 who experienced nausea for the entire first week that she took PPA.

4.3.4 Statitistical Analysis of Data

As discussed at the beginning of this chapter, in order to perform a crossover comparison of trial data, equal numbers of subjects assigned to test medication A (TM A) and test medication B (TM B) in the first phase and crossed over in the second phase, are needed. However, due to the unforeseen complications of subject non-compliance with the biphasic trial schedule due to illness (see section 4.3.2), only 2 subjects were assigned to PPA in the first phase as opposed to 4 subjects assigned to placebo. Because the distribution of the order of assignment was unbalanced, that is, an unequal sample population was assigned to each test medication, it proved impossible to perform a crossover comparison of the trial data and thus no determination of possible sequence effects could be made.

As six subjects completed the full crossover, i.e. 6 people took both PPA and placebo on two different occasions for the entire length of the trial (with an additional subject (Subject 7) completing only a portion of one phase of the trial), the only other option available was to conduct a parallel-groups comparison of the trial data. This method involves a comparison of the response data obtained from the subjects whilst they were taking PPA compared to when they were taking placebo, irrespective of which phase they were administered either test medication.

Where appropriate, one-way and two-way analysis of variance (ANOVA) procedures for repeated measures were used to determine differences in response to PPA and placebo ingestion. Two-way analysis of variance was followed by Scheffe's *post hoc* test for multiple range analysis with

factors in the analysis being drug condition [i.e. either PPA (TM A) or placebo (TM B)] and measurement occasion (weeks). The ANOVA technique compares the variation between the samples with the variation within the samples. A conservative F test was undertaken and a 5% level of significance was used to test for significant differences i.e. a P value < or equal to 0.05.

These two ANOVA procedures were used to test the data in three ways:

TEST 1) Baseline comparisons i.e. week 1 phase 1 with week 1 phase 2.

TEST 2) Comparison of weeks on test medication (weeks 2-5) with baseline (week 1) for phase 1 and likewise for phase two (weeks 8-11 compared with week 7).

TEST 3) Comparison between test medication phases i.e. Week 2-5 (phase 1) with week 8-11 (phase 2), excluding baseline data.

Comparisons were performed on the mean data obtained from the sample of 7 subjects (data obtained from subject 8 was excluded from the analyses for reasons given in section 4.3.2, but are reported in the appendix tables) and from individual subjects. It was decided, for the overall comparison of mean subject data, to include the data from subject 7 until the end of week 3 for both phases, whilst analyses of individual subjects were performed only on subjects 1-6.

Separate analyses were undertaken for each of the dependent variables and ANOVA tests were performed on paired data only, that is, data present at any measurement occasion in either phase and absent at the same measurement occasion in the opposite phase, were omitted from the analyses.

Two-way analysis of variance was used to compare overall subject means between test medication phases as detailed in 3) above, except where indicated for specific variables. One-way analysis of variance procedures with drug condition (i.e. either TM A or TM B) as the factor were carried out on the remaining tests, for individual and overall subject means.

All results tabulated in the following section are the mean values $\pm$ the

standard error of the mean (SEM) obtained for the PPA (TM A) phase and the placebo (TM B) phase. The *F* ratios and *P* values are also given. In addition, where applicable, the two superscripted characters § and ¶ indicate levels of statistical significance of the magnitude $0.015 < P < 0.05$ and $P < 0.01$, respectively. Bold, italicised *F Ratios* and *P Values* indicate the statistics for week 1 comparison across both drug treatment phases (Test 1).

Where the statistical analysis of each variable for individual subjects is given, TM A corresponds to phase 1 for subjects 1 and 2, with TM B representing phase 2. The reverse applies for subjects 3 - 6, that is TM A corresponds to phase 2, with TM A representing phase 1.

4.3.5 Physical Measurements

4.3.5.1 Body Weight and Weight Loss

The daily body mass, weekly weight change and % weight change tables for each individual are shown in Appendix 5 (Tables A5.1.1-5.1.8 and A5.2.1-A5.2.8, respectively). The average body mass data, *F* ratios and *P* values depicted in Table 4.6 were obtained from a two-way ANOVA test (TEST 3, section 4.3.4). Raw data was obtained from each daily weighing from week 2 to 5 for each phase and the mean values for 7 subjects are reported. Weight loss and percentage weight loss were analysed using one-way ANOVA procedures with drug condition as the factor. Weight loss was calculated by subtracting the final weight (week 5 day 5) from the initial weight (week 2 day 1) for each phase. The final weight for subject 7 was taken on week 3 day 5, for reasons given in section 4.3.4.

It is apparent from Table 4.6, that no statistically significant differences in the average body mass of seven subjects occurred whilst the subjects were taking PPA or placebo. However, a statistically significant drug effect was observed for weight loss and percentage weight loss. The subjects had a mean weight loss of 2.05 kg and a mean percentage weight loss of 2.52 % whilst they were taking PPA, compared to a mean weight loss and percentage weight loss of 0.76 kg and 0.85 % respectively, on placebo.

Measure	TM A $\pm$ SEM	TM B $\pm$ SEM	F Ratio	P	n	df
Average Body Mass	68.56 $\pm$ 0.600	69.80 $\pm$ 0.580	2.16	0.1422	135	1,262
Weight Loss	-2.05 $\pm$ 0.365	-0.76 $\pm$ 0.339	6.22 [§]	0.0282	7	1,12
% Weight Loss	-2.52 $\pm$ 0.414	-0.85 $\pm$ 0.345	9.54 [¶]	0.0094	7	1,12

§ indicates a P value between 0.015 and 0.05.

¶ indicates a P value < 0.01

TABLE 4.6 Average Body Mass, Weight Loss and Percentage Loss (Mean values for 7 subjects)

Table 4.7 depicts the initial and final weights of individual subjects and Table 4.8 shows the weight change and percentage weight change for each subject for weeks 1 and weeks 2-5 for each phase. Percentage weight loss was calculated using the following formula (Eqn 4.4):

$$\% \text{ Weight Loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100 \quad \text{Eqn 4.4}$$

It is evident from the run-in period data in Table 4.8 that 2 subjects (EA and EG) gained a small amount of weight, 2 subjects (VW and LI) maintained a constant weight whilst the remaining 4 subjects (SS, CA, LE and CV) lost weight in anticipation of the study during the run-in period preceding phase 1. In addition, it can be seen that, during the second phase, 3 subjects (CA, LI and EG) gained weight, whilst the remaining 5 subjects lost weight during the run-in period.

Subject	Initial Weight		Final Weight	
	Week 2 Day 1		Week 5 Day 5	
	TM A	TM B	TM A	TM B
SS (1)	70.20	68.87	68.80	68.60
CA (2)	61.27	63.33	60.53	63.27
LE (3)	76.20	76.40	73.27	75.20
EA (4)	62.73	65.80	59.73	63.33
VW (5)	71.53	71.93	69.53	70.67
LI (6)	82.13	81.07	78.87	81.20
EG (7)	62.00	60.80	61.27	60.87
CV (8)	66.27	62.47	62.53	-

TABLE 4.7 Initial and Final Body Weights for Individual Subjects

From the weight change data depicted in Table 4.8, it can be seen that during the weeks that the subjects took the test medications (weeks 2 - 5), each subject lost more weight, with a higher percentage of weight lost whilst they were taking PPA (TM A) compared to placebo (TM B). Subjects 1 - 5 lost weight while they were taking placebo (TM B), whilst subjects 6 and 7 gained weight on placebo (TM B). During the phase that the subjects were taking PPA (TM A), 4 subjects (LE, EA, LI and CV) lost more than 2 kg, 2 subjects (SS, VW) lost between 1 and 2 kg, whilst the remaining 2 subjects (CA and EG) lost less than 1 kg.

Subject	Week 1 (Run-in Period) ³				Weeks 2-5 (Test Medication) ⁴			
	Weight Change (kg)		Weight Change (%)		Weight Change (kg)		Weight Change (%)	
	Phase 1	Phase 2	Phase 1	Phase 2	TM A	TM B	TM A	TM B
SS (1)	- 1.20	- 0.67	- 1.70	- 0.97	- 1.40	- 0.27	- 1.99	- 0.39
CA (2)	- 0.33	+ 0.54	- 0.53	+ 0.87	- 0.74	- 0.06	- 1.21	- 0.09
LE (3)	- 0.87	- 0.40	- 1.13	- 0.52	- 2.93	- 1.20	- 3.85	- 1.57
EA (4)	+ 0.07	- 0.93	+ 0.11	- 1.45	- 3.00	- 2.38	- 4.78	- 3.63
VW (5)	0.00	- 0.13	0.00	- 0.18	- 2.00	- 1.26	- 2.80	- 1.75
LI (6)	0.00	+ 0.33	0.00	+ 0.40	- 3.26	+ 0.13	- 3.97	+ 0.16
EG (7)	+ 0.33	+ 0.13	+ 0.53	+ 0.21	- 0.73	+ 0.07	- 1.18	+ 0.12
CV (8)	- 0.07	- 0.67	- 0.11	- 1.07	- 3.74	-	- 5.64	-

3 Indicates the run-in period (week 1 for each phase) preceeding phase 1 and 2

4 Indicates the period (weeks 2 - 5 for each phase) that the subjects took TM A and TM B

TABLE 4.8 Weight Change and Percentage Weight Change for Individual Subjects

The data depicted in Appendix 5, Tables A5.3.1 - A5.3.3 are mean values for 7 subjects for the average weekly body mass, weight loss and percent weight loss, respectively. The F ratios and P values were obtained from a one-way ANOVA test and show that no significant differences in treatment with PPA (TM A) or placebo (TM B) were observed for each week when compared to baseline weights (TEST 2, section 4.3.4). The bold italicised F ratios and P values indicate that baseline weights were comparable across test medication phases (TEST 1, section 4.3.4).

The average body mass for each individual subject during both treatments are shown in Table 4.9. It is apparent that subjects 2 - 6 had a lower average mass during the phase that they were taking PPA (TM A) compared to

the placebo (TM B) phase. The F ratios and P values are extremely significant due to a smaller within subject variation. However, although subject 1 had a higher average body mass on PPA (TM A) than on placebo (TM B), it can be seen from Table 4.8 that she lost 1.40 kg on PPA (TM A) as opposed to a 0.27 kg loss on placebo (TM B).

Subj	TM A $\pm$ SEM	TM B $\pm$ SEM	F Ratio	P
1	69.41 $\pm$ 0.095	68.86 $\pm$ 0.101	15.33 [†]	0.0004
2	60.83 $\pm$ 0.081	63.27 $\pm$ 0.090	407.56 [†]	0.0000
3	74.76 $\pm$ 0.224	76.49 $\pm$ 0.126	45.33 [†]	0.0000
4	61.12 $\pm$ 0.201	64.55 $\pm$ 0.200	147.66 [†]	0.0000
5	70.54 $\pm$ 0.133	71.34 $\pm$ 0.103	22.72 [†]	0.0000
6	79.86 $\pm$ 0.196	80.96 $\pm$ 0.092	25.70 [†]	0.0000

n = 20 (i.e. 5 measures per week for 4 weeks for each subject),
df = 1,38

† indicates a P value of less than 0.01

TABLE 4.9 Average Mass per Individual Subject

The average weekly mass for each volunteer is shown in Appendix 5, Table A5.3.4. The F ratios and P values were obtained using a one-way ANOVA test (TEST 1 and 2, section 4.3.4). The P values are again extremely significant due to a smaller within subject variation. Scheffe's multiple range test (MRT) was performed to determine which weeks were significantly different. The asterisk in the MRT columns indicate where these differences occurred.

For example, during the phase that subject 1 was treated with PPA (TM A), her average body mass during weeks 3, 4 and 5 were significantly lower than during weeks 1 and 2, and her average mass was relatively constant during the placebo (TM B) phase. Subject 2's average mass during weeks 2, 3 and 5 was significantly lower than during weeks 1 and 4, for the phase that she took PPA (TM A), and her average mass during weeks 2, 4 and 5 was significantly higher than during weeks 1 and 3 for the placebo (TM B) phase. During the phase that the remaining 4 subjects took PPA (TM A), the average mass of subjects 3, 4 and 6 was significantly lower during weeks 2 - 5 when compared to week 1, with week 5 being significantly lower than weeks 1 - 4 for subject 5.

During the placebo (TM B) phase, subject 3 maintained a constant average weekly mass, and subject 4 experienced a significant reduction in weight during weeks 4 and 5, when compared to weeks 1 - 3. During the same phase (TM B) subject 5 showed a significant decrease in average body mass during weeks 2 - 5 when compared to baseline (week 1), and the average body mass for subject 6 was statistically lower during week 4 when compared to weeks 1-3 and 5.

The bold italicised F ratios and P values corresponding to week 1 indicate the significance of the baseline (week 1) comparisons across treatment phases (TEST 1, section 4.3.4). It can be seen that of the two subjects (1 and 2) treated in the order TM A followed by TM B, subject 1 had a lower, and subject 2 had a higher average body mass during the first week of the second phase (TM B). The 4 remaining subjects were treated in the order TM B followed by TM A, and it can be seen that 2 (subjects 3 and 6) had comparable average masses across treatments, whilst subjects 4 and 5 had a lower average body mass in the first week of the second phase (TM A).

4.3.5.3 Skinfold Thickness Measurements

Individual weekly skinfold thickness measurements are given in Appendix 6 (Tables A6.1 - 6.8). Table 4.10 gives the sum of three skinfolds and the percentage body fat determined from standard tables (237).

Subject	Age	Phase 1				Phase 2			
		Skinfold Thickness (sum of 3)		% Body Fat		Skinfold Thickness (sum of 3)		% Body Fat	
		Init	Fin	Init	Fin	Init	Fin	Init	Fin
SS (1)	38	74.00	75.50	28.50	29.40	70.17	69.00	28.30	27.60
CA (2)	22	88.00	90.00	31.70	32.50	87.83		31.57	
LE (3)	36	83.00		31.70		82.67	78.83	30.90	29.80
EA (4)	37	81.00	79.17	30.90	30.00	62.33	58.50	25.50	24.20
VW (5)	20	81.00	83.50	30.10	30.90	10.83	66.50	26.60	25.70
LI (6)	32	108.0	105.2	36.90	36.30	103.5		35.70	
EG (7)	42	77.00		30.30		70.33	75.33	27.60	29.40
CV (8)	32	64.00	52.33	25.20	21.10	51.00		51.10	

Init: Initial skinfolds taken on the first day of Week 2, for each phase.

Fin: Final skinfolds taken on the final day of each phase.

TABLE 4.10 Initial and Final Sum of Three Skinfolds and % Body Fat for each Subject.

Statistical evaluation of the data was not performed as very little confidence could be placed in these results due to missing values and the inexperience of the experimenter in performing these measurements. In addition, as discussed in section 3.3.1, skinfold thickness measurements are not useful to assess the slow, gradual weight loss experienced by the given sample population. The reason for missing data sets in the individual skinfold thickness measurements tables in Appendix 6, was that the subjects complained that the measurements were extremely uncomfortable and intrusive, and to minimise the possibility of subject "drop-outs" it was decided to reduce the number of observations.

Assuming we were confident of the data however, the final vs initial and weekly % body fat could have been determined statistically and used as an additional measure of weight loss.

4.3.5.2 Blood Pressure Measurements

Individual daily supine systolic and diastolic blood pressures for each subject are given in Appendix 7 (Tables A7.1.1 - 7.1.8). Data depicted in Table 4.11 represent the mean supine systolic and diastolic blood pressures (BP's) for 7 subjects obtained throughout the trial and the F ratios and P values were obtained using a two-way ANOVA (TEST 3, section 4.3.4). From this table, it is evident that no significant differences in mean BP's occurred whilst the subjects were taking PPA (TM A) or placebo (TM B).

Blood Pressure	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
Systolic	107.71 $\pm$ 0.56	109.04 $\pm$ 0.58	2.69	0.1019
Diastolic	68.59 $\pm$ 0.45	68.87 $\pm$ 0.49	0.18	0.6782

n = 193, df = 1,378

TABLE 4.11 Average supine systolic and diastolic blood pressure (Mean 7 Subjects)

The data depicted in Table A7.2.1 and A7.2.2 are the mean values for 7 subjects for the average weekly systolic and diastolic blood pressures, respectively. The F ratios and P values were obtained from a one-way ANOVA test and show that no significant differences in treatment with PPA (TM A) or placebo (TM B) were observed for each week when compared to baseline

blood pressures (TEST 2, section 4.3.4). The bold italicised F ratios and P values indicate that baseline blood pressures were comparable across phases (TEST 1, section 4.3.4).

Table 4.12 depicts the average weekly supine systolic blood pressure (BP) for each of the volunteers. The F ratios and P values were obtained from a one-way ANOVA test (TEST 1 and 2, section 4.3.4). The bold, italicised F ratios and P values indicate that baseline supine systolic blood pressures were comparable for each subject across both treatment phases (TEST 1), with the exception of subject 5 whose systolic pressure was significantly higher during the first week (baseline, week 1) prior to receiving TM B.

Subj	Week	TM A $\pm$ SEM	MRT	F Ratio	P	TM B $\pm$ SEM	MRT	F Ratio	P
1	1	115.80 $\pm$ 1.91		2.31	0.0819	115.60 $\pm$ 1.72		<i>0.01</i>	<i>0.9407</i>
	2	113.80 $\pm$ 1.59				111.20 $\pm$ 1.67			
	3	113.22 $\pm$ 1.20				109.33 $\pm$ 1.70			
	4	109.20 $\pm$ 0.80				108.40 $\pm$ 1.72			
	5	109.60 $\pm$ 2.48				110.40 $\pm$ 0.75			
2	1	100.40 $\pm$ 1.29		0.	0.6036	96.20 $\pm$ 2.06		<i>2.99</i>	<i>0.1220</i>
	2	98.60 $\pm$ 1.90				98.20 $\pm$ 1.28			
	3	97.44 $\pm$ 2.22				102.00 $\pm$ 1.60			
	4	95.60 $\pm$ 1.47				93.60 $\pm$ 3.87			
	5	96.00 $\pm$ 2.19				94.40 $\pm$ 2.64			
3	1	114.40 $\pm$ 0.98		1.54	0.2157	112.40 $\pm$ 1.72		<i>1.02</i>	<i>0.3420</i>
	2	112.90 $\pm$ 1.42				113.20 $\pm$ 1.68			
	3	108.89 $\pm$ 1.67				112.22 $\pm$ 2.07			
	4	111.60 $\pm$ 1.17				114.80 $\pm$ 1.96			
	5	109.20 $\pm$ 1.67				115.00 $\pm$ 1.84			
4	1	112.60 $\pm$ 1.08		0.37	0.8256	113.60 $\pm$ 1.17	*	<i>0.40</i>	<i>0.5528</i>
	2	113.80 $\pm$ 2.15				120.00 $\pm$ 1.97	*		
	3	112.22 $\pm$ 1.47				114.78 $\pm$ 1.43	*		
	4	115.20 $\pm$ 2.06				112.40 $\pm$ 2.23	*		
	5	114.40 $\pm$ 1.72				112.20 $\pm$ 3.17	*		
5	1	113.20 $\pm$ 1.20		0.97	0.4379	119.20 $\pm$ 0.80		<i>17.31[†]</i>	<i>0.0032</i>
	2	108.90 $\pm$ 2.79				113.20 $\pm$ 1.88			
	3	108.44 $\pm$ 1.82				112.33 $\pm$ 2.42			
	4	112.80 $\pm$ 1.85				111.80 $\pm$ 2.42			
	5	107.20 $\pm$ 2.87				114.60 $\pm$ 2.56			
6	1	103.80 $\pm$ 1.85		1.80	0.1552	107.80 $\pm$ 1.32		<i>3.09</i>	<i>0.1169</i>
	2	106.00 $\pm$ 1.84				103.80 $\pm$ 2.15			
	3	99.11 $\pm$ 2.77				105.22 $\pm$ 1.60			
	4	103.60 $\pm$ 1.60				103.20 $\pm$ 3.14			
	5	100.20 $\pm$ 2.15				105.40 $\pm$ 1.60			

The mean systolic blood pressures for week 1 prior to both treatments are given in the body of the table. For baseline (week 1) comparisons across phases $n = 5$ for each subject per phase, $df = 1,7$. Bold italicised F ratios and P values indicate the significance for weeks 1.

For the comparison of treatment weeks (2-5) with week 1, $n = 34$, $df = 4,32$

The *'s in the MRT columns indicate where the differences in the weeks occurred.

^s indicates a P value of between 0.015 and 0.05.

[†] indicates a P value of less than 0.01.

TABLE 4.12 Average Weekly Systolic Blood Pressures per Volunteer

It is evident from Table 4.12, that no statistically significant differences in average weekly systolic pressures occurred during the weeks that each subject took PPA (TM A), when compared to baseline. A similar scenario unfolds for each individual for the weeks that they were taking placebo (TM B), with the exception of subject 4. Application of Scheffe's multiple range test to the systolic BP for subject 4 during treatment with placebo (TM B) revealed that her average systolic BP was significantly higher during the second week.

Table 4.13 shows the individual average systolic BP for the weeks that each subject was administered PPA (TM A) and placebo (TM B). The F ratios and P values were obtained from a one-way ANOVA test (TEST 3, section 4.3.4), with drug condition as the factor.

From Table 4.13 it can be seen that, although subject 5 experienced a statistically significant lowering of systolic BP during the phase that she was taking PPA (TM A), this haemodynamic variable remained relatively stable in the remaining 5 subjects during treatment with PPA (TM A) and placebo (TM B).

Subj	TM A $\pm$ SEM	TM B $\pm$ SEM	F Ratio	P
1	112.10 $\pm$ 0.85	110.00 $\pm$ 0.83	3.15	0.0814
2	97.28 $\pm$ 1.03	97.93 $\pm$ 1.51	0.18	0.6776
3	110.79 $\pm$ 0.97	113.14 $\pm$ 0.96	3.89	0.0537
4	113.66 $\pm$ 0.96	115.72 $\pm$ 1.17	1.87	0.1764
5	109.14 $\pm$ 1.25	112.93 $\pm$ 1.12	5.14 ^s	0.0273
6	102.45 $\pm$ 1.25	104.41 $\pm$ 1.04	1.47	0.2300

n = 29, df = 1,56

^s indicates a P value of between 0.015 and 0.05

TABLE 4.13

Average Systolic Blood Pressure per Volunteer

Table 4.14 depicts the average weekly supine diastolic blood pressure for each of the volunteers. The F ratios and P values were obtained from a one-way ANOVA test (TEST 1 and 2, section 4.3.4). The bold, italicised F ratios indicate that baseline supine diastolic blood pressures were comparable for each subject across both treatment phases (TEST 1), with the exception of subject 1 whose diastolic pressure was significantly higher during the

first week prior to receiving TM B.

It is evident from Table 4.14, that no statistically significant differences in average weekly diastolic pressures occurred during the weeks that each subject took PPA (TM A), when compared to the corresponding baseline week. The same non-significance is apparent for each individual for the weeks that the subjects were taking placebo (TM B).

Subj	Week	TM A $\pm$ SEM	MRT	F Ratio	P	TM B $\pm$ SEM	MRT	F Ratio	P
1	1	67.00 $\pm$ 0.45				73.60 $\pm$ 2.04		9.99[§]	0.0134
	2	72.40 $\pm$ 2.11				71.30 $\pm$ 1.60			
	3	67.67 $\pm$ 1.37		1.48	0.2378	71.56 $\pm$ 1.56		0.61	0.6572
	4	67.60 $\pm$ 1.94				67.20 $\pm$ 3.44			
	5	68.80 $\pm$ 3.01				71.60 $\pm$ 5.42			
2	1	59.60 $\pm$ 1.50				63.00 $\pm$ 2.83		1.13	0.3195
	2	62.60 $\pm$ 1.30				73.20 $\pm$ 1.47			
	3	62.89 $\pm$ 1.38		1.53	0.2190	63.67 $\pm$ 1.45		0.85	0.5044
	4	61.00 $\pm$ 1.18				58.80 $\pm$ 2.87			
	5	64.80 $\pm$ 0.97				61.60 $\pm$ 2.23			
3	1	67.60 $\pm$ 1.60				70.40 $\pm$ 2.48		0.90	0.3806
	2	68.60 $\pm$ 1.45				71.20 $\pm$ 1.01			
	3	70.44 $\pm$ 2.40		0.42	0.7922	75.11 $\pm$ 0.81		2.72	0.0500
	4	71.60 $\pm$ 1.60				72.80 $\pm$ 1.02			
	5	69.20 $\pm$ 3.67				70.20 $\pm$ 1.56			
4	1	70.40 $\pm$ 2.98				69.20 $\pm$ 0.80		0.15	0.7112
	2	73.30 $\pm$ 1.45				75.90 $\pm$ 1.93			
	3	72.67 $\pm$ 1.86		0.78	0.5489	76.00 $\pm$ 1.76		2.69	0.0508
	4	72.80 $\pm$ 1.96				70.40 $\pm$ 0.40			
	5	76.00 $\pm$ 1.79				72.80 $\pm$ 2.42			
5	1	75.60 $\pm$ 1.72				73.20 $\pm$ 2.73		0.55	0.4857
	2	70.10 $\pm$ 2.57				74.70 $\pm$ 1.62			
	3	69.33 $\pm$ 1.29		1.40	0.2601	70.11 $\pm$ 0.98		2.36	0.0768
	4	73.20 $\pm$ 4.03				70.60 $\pm$ 1.17			
	5	67.60 $\pm$ 1.47				76.00 $\pm$ 1.79			
6	1	62.80 $\pm$ 2.06				66.00 $\pm$ 2.53		0.96	0.3655
	2	69.40 $\pm$ 1.63				63.50 $\pm$ 1.56			
	3	65.78 $\pm$ 2.61		1.84	0.1477	65.11 $\pm$ 1.53		0.33	0.8535
	4	65.40 $\pm$ 1.33				65.00 $\pm$ 1.34			
	5	61.80 $\pm$ 2.76				63.60 $\pm$ 2.23			

The mean diastolic blood pressures for week 1 prior to both treatments are given in the body of the table. For baseline (week 1) comparisons across phases $n = 5$ for each subject per phase, $df = 1,7$. Bold italicised F ratios and P values indicate the significance for weeks 1.

For the comparison of treatment weeks (2-5) with week 1, $n = 34$, $df = 4,32$

§ indicates a P value of between 0.015 and 0.05.

TABLE 4.14

Average Weekly Diastolic Blood Pressures per Volunteer

Table 4.15 shows the individual average diastolic BP for the weeks that each subject was administered PPA (TM A) and placebo (TM B). The F ratios and P values were obtained from a one-way ANOVA test (TEST 3, section 4.3.4). From this table it can be seen, that although subject 3

experienced a statistically significant lowering of systolic BP during the phase that she was taking PPA (TM A), no statistically significant fluctuations in diastolic BP occurred in the remaining 5 subjects during treatment with PPA (TM A) and placebo (TM B).

Subj	TM A $\pm$ SEM	TM B $\pm$ SEM	F Ratio	P
1	69.48 $\pm$ 1.07	70.72 $\pm$ 1.27	0.56	0.4650
2	62.79 $\pm$ 0.68	62.31 $\pm$ 0.93	0.18	0.6803
3	69.79 $\pm$ 1.09	72.52 $\pm$ 0.62	4.73 [§]	0.0339
4	73.48 $\pm$ 0.87	74.45 $\pm$ 1.00	0.53	0.4780
5	69.97 $\pm$ 1.20	72.79 $\pm$ 0.84	3.74	0.0583
6	66.28 $\pm$ 1.18	64.27 $\pm$ 0.82	1.95	0.1678

n = 29, df = 1,56

[§] indicates a P value of between 0.015 and 0.05

TABLE 4.15

Average Weekly Diastolic Blood Pressure per Volunteer

4.3.6 Behavioural Measurements

4.3.6.1 Analysis of Mood Questionnaires

The processed response data to each of the three subdivisions of the MQ, i.e., the ARCI, POMS and VAS for each subject per measurement occasion, are given in Appendices 8 (Tables A8.1.1 - A8.1.8), 9 (Tables A9.1.1 - A9.1.8) and 10 (Tables A10.1.1 - A10.1.8), respectively. The ARCI raw data were processed using the ARCI data capture and processing program discussed in section 3.4.1.1 and the POMS raw data was processed using the corresponding POMS data capture and processing program explained in section 3.4.2.1. For analysis of the VAS response data, the answer mark on the line of each scale was measured to the nearest millimetre to produce a score of between 0 and 100 for each determination (section 3.3.2.1.2).

4.3.6.1.1 The Addiction Research Centre Inventory (ARCI) Results

The average responses for 7 subjects to each of the five ARCI scales i.e., the PCAG, BG, LSD, MBG and A scale, are given in Table 4.16. The mean response per test medication phase, F ratios and P values were obtained from a two-way ANOVA test (TEST 3, section 4.3.4). From this table it can be seen that no statistically significant effects for any of the 5 scales occurred across the test medication phases.

The data depicted in Appendix 8, Table A8.2.1 are the mean responses for 7 subjects to each of the ARCI scales. The F ratios and P values were obtained using one-way ANOVA procedures and show that no significant differences in treatment with PPA (TM A) or placebo (TM B) were observed for each week when compared to baseline ARCI responses (TEST 2, section 4.3.4). The bold, italicised F ratios and P values indicate that baseline responses to each of the ARCI variables were comparable across test medication phases (TEST 1).

ARCI Scale	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
PCAG	3.17 $\pm$ 0.26	3.21 $\pm$ 0.26	0.01	0.9279
BG	6.18 $\pm$ 0.31	5.99 $\pm$ 0.27	0.29	0.5986
LSD	3.45 $\pm$ 0.17	3.79 $\pm$ 0.15	2.42	0.1211
MBG	5.83 $\pm$ 0.49	4.76 $\pm$ 0.44	2.63	0.1060
A	3.45 $\pm$ 0.36	3.28 $\pm$ 0.31	0.13	0.7189

n = 121, df = 1,234

TABLE 4.16 Average Addiction Research Centre Inventory Responses (Mean F ratios and P values for 7 Subjects)

The average Pentobarbital-Chlorpromazine-Alcohol Group (PCAG), Benzedrine Group (BG), Lysergic Acid Diethylamide Group (LSD), Morphine-Benzedrine Group (MBG) and Amphetamine (A) responses are depicted in Tables A8.2.3 - A8.2.6 respectively, for each test medication phase per volunteer. The mean response per test medication phase, F ratios and P values were obtained from a one-way ANOVA test (TEST 3, section 4.3.4), with drug condition as factor. From the mean individual PCAG response data shown in Table A8.2.2 it can be seen that the degree of sedation experienced by each subject was not statistically different across test medication phases.

Table A8.2.3 shows that 4 out of the 6 subjects did not experience any change in intellectual efficacy or energy (BG responses) across treatments. Of the two subjects who showed significantly altered responses to the BG scale across treatment phases, one (subject 1) showed an increased, whilst the other (subject 6) showed a decrease in intellectual efficacy and energy during the phase that they received PPA (TM A), compared to placebo (TM B).

Table A8.2.4 shows that 4 out of the 6 subjects did not experience any significant alteration in LSD response across treatment phases. Of the remaining two, subject 1 showed a significant lowering of dysphoric response during the phase that she received PPA (TM A), whilst subject 3 exhibited a pronounced equality in LSD response during both test medication phases.

Table A8.2.5 shows that 4 out of the 6 subjects did not experience any significant change in MBG response across test medication phases. Both of the remaining two subjects (subject 1 and 4) showed a significant elevation of euphoric response and well-being during the phase that they received PPA (TM A) compared to placebo (TM B). Subject 3 again showed marked similarity in response to the MBG scale across treatments, although this anomalous response was not statistically significant.

Table A8.2.6 shows that 3 out of the 6 subjects did not experience any significant change in A response across test medication phases. Subjects 1 and 2 showed a significant elevation in amphetamine-like response, during the phase that they received PPA (TM A), whilst subject 3 exhibited a remarkable parity in response to the amphetamine scale during both test medication phases.

4.3.6.1.2 The Profile of Mood States (POMS) Results

The average responses for 7 subjects to each of the ten POMS scales (anxiety, depression, anger, vigour, fatigue, confusion, friendliness, elation, arousal and positive mood) are given in Table 4.17. The mean response per test medication phase, F ratios and P values were obtained from a two-way ANOVA test (TEST 3, section 4.3.4) with drug condition and weeks as factors in the analysis. From this table it can be seen that no statistically significant effects for any of the 10 scales occurred across the test medication phases.

The data depicted in Appendix 9, Table A9.2.1 are the mean weekly responses for 7 subjects to each of the POMS scales. The F ratios and P values were obtained using one-way ANOVA procedures and show that with the exception of the "depression" response no significant differences in treatment with

PPA (TM A) or placebo (TM B) were observed for each week when compared to baseline POMS responses (TEST 2, section 4.3.4). Application of Scheffe's multiple range test (MRT) to the average weekly "depression" responses for the PPA (TM A) phase showed that the subjects were significantly more depressed during the last 3 weeks when compared to the first 2 weeks.

POMS Scale	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
Anxiety	0.31 $\pm$ 0.02	0.32 $\pm$ 0.03	0.26	0.6142
Depression	0.12 $\pm$ 0.04	0.14 $\pm$ 0.04	0.23	0.6407
Anger	0.15 $\pm$ 0.03	0.15 $\pm$ 0.04	0.06	0.9399
Vigour	1.44 $\pm$ 0.09	1.29 $\pm$ 0.07	1.69	0.1948
Fatigue	0.20 $\pm$ 0.05	0.16 $\pm$ 0.04	0.39	0.5396
Confusion	0.41 $\pm$ 0.03	0.47 $\pm$ 0.04	2.15	0.1441
Friendliness	1.88 $\pm$ 0.08	1.78 $\pm$ 0.07	0.89	0.3560
Elation	1.32 $\pm$ 0.09	1.23 $\pm$ 0.07	0.60	0.4481
Arousal	1.14 $\pm$ 0.12	0.97 $\pm$ 0.10	1.11	0.2924
Positive Mood	1.20 $\pm$ 0.10	1.09 $\pm$ 0.08	0.68	0.4188

n = 119, df = 1,230

TABLE 4.17 Average Responses to the Profile of Mood States (Mean F ratios and P values for 7 Subjects)

The bold, italicised F ratios and P values in Table A9.2.1 indicate that baseline responses to each of the POMS scales were comparable across test medication phases (TEST 1, section 4.3.4), with the exception of the "anxiety", "depression" and "confusion" responses, which were significantly higher during the baseline week prior to treatment with placebo (TM B).

The average responses to the individual POMS scales are depicted in Appendix 9, Tables A9.2.2 - A9.2.11 respectively, for each test medication phase per volunteer. The mean response per test medication phase, F ratios and P values were obtained from a one-way ANOVA test (TEST 3, section 4.3.4). with drug condition as factor.

Table A9.2.2 shows that 2 out of the 6 subjects showed a statistically significant change in "anxiety" responses across treatment phases, with subject 1 being less anxious and subject 6 being more anxious during treatment with PPA (TM A), compared to treatment with placebo (TM B). From

Table A9.2.3, it can be seen that the responses to the POMS "depression" scale for each individual subject were not significantly different across test medication phases.

Table A9.2.4 shows that while 4 out of the 6 subjects did not show any alteration in the POMS "anger" response across treatment phases, 2 subjects (subject 1 and 6) were significantly more angry during the phase that they received PPA (TM A). The average "vigour" responses for each subject during both test medication phases are depicted in Table A9.2.5 and show that while 2 subjects (1 and 2) were significantly more vigorous, 1 subject (subject 3) was significantly less vigorous during the phase that they were treated with PPA (TM A).

Table A9.2.6 shows that only 1 subject (subject 4) experienced significant lowering in the "fatigue" response during the phase that she received PPA (TM A), whilst the responses of the remaining 5 subjects to this scale were unaffected by the administration of PPA (TM A).

Two subjects (subject 1 and 4) exhibited significantly lower responses to the "confusion" scale (Table A9.2.7) and significantly higher responses to the "friendliness" scale (Table A9.2.8) during the phase that they were treated with PPA (TM A), while the responses of the remaining 4 subjects to both of these scales were unchanged across test medication phases.

Table A9.2.9 shows that while 4 out of the 6 subjects did not experience any change in the "elation" response across test medication phases, 2 subjects exhibited opposing responses during the phase that they were treated with PPA (TM A), with subject 1 being more "elated" and subject 3 being less "elated" during this phase. The same picture emerges for the "positive mood" scale depicted in Table A9.2.11.

Table A9.2.10 shows that whilst the "arousal" responses of subjects 1 and 4 were significantly higher during the phases that they were treated with PPA (TM A), subject 3 once again exhibited a negative response to this POMS variable during the same treatment.

4.3.6.1.3 The Visual Analogue Scales (VAS) Results

The average responses for 7 subjects to each of the six visual analogue scales (stimulation, high, anxious, sedated, down and hungry) are given in Table 4.18. The mean response per test medication phase, F ratios and P values were obtained from a two-way ANOVA test (TEST 3, section 4.3.4) with drug condition and weeks as factors in the analysis. From this table it can be seen that whilst both the "stimulation" and "high" scales were significantly lower during treatment with PPA (TM A), no statistically significant effects for the remaining 4 scales occurred across the test medication phases.

The data depicted in Appendix 10, Table A10.2.1 are the mean responses for 7 subjects to each of the 6 VAS scales. The F ratios and P values were obtained using one-way ANOVA procedures and show that with the exception of the "stimulated" and "high" responses during the PPA (TM A) phase and the "stimulated" responses during the placebo (TM B) phase, no significant differences in treatment with PPA or placebo for the remaining VAS variables were observed for each week when compared to baseline responses (TEST 2, section 4.3.4).

Measure	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
Stimulation	8.86 $\pm$ 0.73	19.27 $\pm$ 1.66	33.43	0.0000
High	8.03 $\pm$ 0.89	15.78 $\pm$ 1.69	16.63	0.0000
Anxious	9.56 $\pm$ 1.25	11.89 $\pm$ 1.41	1.52	0.2187
Sedated	8.06 $\pm$ 1.18	7.61 $\pm$ 0.83	0.10	0.7602
Down	12.67 $\pm$ 1.94	11.89 $\pm$ 1.68	0.09	0.7631
Hungry	13.37 $\pm$ 1.62	17.69 $\pm$ 2.06	2.66	0.1042

n = 122, df = 1,236

TABLE 4.18 Average Responses to Visual Analogue Scales (Mean F ratios and P values for 7 Subjects)

Application of Scheffe's multiple range test (MRT) to the average weekly "stimulated" responses for both the PPA (TM A) and placebo (TM B) phases showed that the subjects were significantly more "stimulated" during the first week prior to receiving either TM A or TM B than during the four weeks that they received either test medication. The MRT applied to the

average weekly "high" responses for the PPA (TM A) phase revealed that the subjects were significantly less "high" during the 4 weeks that they took PPA (TM A) when compared to the baseline week. The bold, italicised F ratios and P values in Table A10.2.1 indicate that whilst baseline responses to the "anxious" and "sedated" scales were comparable across test medication phases (TEST 1, section 4.3.4), the responses to the remaining 4 scales ("stimulated", "high", "down" and "hungry"), were significantly lower during the baseline week prior to treatment with PPA (TM A).

The average responses to the individual VAS scales are depicted in Appendix 10, Tables A10.2.2 - A10.2.7 respectively, for each test medication phase per volunteer. The mean response per test medication phase, F ratios and P values were obtained from a one-way ANOVA test (TEST 3, section 4.3.4).

Table A10.2.2 shows that subjects 1, 4 and 5 exhibited a statistically significant lowering in the "stimulation" response during the phase that they were treated with PPA (TM A) when compared to treatment with placebo (TM B), with the response differences from the remaining 3 subjects being statistically insignificant.

From the average response data for the VAS "high" scale depicted in Table A10.2.3, it can be seen that the response from subject 2 was not significantly different across test medication phases, subjects 1, 4, 5 and 6 exhibited a lowered response and subject 3 showed an increased response to the "high" VAS scale during the phase that they were treated with PPA (TM A), when compared to treatment with placebo (TM B).

Table A10.2.4 shows that whilst the "anxious" responses of subjects 1 and 4 were significantly lower during the phase that they were treated with PPA (TM A), subject 3 exhibited the opposite (increased) response during this phase. The same is true for the "down" scale depicted in Table A10.2.6.

Table A10.2.5 shows that whilst the "sedated" responses of subjects 4 and 6 were significantly lower during the phases that they were treated with PPA (TM A), subject 3 once again exhibited a negative response to this VAS variable during the same treatment.

Table A10.2.7 depicts the average "hungry" responses for each test medication phase per volunteer. From this table it can be seen that the responses to this variable were only statistically significant in one subject (subject 4), who was significantly less hungry during the phase that she was treated with PPA (TM A).

4.3.6.2 Problems Associated with Food Intake Data Collection and Subsequent Impact on Dependant Variables and Statistical Analysis

One of the major problems with the trial, was that the food intake data from the test meals for the baseline period of the first phase i.e. week 1, days 1 and 4 and for week 2 day 1 could not be used in the statistical analysis. During this time, the food items were prepared by the university canteen and the potatoes were of poor quality and badly cooked. Following the test meal on week 2 day 1, the subjects complained that the potatoes were inedible and that the food had become cold whilst blood pressures and baseline salivation were being measured. A cursory glance at the amount of potato eaten by each subject confirmed these reports, as very little or none of the potato had been eaten. It could be seen that the carbohydrate ingested by the subjects was not representative of their usual intake. In order to enable the detection of possible differences in carbohydrate intake due to PPA (TM A) administration and to prevent subjects from "dropping out" of the trial, it was decided that a new approach was needed.

Thus, from week 2 day 4 of phase 1 to the end of the trial, potatoes were hand-picked for quality and cooked in their jackets by the trial co-ordinator. In addition, as temperature of the food plays an important role in palatability and hence food intake, once each subject's test meal had been weighed and placed in a segmented dish, the dish was covered with a lid and kept warm on a Bain-maire type arrangement.

However, although this alternate approach was instituted, the baseline food intake data was not comparable across phases and therefore could not be used for statistical analysis. Although this problem was inherent to food intake data only, the problem was extended to the the variables dependent on food intake, such as hunger and satiety ratings, BSQ, stimulus-induced

salivation and the food preference questionnaires. As a result, baseline data obtained from these parameters could not be statistically compared across phases (Test 1, section 4.3.4), nor could the data obtained from weeks 2-5 of phase 1 be compared with data from week 1 (Test 2, section 4.3.4). It followed that data obtained from weeks 7-11 of phase 2 was not analysed in the same manner.

4.3.6.3 Analysis of the Appetite, Hunger (AHQ and BSQ) and the Satiety Questionnaire (SQ and FPQ)

The weekly response data for the 4 questions relating to the AHQ and the BSQ responses are given in Appendix 11 (Tables A11.1.1 -A11.1.16) and the weekly response data for the 6 questions relating to the SQ and the FPQ responses for each subject per measurement occasion are given in Appendix 11 (Tables A11.2.1 - A11.2.16).

The data in Table 4.19 depict the statistical results of the subjective ratings made on the Appetite and Hunger Questionnaires (AHQ). The mean rating for 7 subjects to each of the 4 questions per test medication phase, F ratios and P values were obtained from a two-way ANOVA test (TEST 3, section 4.3.4) with drug condition and weeks as factors in the analysis. Statistically significant drug treatment effects are apparent for the PPA (TM A) phase as opposed to the placebo (TM B) phase. A decrease in the mean hunger ratings, urge to eat or appetite, preoccupation with thoughts of food and estimates of likely food consumption occurred when the subjects were taking active medication (TM A) as opposed to placebo (TM B).

Subjective Ratings	TM A $\pm$ SD	TM B $\pm$ SD	F	P
How hungry are you right now? NOT AT ALL EXTREMELY	28.66 $\pm$ 2.68	41.10 $\pm$ 3.48	7.36 [†]	0.0089
How strong is your urge to eat? NOT AT ALL EXTREMELY	28.19 $\pm$ 3.19	41.98 $\pm$ 3.64	7.68 [†]	0.0076
How preoccupied are you with thoughts of food? NOT AT ALL EXTREMELY	25.03 $\pm$ 2.77	37.24 $\pm$ 3.12	8.70 [†]	0.0047
How much food could you eat? NOTHING A LARGE AMOUNT	33.75 $\pm$ 3.29	45.55 $\pm$ 3.63	5.83 [§]	0.0192

§ indicates a P value between 0.015 and 0.05.

† indicates a P value < 0.01

n = 31, df = 1,54

TABLE 4.19 Subjective Ratings of Hunger and Appetite

The average ratings to the AHQ questions are depicted in Table 4.20, for each test medication phase per volunteer. The mean rating per test medication phase, F ratios and P values were obtained from a one-way ANOVA test (TEST 3, section 4.3.4). It can be seen that out of the 6 subjects, only 1 (subject 4) experienced a statistically significant decrease in response to the first three questions of the AHQ (hunger, urge to eat and preoccupation with thoughts of food) when she was taking PPA (TM A) as opposed to placebo (TM B). The lack of statistical significance as evidenced by higher P values for the remaining 5 subjects for questions 1-3, and for subjects 1-6 for question 4 is mainly due to a large within subject variation.

Subjective Ratings	Subj	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
How hungry are you right now? NOT AT ALL EXTREMELY	1	39.00 $\pm$ 3.48	54.50 $\pm$ 7.32	3.65	0.1045
	2	28.00 $\pm$ 17.62	31.67 $\pm$ 14.50	0.03	0.8817
	3	37.25 $\pm$ 4.23	44.00 $\pm$ 5.58	0.93	0.3823
	4	8.33 $\pm$ 2.60	27.33 $\pm$ 5.04	11.2 [§]	0.0286
	5	20.33 $\pm$ 6.44	53.00 $\pm$ 22.90	1.89	0.2416
	6	32.75 $\pm$ 6.68	34.25 $\pm$ 2.39	0.05	0.8417
How strong is your urge to eat? NOT AT ALL EXTREMELY	1	45.25 $\pm$ 5.68	59.00 $\pm$ 6.65	2.48	0.1667
	2	26.67 $\pm$ 20.51	34.00 $\pm$ 15.89	0.04	0.8492
	3	30.75 $\pm$ 5.14	40.25 $\pm$ 6.56	1.30	0.2978
	4	4.67 $\pm$ 0.67	29.67 $\pm$ 6.49	14.7 [§]	0.0186
	5	20.33 $\pm$ 7.54	55.67 $\pm$ 22.36	2.24	0.2087
	6	35.50 $\pm$ 7.86	36.25 $\pm$ 4.59	0.01	0.9378
How preoccupied are you with thoughts of food? NOT AT ALL EXTREMELY	1	26.50 $\pm$ 6.12	36.75 $\pm$ 7.34	1.15	0.3247
	2	26.33 $\pm$ 15.30	41.33 $\pm$ 2.03	0.94	0.3959
	3	28.25 $\pm$ 2.43	39.00 $\pm$ 8.82	1.38	0.2846
	4	4.00 $\pm$ 0.00	26.67 $\pm$ 2.40	88.9 [¶]	0.0007
	5	23.33 $\pm$ 9.06	55.00 $\pm$ 22.14	1.75	0.2562
	6	37.25 $\pm$ 8.31	31.00 $\pm$ 4.97	0.42	0.5491
How much food could you eat right now? NOTHING A LARGE AMOUNT	1	52.50 $\pm$ 7.98	53.75 $\pm$ 3.40	0.21	0.8917
	2	27.67 $\pm$ 18.12	52.67 $\pm$ 5.49	1.74	0.2572
	3	40.25 $\pm$ 3.20	43.50 $\pm$ 7.66	0.15	0.7131
	4	8.33 $\pm$ 3.67	35.67 $\pm$ 16.68	1.89	0.2416
	5	23.00 $\pm$ 11.14	55.00 $\pm$ 23.29	1.54	0.2829
	6	36.25 $\pm$ 7.22	35.25 $\pm$ 5.33	0.01	0.9160

§ indicates a P value between 0.015 and 0.05.

¶ indicates a P value < 0.01

n = 4, df = 6, for subjects 1, 3 and 6

n = 3, df = 4, for subjects 2, 4 and 5

TABLE 4.20 Average Subjective Ratings of Hunger and Appetite per Volunteer

The results of the BSQ, divided into the number of subjects reporting a sensation and the number of times each sensation was recorded during treatment with PPA (TM A) and placebo (TM B) appear in Table A11.3.1.

From this table it appears that the only sensations possibly influenced by the treatments were rumbling of the stomach, nausea, no gastric sensations signalling hunger, salivation, headache, restlessness, warmth and contented. The data under interpretation in this discussion are from the number of times each particular sensation was recorded. It seems that PPA (TM A) reduced sensations of stomach rumbling, no gastric sensations, salivation, headache and restlessness, whilst sensations of nausea, warmth and contentment were heightened.

The data in Table 4.21 depict the statistical results of the subjective ratings made on the Satiety Questionnaires (SQ). The mean rating for 7 subjects to each of the 6 questions per test medication phase, F ratios and P values were obtained from a two-way ANOVA test (TEST 3, section 4.3.4) with drug condition and weeks as factors in the analysis. From this table it is evident that no statistically significant differences in the responses to the 6 questions of the SQ were observed across test medication phases.

Subjective Ratings	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
How sated / full are you right now? NOT AT ALL EXTREMELY	59.27 $\pm$ 3.66	56.32 $\pm$ 3.11	0.35	0.5609
How strong is your urge to eat after completing your meal? NOT AT ALL EXTREMELY	12.73 $\pm$ 1.62	15.71 $\pm$ 1.62	1.63	0.2068
How preoccupied are you with thoughts of food? NOT AT ALL EXTREMELY	10.11 $\pm$ 1.62	15.29 $\pm$ 2.77	2.43	0.1252
How appealing was the food? NOT AT ALL EXTREMELY	38.65 $\pm$ 4.07	37.79 $\pm$ 4.00	0.02	0.8856
How did the food taste? VERY BAD VERY GOOD	41.68 $\pm$ 3.71	41.10 $\pm$ 3.61	0.01	0.9140
How much of your favourite food could you eat right now? NOTHING A LARGE AMOUNT	21.89 $\pm$ 3.75	26.84 $\pm$ 3.43	0.89	0.3604

n = 31, df = 1,54

TABLE 4.21 Average Subjective Ratings of Satiety (Mean 7 Subjects)

The average ratings to the SQ questions are depicted in Table 4.22, for each test medication phase per volunteer. The mean rating per test medication phase, F ratios and P values were obtained from a one-way ANOVA

test (TEST 3, section 4.3.4), with drug condition as factor. It can be seen that out of the 6 subjects, only one (subject 3) experienced a statistically significant increase in response to question 3 of the SQ (preoccupation with thoughts of food), whilst another (subject 4) exhibited a significant decrease in response to questions 4-6 (appeal, taste and estimate of favourite food consumption) whilst they were taking PPA (TM A) as opposed to placebo (TM B). The responses of the remaining 4 subjects (subjects 1,2,5 and 6) to each of the 6 questions of the SQ were not significantly altered across treatment phases.

Subjective Ratings	Subj	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
How sated / full are you right now? NOT AT ALL EXTREMELY	1	61.25 $\pm$ 3.42	58.25 $\pm$ 2.87	0.45	0.5338
	2	82.00 $\pm$ 8.33	50.67 $\pm$ 22.40	1.72	0.2600
	3	60.00 $\pm$ 1.78	57.00 $\pm$ 4.49	0.39	0.5638
	4	34.00 $\pm$ 4.04	42.33 $\pm$ 8.41	0.80	0.4314
	5	78.33 $\pm$ 4.91	78.00 $\pm$ 22.90	0.00	0.9702
	6	49.50 $\pm$ 1.04	54.25 $\pm$ 3.30	1.88	0.2190
How strong is your urge to eat after completing your meal? NOT AT ALL EXTREMELY	1	14.50 $\pm$ 5.17	15.25 $\pm$ 3.07	0.02	0.9061
	2	0.00 $\pm$ 0.00	6.67 $\pm$ 4.06	2.70	0.1755
	3	18.25 $\pm$ 0.48	16.00 $\pm$ 1.47	2.11	0.1963
	4	10.00 $\pm$ 2.89	22.00 $\pm$ 6.08	3.18	0.1493
	5	2.67 $\pm$ 0.67	1.00 $\pm$ 0.58	3.57	0.1318
	6	20.50 $\pm$ 1.50	19.13 $\pm$ 2.76	0.19	0.6811
How preoccupied are you with thoughts of food? NOT AT ALL EXTREMELY	1	9.50 $\pm$ 2.63	15.25 $\pm$ 8.94	0.38	0.5662
	2	0.00 $\pm$ 0.00	6.67 $\pm$ 6.67	1.00	0.3739
	3	16.75 $\pm$ 1.11	13.00 $\pm$ 0.91	6.82 [§]	0.0401
	4	9.00 $\pm$ 2.08	25.67 $\pm$ 6.57	5.96	0.0728
	5	1.33 $\pm$ 0.67	1.00 $\pm$ 1.00	0.08	0.7980
	6	18.00 $\pm$ 3.12	18.25 $\pm$ 3.30	0.00	0.9589
How appealing was the food? NOTHING A LARGE AMOUNT	1	60.00 $\pm$ 6.28	57.50 $\pm$ 7.67	0.05	0.8278
	2	71.33 $\pm$ 13.97	37.00 $\pm$ 18.77	2.15	0.2162
	3	27.75 $\pm$ 6.84	31.00 $\pm$ 1.58	0.22	0.6643
	4	32.22 $\pm$ 5.61	59.33 $\pm$ 5.81	11.2 [§]	0.0287
	5	17.67 $\pm$ 8.84	27.33 $\pm$ 4.81	0.92	0.4007
	6	38.50 $\pm$ 8.93	30.00 $\pm$ 8.15	0.49	0.5157
How did the food taste? VERY BAD VERY GOOD	1	63.50 $\pm$ 4.09	60.75 $\pm$ 8.01	0.09	0.7734
	2	65.67 $\pm$ 14.86	35.00 $\pm$ 17.60	1.78	0.2533
	3	29.25 $\pm$ 6.56	30.75 $\pm$ 1.97	0.05	0.8362
	4	36.67 $\pm$ 6.33	62.33 $\pm$ 3.76	12.2 [§]	0.0252
	5	25.00 $\pm$ 13.23	30.67 $\pm$ 1.76	0.18	0.6872
	6	43.25 $\pm$ 4.92	41.25 $\pm$ 9.20	0.04	0.8562
How much of your favourite food could you eat right now? NOTHING A LARGE AMOUNT	1	20.50 $\pm$ 5.27	25.50 $\pm$ 0.50	0.89	0.3909
	2	1.33 $\pm$ 0.67	47.00 $\pm$ 26.58	2.95	0.1610
	3	26.75 $\pm$ 4.27	20.25 $\pm$ 1.93	1.92	0.2147
	4	10.33 $\pm$ 3.84	33.00 $\pm$ 5.03	12.8 [§]	0.0232
	5	2.33 $\pm$ 0.33	1.67 $\pm$ 0.88	0.50	0.5256
	6	59.00 $\pm$ 6.10	43.00 $\pm$ 4.14	4.71	0.0730

§ indicates a P value between 0.015 and 0.05.

n = 4, df = 6, for subjects 1, 3 and 6

n = 3, df = 4, for subjects 2, 4 and 5

TABLE 4.22 Average Subjective Ratings of Satiety per Volunteer.

The results of the FPQ, divided into the numbers of total food, protein and carbohydrate items checked during treatment with PPA (TM A) and placebo (TM B) appear in Table 4.23.

MEASURE	TM A	TM B
Total Food Items	9.28	8.40
High Protein Items	4.36	4.16
High Carbohydrate Items	4.92	4.24

TABLE 4.23 Effect of Treatments on the FPQ

From this table it appears that treatment with PPA (TM A) resulted in a slight increase in the number of preferred food items checked, as well as preferences for protein and carbohydrate items.

4.3.6.4 Analysis of Food Intake Data

Quantities of each food commodity presented, remaining and eaten at each test meal and the processed total food intake and macro-nutrient consumption data for each subject are given in Appendix 12, Tables A12.1.1 - A12.1.8 and Tables A12.2.1 - A12.2.8, respectively.

The data in Table 4.24 depict the results of the amount (g and kJ) and type (macro-nutrient breakdown) of particular foods consumed at the test meals. The mean intakes for 7 subjects per test medication phase, F ratios and P values were obtained from a two-way ANOVA test (TEST 3, section 4.3.4) with drug condition and weeks as factors in the analysis. It is apparent from this table that statistically significant decrements occurred in total food and carbohydrate intake whilst the subjects were taking PPA (TM A) as opposed to placebo (TM B). Although total protein and fat intake appeared to be reduced during the PPA (TM A) phase compared to the placebo (TM B) phase, this difference was not statistically significant. In addition, protein, carbohydrate and fat energy percentages were not significantly different across treatment phases.

The average amount and type of food eaten at the test meals are depicted in Table A12.3.1, for each test medication phase per volunteer. The mean intake per test medication phase, F ratios and P values were obtained from a one-way ANOVA test (TEST 3, section 4.3.4), with drug condition as the

factor. It can be seen that when they were taking PPA (TM A) as opposed to placebo (TM B), 4 (subjects 1 and 4-6) experienced a statistically significant decrease in total food intake (g), whilst only 2 (subjects 4 and 6) having significantly reduced total kilojoule intakes. Two subjects (3 and 4) experienced significantly reduced total protein intake (g and kJ) and 4 (subjects 1,3,4 and 6) experienced a significant decrease in total carbohydrate intake (g and kJ) during the PPA (TM A) phase compared to the placebo (TM B) phase. No significant effects occurred for total fat intake and protein, carbohydrate and fat energy percentages across treatment phases.

Measure	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
Total Food Intake (g)	297.64 $\pm$ 19.32	359.47 $\pm$ 14.53	5.91 [§]	0.0196
Total Food Intake (kJ)	2251.68 $\pm$ 156.78	2734.86 $\pm$ 115.91	5.69 [§]	0.0219
Total Protein Intake (g)	22.41 $\pm$ 1.64	26.44 $\pm$ 1.12	4.03	0.0514
Total Protein Intake (kJ)	376.46 $\pm$ 27.59	444.17 $\pm$ 19.66		
Total Carbohydrate Intake (g)	49.41 $\pm$ 4.65	65.97 $\pm$ 4.08	6.49 [§]	0.0148
Total Carbohydrate Intake (kJ)	830.06 $\pm$ 78.19	1108.32 $\pm$ 68.58		
Total Fat Intake (g)	27.65 $\pm$ 1.70	31.29 $\pm$ 1.28	2.84	0.1000
Total Fat Intake (kJ)	1045.15 $\pm$ 64.43	1182.37 $\pm$ 48.38		
Protein Energy %	16.85 $\pm$ 0.87	16.51 $\pm$ 0.70	0.09	0.7703
Carbohydrate Energy %	36.05 $\pm$ 1.92	39.69 $\pm$ 1.35	2.43	0.1272
Fat Energy %	47.10 $\pm$ 1.28	43.79 $\pm$ 1.06	4.05	0.0512

§ indicates a P value between 0.015 and 0.05.
n = 24, df = 1,40

TABLE 4.24 Total Food Intake and the Elective Consumption of Macro-nutrients (Mean 7 Subjects).

4.3.6.5 Analysis of Salivation Data

The weight of saliva recorded in grammes before (baseline) and after (stimulus-induced) presentation of each test meal appear in Appendix 13, Tables A13.1.1 - A13.1.8. The statistical results of the effects of PPA (TM A) and placebo (TM B) on baseline and stimulus-induced salivation are depicted in Table 4.25. The average salivation response of the subjects per test medication phase, F ratios and P values were obtained from a two-way ANOVA test (TEST 3, section 4.3.4) with drug condition and weeks as factors

in the analysis. It is apparent from this table that statistically significant decreases in both baseline ($P < 0.005$) and stimulus-induced ($P < 0.001$) salivation occurred when the subjects were taking PPA (TM A) as opposed to placebo (TM B).

Salivation	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
Baseline	1.15 $\pm$ 0.10	1.67 $\pm$ 0.14	8.96 [†]	0.0032
Stimulus-induced	1.28 $\pm$ 0.09	1.88 $\pm$ 0.15	11.85 [†]	0.0007

[†] indicates a P value < 0.01
 $n = 93$, $df = 1,178$

TABLE 4.25 Average Baseline and Stimulus-induced Salivation Measurements (Mean 7 Subjects)

The average baseline and stimulus-induced salivation responses are depicted in Table 4.26, for each test medication phase per volunteer. The mean response per test medication phase, F ratios and P values were obtained from a one-way ANOVA test (TEST 3, section 4.3.4), with drug condition as factor. It can be seen that when they were taking PPA (TM A) as opposed to placebo (TM B), all of the subjects except 1 (subject 5) experienced a statistically significant decrease in baseline salivation, whilst only 2 (subjects 1 and 2) experienced a significant reduction in stimulus-induced salivation.

Sub	Baseline Salivation				Stimulus-Induced Salivation			
	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	1.69 $\pm$ 0.18	3.83 $\pm$ 3.83	38.1 [†]	0.0000	2.07 $\pm$ 0.24	4.34 $\pm$ 0.22	50.2 [†]	0.0000
2	0.86 $\pm$ 0.07	1.23 $\pm$ 0.10	8.60 [†]	0.0097	1.07 $\pm$ 0.14	1.86 $\pm$ 0.13	16.3 [†]	0.0010
3	0.65 $\pm$ 0.07	1.03 $\pm$ 0.10	50.2 [†]	0.0050	0.86 $\pm$ 0.05	1.07 $\pm$ 0.09	4.11	0.0550
4	0.33 $\pm$ 0.03	0.50 $\pm$ 0.04	11.0 [†]	0.0044	0.49 $\pm$ 0.06	0.61 $\pm$ 0.06	2.19	0.1584
5	1.30 $\pm$ 0.12	1.17 $\pm$ 0.09	0.75	0.4090	1.64 $\pm$ 0.10	1.72 $\pm$ 0.18	0.18	0.6818
6	0.62 $\pm$ 0.07	0.96 $\pm$ 0.08	9.06 [†]	0.0064	0.72 $\pm$ 0.08	0.74 $\pm$ 0.06	0.04	0.8442

[†] indicates a P value < 0.01
 $n = 12$, $df = 1,22$ for subjects 1, 3 and 6
 $n = 9$, $df = 1,16$ for subjects 2, 4 and 5

TABLE 4.26 Average Baseline and Stimulus-induced Salivation Responses per Volunteer

4.3.6.6 Observational Studies and Diet Diaries

As the trial was conducted under double-blind conditions, the processing and analysis of the preceding data was carried out after completion of the entire trial and proved to be an extremely lengthy procedure. Due to the limited period of time left to complete the clinical study, it was felt that processing the observational and diet diary data was beyond the scope of this trial. These data, however, remain on file at the School of Pharmaceutical Sciences, Rhodes University, Grahamstown, South Africa.

4.4 DISCUSSION

The primary objective of performing a pilot feasibility trial is to expose the possible problems that can be encountered with design, approach and methods used in the trial and indeed, in this study, this objective was realised.

The clinical trial was restricted in terms of available facilities and number of trial monitors, which governed the small number of subjects used. In addition the longer testing period required to perform a cross-over comparison of the two treatments caused additional problems in terms of subject "drop-outs" due to illness. Because the cross-over broke down, the only way in which the trial data could be salvaged was to perform a parallel-groups comparison of the data which resulted in a smaller and less powerful study. As the presence of period effects was unfortunately impossible to ascertain, the parallel-groups analysis was performed on the assumption that if period effects were indeed present, these effects would be our least important concern.

As the ethical requirements for using humans in a clinical study insist that volunteers are well-informed and aware of the nature of the trial, classic double-blind conditions were not actually imposed during this trial as the subjects knew that they would receive an active medication (PPA) and a placebo on two different occasions, although they were unaware of which phase they would receive each treatment.

Body mass and blood pressure, being objective measures, were easy to monitor. The average weight loss experienced by the subjects for the 4 weeks that they were taking PPA was significantly greater ($2.05 \text{ kg} \pm 0.37$) than whilst they were taking placebo ($0.76 \text{ kg} \pm 0.34$), and is comparable to published data (59). Although the weight loss experienced by each subject varied greatly ($0.73 - 3.26 \text{ kg}$) following treatment with PPA, all the subjects lost more weight on PPA than placebo.

The supine diastolic and systolic blood pressures of the subjects remained relatively stable during both treatment with PPA and placebo. Although some volunteers did show significant increases in BP during treatment with placebo, no significant rises in BP were encountered during treatment with PPA.

The mood questionnaires were easy to administer, although the ARCI and POMS questionnaires were extremely time-consuming in terms of data capture and analysis. In addition, a possible short-coming of using these questionnaires and specifically as often as in this trial, is monotony and carelessness in completion. However, the validity of using these questionnaires to illuminate possible stimulant effects and abuse potential of anorexiant has been proven repeatedly (133, 134, 136, 137, 191, 282) and is necessary to assess the safety of this class of drugs.

Although no significant differences in overall response to the various scales of the ARCI, POMS and VAS questionnaires were seen following treatment with PPA or placebo, marked deviations in individual responses were apparent, with some subjects experiencing significant mood alterations following treatment with PPA. Generally, subjects 1 and 4 appeared to be more aroused and more influenced by the mood elevating effects of PPA, without experiencing negative effects, whilst the opposite was true for subject 3. However, because of the highly subjective nature of the responses under investigation, these effects could have been due to various factors such as the time that the questionnaires were administered or extraneous cognitive variables, for example, and may not necessarily be drug-induced. In addition, it could well be likely that these effects were influenced by the order of drug treatment assignment.

The questionnaires (AHQ, BSQ, SQ and FPQ) used to monitor hunger and satiety were relatively quick and simple to administer and analyse. Significant decrements occurred in the responses of the subjects to the hunger\appetite questionnaires whilst they were taking PPA as opposed to placebo, whilst no significant differences occurred in the responses to the satiety questionnaires across treatments. Although no definite statements can be made from the responses to the BSQ and FPQ due to the limited number of observations and small population studied, it appears that PPA reduced sensations of stomach rumbling and salivation (possibly indicating reduced hunger/appetite) and slightly increased the number of preferred foods chosen following meal completion (possibly indicating lack of effect on the satiety mechanism). These observations would appear to be consistent with the results obtained from the AHQ and the SQ.

The composition of the test meal attempted to represent normal intake as far as possible and permitted calculation of the amounts of different macro-nutrients consumed following each treatment. Phenylpropanolamine significantly reduced the total amount of food and carbohydrate items consumed by the subjects whilst exerting no significant effect on the amount of fat intake. In addition, although PPA appeared to reduce the amount of protein consumed at the test meals, this effect was not statistically significant.

The SHP method of measuring salivation was relatively uncomplicated, although it required a great deal of subject participation and compliance, and the subjects complained that the method was uncomfortable. However, pronounced effects on baseline and stimulus-induced salivation were seen following treatment with PPA. Significant decreases in both salivation measures were observed whilst the subjects were taking PPA as opposed to placebo, with the effect on stimulus-induced salivation being more significant than on baseline salivation. These decreases in salivation are confirmed in the side-effect reports and the BSQ, as dry mouth was noted during treatment with PPA.

It is well known that one of the side-effects of the sympathomimetic class of drugs regularly encountered and reported, is dryness of the mouth. However, some researchers regard a reduction in salivation, and

particularly stimulus-induced salivation, as a putative measure of appetite suppression. Indeed, one author (331) goes so far as to suggest that dryness of the mouth observed during treatment with sympathomimetic anorectics need not be a disadvantageous side effect, but by intensifying appetite suppression, is rather indicative of the effectiveness of the drug.

The most elementary research on feeding is directed towards mechanisms responsible for initiation, maintenance and termination of eating and can be partitioned into studies of the control of caloric intake, selection of foods and nutrients and the distribution of eating episodes. Such investigations are intended to provide explanations for disordered eating, whether represented by over- or underingestion of calories, abnormal preferences and selection of foods, or aberrant sizes or patterns of eating episodes.

In order to treat overweight patients successfully it is necessary to establish which factors contribute to abnormalities in the eating sequence (see section 2.4). Likewise, in order to institute efficacious pharmacological treatment of the overweight patient, it is vital to establish which variables in the eating response are affected by the anorectic agent. For example, if an overweight person has a penchant for carbohydrate food items, it would be advisable to recommend an anorexiant agent that would reduce, specifically, the amount of carbohydrate consumed by that patient.

In the present study, various measures of safety and efficacy were monitored in an attempt to assess the global effect of PPA as an appetite suppressant. Although certain measures were time-consuming (ARCI, POMS, VAS) and intrusive (salivation measurements), their inclusion in the study was vital and elicited important information regarding the effects of PPA. While the present pilot study cannot irrevocably assure the safety and efficacy of PPA as an appetite suppressant due to the problems encountered with the design and methods used, the valuable data afforded by each of the measurements performed during the present trial demonstrate the feasibility of the multidimensional approach for evaluating the safety and efficacy of PPA.

CHAPTER 5

ANALYTICAL METHODS

5.1 INTRODUCTION

High performance liquid chromatography (HPLC) has become universally popular as an analytical tool in a multitude of chemical, biochemical, pharmaceutical and clinical applications (293). Chromatography originated as a separation technique in 1903, when the Russian botanist Tswett separated plant pigments by adsorption chromatography (293). In 1941, Martin and Synge (296) established the groundwork for HPLC and introduced the concept of the "height equivalent to a theoretical plate" (HETP) which is now employed as a general measure of chromatographic efficiency.

Since then many forms of liquid chromatography have been developed including partition, ion-exchange, ion-pair and size exclusion chromatography. All liquid chromatographic techniques are based on the principle that solute separation results from different rates of zone migration caused by differences in relative affinities for a solid stationary phase and a liquid mobile phase. Modern HPLC is considerably versatile and is characterised by precision, good sensitivity, short analysis times, high efficiency and continuous detection of eluting components (293, 294, 297).

In reverse-phase (RP) chromatography, the stationary phase is made by covalently linking the silica support with a hydrocarbon chain such as an organochlorosilane or similar reagent to render a non-polar bonded stationary phase of varying degrees of lipophilicity. The RP mode of chromatography is more suitable for analysis of aqueous samples as the mobile phase is aqueous. In addition RP chromatography is ideally suited to drug analysis in biological fluids, as the drug is likely to be one of the most lipophilic components of the sample and will thus be retained on the column longer than most endogenous substances due to interaction with the stationary phase (298).

In Paired-Ion Chromatography (PIC), a relatively new liquid chromatographic (LC) variation, addition of a suitable counter-ion to acidic or basic compounds results in the formation of an electrically neutral lipophilic ion-pair complex which greatly augments retention of these sample components on RP systems by hydrophobic interaction. Unlike conventional ion-exchange chromatographic techniques, PIC can be used to separate nonionic and ionic compounds in the same sample. Mobile phase composition can be adjusted to allow the separation of nonionic compounds to be optimized. If ionizable compounds are present, pH adjustment is required for the formation of the ion-pair complex (294, 295, 299).

For basic samples, alkyl sulfonates ($pK_a < 1$) are used. The pK_a of an alkyl sulfonic acid counter-ion should be less than pH 3 for ion-pair formation with bases to enable the sample to exist in its ionic form. In PIC, the variables include concentration, type and size of the counter-ion, pH, solvent polarity, temperature and stationary phase, and enable additional possibilities for optimizing selectivity (299).

5.2 ANALYSIS OF PHENYLPROPANOLAMINE RAW MATERIAL AND DOSAGE FORMS

Numerous methods have been developed and used for the determination of PPA in pharmaceutical formulations and include UV spectrophotometric (300, 302), colorimetric (302, 303), spectrofluorometric (304), titrimetric (305) and Raman spectroscopic (306) analysis. While column (307, 308), paper (309) and thin-layer (310) chromatographic methods have been used, gas chromatography and HPLC (311) have been used extensively for the determination of PPA in pharmaceutical preparations and, to a lesser extent, for the determination of the drug in biological fluids.

5.3 DEVELOPMENT OF AN HPLC METHOD FOR THE DETERMINATION OF PHENYLPROPANOLAMINE

The HPLC method used to determine PPA concentrations in serum and to elucidate steady-state pharmacokinetic parameters was based on an adaptation by Scherzinger *et al* (10) of a published HPLC method of PPA assay (8, 170).

5.3.1 Experimental

5.3.1.1 Reagents

All reagents and chemicals were used without further purification and were of at least analytical grade. The HPLC grade water used in the preparation of the standards and the mobile phase was purified through a Milli-Q purification system (Waters Associates). Phenylpropanolamine hydrochloride¹, ephedrine hydrochloride², hydrochloric acid³, the sodium salt of 1-heptane sulphonic acid⁴ and distilled-in-glass grade acetonitrile⁵ were obtained commercially. The mobile phases were filtered through 0,6 μ m cellulose acetate filters⁶ and deaerated under vacuum.

1. Aldrich Chemical Co., Milwaukee, Wis., United States of America.
2. Holpro Analytics (Pty) Ltd., Johannesburg, South Africa.
3. BDH Chemicals Ltd., Poole, England.
4. Sigma Chemical Co., St Louis, United States of America.
5. Burdick and Jackson Lab. Inc., Muskegon, Mich., United States of America.
6. Type BD, Millipore Corp., Bedford, Mass., United States of America.

The drug sample solutions were prepared in A-grade volumetric flasks by the addition of HPLC grade water.

5.3.1.2 The High-Performance Liquid Chromatographic System

The HPLC system used throughout analysis of dosage form purity and biological samples consisted of:

- 1) Model 510 solvent delivery system (Millipore-Waters).
- 2) Model 7125 20 μ L liquid sampling unit (Rheodyne).
- 3) Model 481 Lambda-Max LC spectrophotometer (Millipore-Waters).
- 4) Model 561 chart recorder (Perkin Elmer).

Separation was achieved on a custom-packed 25 cm x 3.9 i.d. Techsil C₁₈ (5 µm) reverse phase column (HPLC Technology) which was encased by a Model LC-22 temperature controller (Bioanalytical Systems Inc.) to allow the desired temperature to be maintained.

5.3.1.3 Ultraviolet (UV) Detector

The liquid chromatographic detector provides the informative nucleus for the quantitative and qualitative assessment of the compounds of interest. UV absorption detectors are the most widely employed detectors in HPLC as they are relatively insensitive to both flow rate and temperature changes and are highly sensitive, stable and have a wide linear range (312).

The Lambda-Max Model 481 LC spectrophotometer is a solid-state continuously-variable modular instrument especially designed for HPLC applications. A true dual beam is produced through fibre optics for sensitivity detection and stability and can be placed in any order when run in series due to the high pressure capacity (1000 psi) of the analytical cell. The detector was operated at 210 nm at a sensitivity setting of 0.005 absorbance units full scale (AUFS) for analysis of biological samples and at 0.5 AUFS for dissolution and dosage form purity analysis.

5.3.1.4 Columns and Mobile Phase

The column used throughout the entire standardization and analytical procedures was a 25 cm x 3.9 mm i.d. steel column packed with Techsil 5 µm octadecylsilane (C₁₈) material (HPLC Technology) by the method described in section 5.3.1.7. The optimum operating conditions for this column are summarised in section 5.5.2.2. When the formation of a top-end void became evident, it was repaired by the application of a paste of 5 µm C₁₈ Techsil in methanol.

5.3.1.5 Guard Column

A 10 µm C₁₈ cartridge guard column (HPLC Technology Ltd) housed in a cartridge holder (HPLC Technology) was employed during analysis of biological samples to protect the analytical column and to prevent the non-eluting samples from accumulating on the analytical column. The guard column serves as a buffer, protecting the HPLC column against the negative influences of the sample and the chromatographic system. In addition, the

guard column absorbs the pressure surges of the solvent delivery system which could damage the column packing bed. The guard column did not demonstrate any contribution to dead volume or extra-column effects. When the guard column cartridge lost efficiency or caused double peaks it was discarded and replaced by a new cartridge which was obtained commercially.

5.3.1.6 Mobile Phase Preparation

The mobile phase was prepared by mixing a 0.005 M 1-heptanesulfonate (HSS) solution (750 ml) with acetonitrile (224 ml) and adding 1 M HCl solution (1.5 ml). The 0.005 M HSS solution was prepared by dissolving 1.011 g of the sodium salt in 1.0 l of HPLC grade water. The resultant mobile phase (pH 2.67) was filtered under vacuum (Eyela Aspirator, Tokyo) to expel dissolved gases. The system was allowed to equilibrate for one hour before commencement of analysis. The mobile phase was recycled, resulting in a stable baseline with minimal drift. Upon completion of the analysis, the column was flushed with 100 ml of water, followed by 100 ml of methanol to remove any residues or halides that are detrimental to the stainless steel HPLC components.

5.3.1.7 Column Packing Procedure

Columns were packed as follows using a pneumatic column packing pump. The packing material from a used 25 cm x 3.9 mm i.d. steel casing (μ Bondapak, Waters Associates) was removed and the column thoroughly rinsed with methanol. The column end-frits and sieves were sonicated in an ultrasonic cleaner (Cole-Parmer Instrument Company, Chicago) for 20 minutes in methanol. Three grams of packing material (5 μ m C18 Techsil) were slurried in 30.0 ml HPLC-grade carbon tetrachloride and sonicated to enable dispersion of the agglomerates. After rapidly loading the carbon tetrachloride slurry into the column packing reservoir, 250.0 ml of degassed and filtered HPLC-grade methanol was pumped through the column at a pressure of 5000 psi. Thereafter, the column was inverted without interruption of flow and a further 250.0 ml methanol was pumped through the column before removal from the column packer. The column was then removed from the packing system and washed with 50.0 ml of a degassed acetonitrile/water (75/25) solution and tested using this mobile phase and a C₁₈ column test mixture prepared as follows:

Ten micrograms of benzamide, benzophenone and biphenyl, plus 0.5 ml of a 1 in 50 solution of benzene were made up to 20.0 ml with acetonitrile. Twenty microlitres of this solution was injected onto the column at a flow rate of 1.0 ml/min with UV detection at 254 nm, a sensitivity setting of 0.2 AUFS and a chart speed of 6 cm/min. The number of theoretical plates (N) was calculated for each column packed (Equation 5.1) to measure column efficiency. Column performance was measured periodically as part of the HPLC method protocol to minimize instrument error.

$$N = 5,54 \frac{t_1^2}{w_1} \quad \text{Eqn 5.1}$$

Where t_1 = retention time of peak

w_1 = width at half peak height

5.3.2 Results and Discussion

Phenylpropanolamine hydrochloride absorbs in the low ultraviolet range but its intrinsic molar absorptivity is low (313). The need to detect low concentrations of PPA in biological fluids (12.5 ng/ml) necessitated the choice of a wavelength where the absorbance was relatively high. A wavelength of 210 nm has been shown by Dowse *et al* (8) to provide sufficient sensitivity when monitoring PPA concentrations of 10 ng/ml and more.

The compound chosen as the internal standard should preferably have physico-chemical properties similar to the analyte and homologous or analogous compounds and isomers are preferred to other substances (297). Ephedrine hydrochloride (EPH. HCl) was chosen as the internal standard as it was readily detectable at 210 nm and eluted after PPA. Peak shape was sharp and symmetrical and resolution between PPA and EPH peaks was satisfactory on the chromatographic system used.

The necessity of having an ion-pairing agent in the mobile phase for the elution of PPA from a C_{18} column has been established in two previous studies (8, 10). A 0.005 M sodium 1-heptanesulfonate (HSS) solution in the mobile phase yielded satisfactory retention time and good baseline resolution.

As it was necessary to decrease the pH of the mobile phase to reduce tailing of the analytes separated, hydrochloric acid was included since it did not interfere with detection at 210 nm. However, for monomeric C₁₈ columns a pH range of 3-7 is recommended and therefore only 0.15% 1 M HCl was used in the mobile phase.

The mobile phase consisting of 23% acetonitrile/ 77% HSS solution (0.005 M) with 0.15% 1 M HCl afforded satisfactory baseline resolution at 35 °C and was used for the determination of all serum determinations. The 5 µm C₁₈ Techsil column could be operated at modest back pressures (2.75 kpsi) and yielded good separation efficiency.

5.4 ANALYSIS OF PHENYLPROPANOLAMINE IN SERUM

Quantitative analysis of phenylpropanolamine in biological fluids is necessary for the investigation of pharmacokinetics and to correlate toxic effects with drug levels. Since many of these studies are performed with very low doses, the requirements on determination limits are demanding and may be in the lower nanogram range.

Over the last few years, HPLC has become a popular and widely used method for the determination of drugs in biological fluids. The methods used to treat biological samples prior to their introduction onto an HPLC column generally fall into two categories - extraction or direct injection. With the extraction method, the analyte of interest is removed from the biological matrix such as serum or urine using a suitable solvent and pH which enables undesirable material to be left behind. Although the direct-injection technique is the simplest and most rapid of the two methods, rapid increase in back-pressure and deterioration of column performance occurs (314, 315) due to the precipitation of plasma proteins.

Numerous HPLC methods have been developed that involve derivatisation of the extract (316 - 319), which are relatively time-consuming, or involve post-column manipulations (320, 321). Determination of PPA in serum and urine without prior derivitisation has been described by Scherzinger *et al* (10). The method is an adaptation of the method reported by Dowse *et al* (8, 171) and involves extraction at a basic pH with methylene chloride

(dichloromethane), a single back extraction into acid followed by chromatographic analysis on a reverse-phase column. The resulting chromatograms were devoid of interfering endogenous contaminants with detection limits for PPA in serum of 5 ng/ml and 5 µg/ml in urine.

5.4.1 Experimental

5.4.1.1 Reagents

The potassium hydroxide¹, hydrochloric acid¹ and the HPLC-grade methylene chloride² were obtained commercially.

1. B.D.H. Chemicals Ltd., Poole. England.
2. Burdick and Jackson Laboratories, Muskegon, Mich., United States of America.

5.4.1.2 Sample Preparation

5.4.1.2.1 Phenylpropanolamine hydrochloride serum stock solution

Twenty five milligrams of PPA.HCl was accurately weighed, dissolved in 50 ml water and 1 ml of this solution was diluted to 20 ml with water. One millilitre of this solution was made up to volume with blank serum to yield a resultant concentration in serum of 500 ng/ml. The stock solution was mixed slowly to ensure sample homogeneity. Appropriate dilutions were then made.

5.4.1.2.2 Internal standard stock solution

Twenty milligrams of EPH.HCl was weighed and dissolved in 50 ml of water. One millilitre of this solution was made up to 20 ml with water to yield a concentration of 2 µg/ml. This was used as the internal stock solution.

The serum used to prepare the serum stock solution was obtained from Settlers' Hospital, Grahamstown, South Africa. Before the serum was used, blank serum sample extracts were subjected to HPLC analysis to ensure freedom from interfering contaminants.

5.4.1.3 Chromatographic Conditions

HPLC system:	Section 5.3.1.2
Column:	C ₁₈ 5µm Techsil
Flow rate:	1.3 ml.min ⁻¹
Pressure:	2750 psi
Detection wavelength:	210 nm
Attenuation:	0.005 AUFS
Temperature:	35°C
Recorder input:	10 mV
Chart speed:	5 mm.min ⁻¹
Mobile phase:	0.005 M HSS solution/acetonitrile (77/23) with 0.15% 1 M HCl pH = 2.65

5.4.1.4 Extraction Procedure

One millilitre of serum, 100 µl EPH.HCl solution (2 µg/ml) and 100 µl of a 10% potassium hydroxide solution, which adjusted the pH of the mixture to 12.25, were vortexed (Vortex-Genie, Scientific Industries Inc., United States of America) for 20 seconds in a centrifuge tube. Eight millilitres of methylene chloride were added, the tube stoppered, vortexed for 15 seconds and centrifuged (IEC Centrifuge, Model HN-SII, Damon/IEC Division, Mass.) at 3500 rpm for 2 min. A further 2 ml increment of methylene chloride was added and the tube re-centrifuged for 3 min at 3500 rpm. A disc formed between the aqueous organic phases and the aqueous layer above this disc was removed by aspiration and discarded. A pasteur pipette was used to transfer the methylene chloride layer to a tapered centrifuge tube containing 120 µl of a 0.1 M HCl solution. Care was taken to ensure that no serum was transferred. The tube was vortexed for 30 seconds and centrifuged (BAS Microfiltration Centrifuge, Bioanalytical Systems Inc.) at 1500 rpm for 2 min. The methylene chloride layer was reduced by aspiration to approximately 200 µl and the tube was re-centrifuged at 1500 rpm for an additional 2 min. Twenty microlitre aliquots of the hydrochloric acid extract were injected directly onto the column.

It is known that too vigorous shaking during the mixing of an alkaline aqueous phase and halogenated solvents results in emulsion formation. Care was thus taken to avoid too vigorous vortexing of the samples.

5.4.1.5 Calibration Curve

The serum stock solution of 500 ng/ml was diluted to yield six different concentrations, the stock solution itself providing the seventh. Concentrations ranged from 12.5 to 500 ng/ml and each concentration was assayed in triplicate. The calibration curve was constructed by plotting the ratio of the peak height of PPA.HCl to that of the internal standard, EPH.HCl versus the respective PPA.HCl concentration. The data were fitted by least-squares linear regression analysis.

5.4.1.6 Precision

With-in run precision was evaluated by extracting six spiked serum samples at the lower (12.5 ng/ml), middle (100 ng/ml) and upper (500 ng/ml) concentrations, and three spiked serum samples at the intermediate concentrations (25, 50, 200 and 300 ng/ml).

5.4.1.7 Extraction Efficiency

(i) For this study, in which the analytical recovery of PPA from serum was assessed, spiked serum samples were assayed six times at four different concentrations. A similar extraction procedure to the one described in section 5.4.1.4 was applied to all the samples with one modification. One hundred microlitres of water was substituted for the internal standard solution at the start of the procedure. A 2 µg/ml EPH.HCl solution was made up in hydrochloric acid (0.1 M), and as the internal standard was added at the end, it was thus not carried through the initial stages of the extraction procedure.

Standard aqueous solutions of PPA.HCl were made up and internal standard solution added in concentrations corresponding to those extracted above. The internal standard therefore accounted for variations in sample volumes injected. To determine the percentage recovery of analyte from serum, the ratios obtained from the serum extracts were compared to those resulting from the relevant standard solutions of equivalent concentrations.

(ii) Analytical recovery of PPA.HCl from serum was also evaluated excluding the addition of EPH.HCl at any stage during the extraction procedure described in i) above. This assessment proved possible with the use of the Rheodyne injector with a fixed 20 µl loop, as there is

negligible variation (0.01%) in sample volumes injected. Spiked serum samples were assayed six times at four concentrations.

Standard aqueous solutions of PPA.HCl were made up in concentrations corresponding to the serum samples extracted. To determine percentage recovery, the peak heights obtained from the serum extracts were compared to those resulting from relevant aqueous standard solutions of equivalent concentrations.

5.4.2 Results and Discussion

5.4.2.2 Linearity and Calibration

Linearity was established for the range of concentrations studied (12.5-500.0 ng/ml). The line had a slope of 0.007451, a y-intercept of -0.01824 and a correlation coefficient of 0.9996. The calibration curve for phenylpropanolamine in serum is shown in Figure 5.1. Chromatograms of a blank serum extract and a spiked serum extract containing phenylpropanolamine and ephedrine as internal standard are depicted in Figure 5.2. The retention time of PPA was 5.2 min and that of EPH was 6.1 min.

FIGURE 5.1 Calibration Curve of PPA in Serum

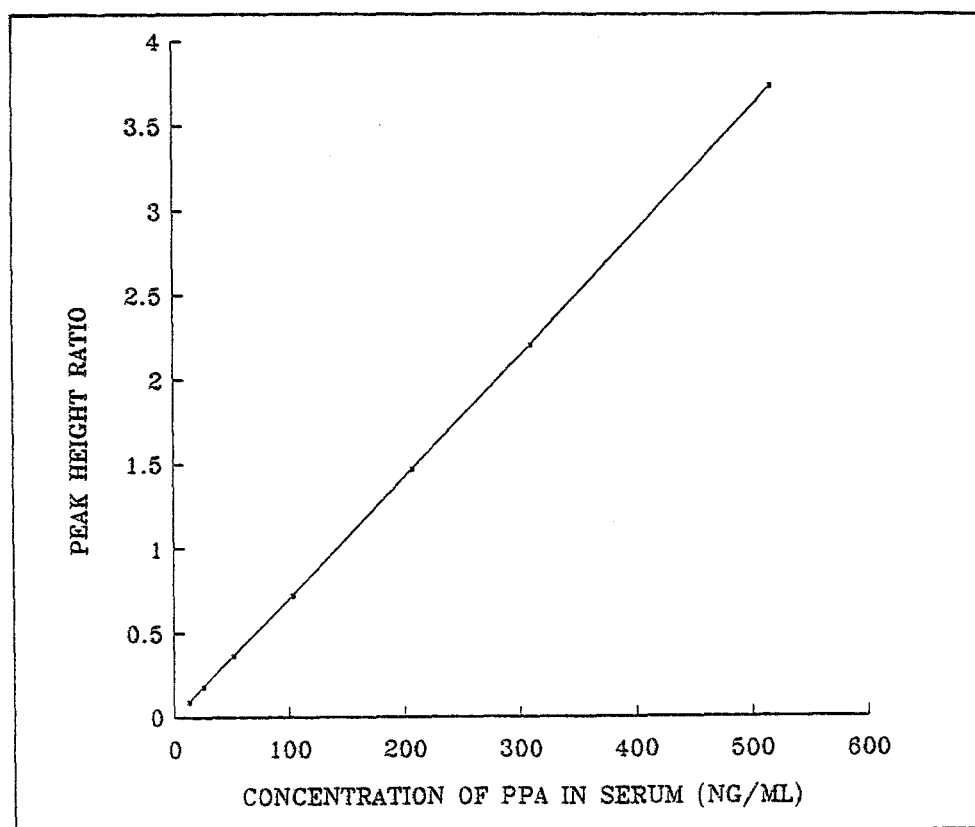
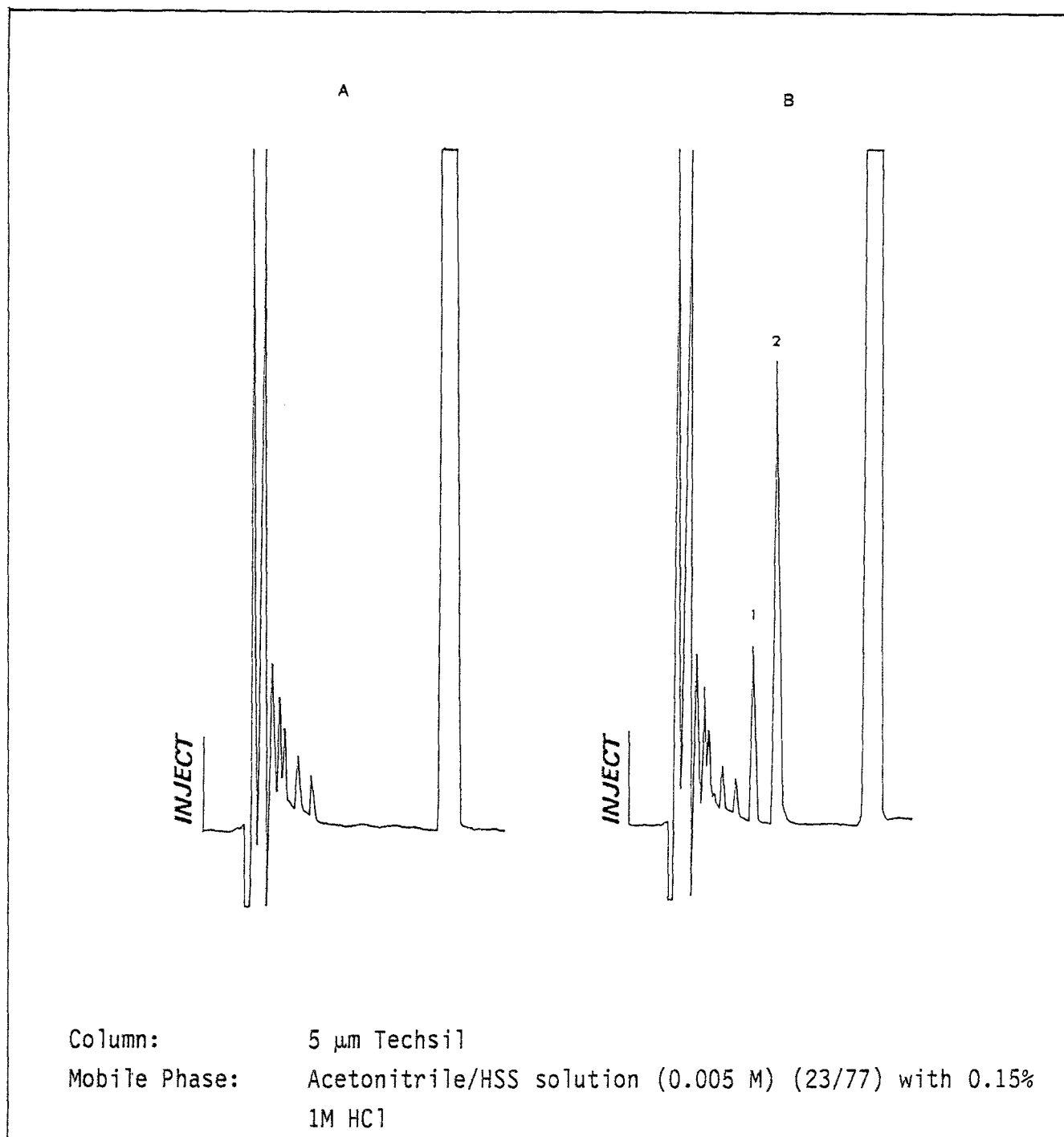


FIGURE 5.2

Chromatograms of (A) a blank serum extract and (B) a serum extract containing PPA (50 ng/ml) (1) and EPH (2)



5.4.2.3 Precision

Results of the with-in run precision study are depicted in Table 5.1. The method was found to be highly reproducible with R.S.D. values less than 5% at all concentrations.

TABLE 5.1 Within-run precision study on PPA.HCl serum assay

Spiked Conc (ng/ml)	Concentration measured (ng/ml)						Mean	± SD	RSD %
	Replicate number								
	1	2	3	4	5	6			
12.5	15.48	14.53	14.18	14.20	14.08	14.53	14.50	± 0.52	3.55
25	26.72	26.97	27.61				27.10	± 0.46	1.69
50	52.25	52.10	52.10				52.15	± 0.09	0.16
100	103.43	103.27	100.41	99.44	104.11	98.12	101.46	± 2.47	2.44
200	199.79	200.48	215.26				205.18	± 8.74	4.26
300	310.30	301.81	308.11				306.74	± 4.41	1.44
500	516.43	518.58	526.79	515.99	511.88	515.99	517.61	± 4.99	0.97

5.4.2.4 Extraction Efficiency

Table 5.2 (a) and (b) depict the analytical recoveries of PPA from serum for methods A and B, respectively. Results indicate that the recovery of PPA from serum is constant and quantitative over the concentration range (25-500 ng/ml) studied. The mean recovery was 72.76% and 72.39% for methods A and B, respectively.

TABLE 5.2 (a) Analytical recoveries of analyte from serum (Method A)

Serum Conc (ng/ml)	Extraction Efficiency						Mean	± SD	RSD %
	Replicate numbers								
	1	2	3	4	5	6			
25	74.10	76.85	78.67	75.10	72.20	75.96	75.48	± 2.24	2.97
100	66.80	66.11	68.69	66.48	66.48	62.84	66.23	± 1.90	2.87
250	76.07	76.07	68.29	76.32	71.93	67.49	72.70	± 4.07	5.60
500	78.47	73.14	75.09	78.85	76.15	78.17	76.65	± 2.26	2.94
Mean percentage recovery (n = 24)							72.76	± 4.86	6.67

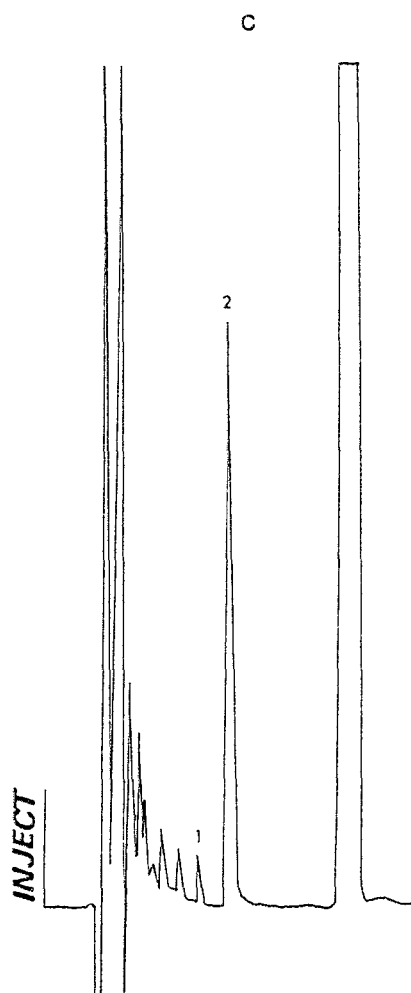
TABLE 5.2 (b) Analytical recoveries of analyte from serum (Method B)

Serum Conc (ng/ml)	Extraction Efficiency						Mean	± SD	RSD %
	Replicate numbers								
	1	2	3	4	5	6			
25	65.72	65.72	65.72	71.19	65.72	65.72	66.63	± 2.23	3.36
100	71.12	71.12	76.81	78.24	68.28	66.86	72.07	± 4.56	6.32
250	71.89	73.03	74.17	76.45	77.59	71.89	74.17	± 2.39	3.23
500	74.49	78.70	78.12	76.96	75.81	75.81	76.65	± 1.58	2.07
Mean percentage recovery (n = 24)							72.38	± 4.65	6.43

5.4.2.5 Sensitivity and Detection Limits

Under the conditions of this assay and based on a minimum signal to noise ratio of 10:1 the detection limit for PPA in serum was 5.0 ng/ml. A chromatogram of a serum extract containing PPA (5 ng/ml) is shown in Figure 5.3.

FIGURE 5.3 Chromatograms of (C) a serum extract containing PPA (5 ng/ml) (1) and EPH (2).



Column: 5 μ m Techsil

Mobile Phase: Acetonitrile/HSS solution (0.005 M) (23/77) with 0.15% 1M HCl

5.4.2.6 Background Interference

The technique of back-extraction eliminated a significant amount of interfering endogenous compounds which had been co-extracted with methylene chloride. The hydrochloric acid eluted at the void volume and peaks from serum constituents did not interfere with the analytes of interest. The large peak at 10 minutes was due to a trace amount of methylene chloride which partitioned into the hydrochloric acid.

5.5 ANALYSIS OF BIOLOGICAL SAMPLES

5.5.1 The Analysis of Serum

Serum samples were analysed in randomised order to avoid sequential effects. The two millilitre aliquots were brought to room temperature and were thoroughly mixed by slow vortexing before analysis. The method of sample preparation and the chromatographic conditions used for analysis are described in section 5.4. In order to assess method reproducibility, both *in vitro* and *ex vivo* serum standards were prepared and analysed under blind conditions. All test and reference preparations obtained from serum samples were stored under identical conditions and assayed by the same method.

5.5.2 In vitro Quality Control for Phenylpropanolamine

The performance of the assay technique was monitored continuously during the entire period of biological sample assay by including quality control specimens containing known concentrations of the analyte.

5.5.3 Ex vivo Quality Control for Phenylpropanolamine

Additional blood was collected from trial subjects at randomised times during the pilot clinical trial and analysed.

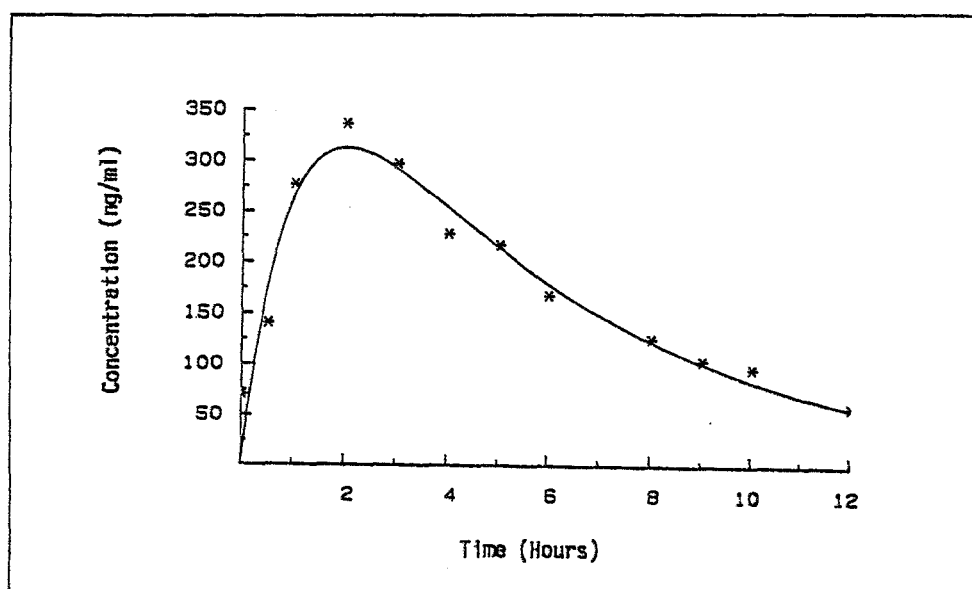
5.5.4 RESULTS AND DISCUSSION

5.5.4.1 Pilot Steady-State Trial

The serum concentrations from the pilot steady-state trial are presented in Appendix 14, Table A14.1 and the final (7th) dose serum concentration profile is shown in Figure 5.4. The concentrations observed were within the quantitative range of the described method. The fitted curve was obtained from inputting observed data into the PC NONLIN Ver 3.0 computer modelling

program (332). Model 3 of this program was chosen (1 Body Compartmental Model (1 BCM), first order input and output, no lag time) as it gave the best fit to the data.

FIGURE 5.4 Observed Vs Fitted Data for the Steady-State Trial



The PC NONLIN program provided estimated primary parameters of vol (volume), k_a (absorption rate constant), k_{el} (elimination rate constant), and secondary parameters of AUC (area under the curve), t_{max} (time to reach maximum concentration) and C_{max} (maximum concentration), to the fitted data. Table 5.3 depicts these estimated parameters.

Parameter	Estimate	Std Error
Vol (l)	163,110	20.876
k_a (hr ⁻¹)	1.018	0.253
k_{el} (hr ⁻¹)	0.190	0.036
AUC (ng/ml.h)	2420.693	208.448
t_{max} (h)	2.027	0.221
C_{max} (ng/ml)	312.863	16.129

TABLE 5.3 Parameter Estimates for Fitted Data

From Table A14.1, it can be seen that for the multiple dose steady-state pilot trial, serum concentration trough values varied between 61.11 and

92.67 ng/ml. In addition, absorption was relatively rapid, with the peak serum concentration of 336.52 ng/ml occurring 2 hours after ingestion of the final test dose.

Table 5.4 depicts the inter-day precision of the analytical method at two concentrations using spiked *in vitro* serum standards. The method of extraction and subsequent determination of PPA from serum was found to be sensitive and precise. The method does not necessitate derivatization, and extraction was relatively simple. The back-extraction step eliminates the need for organic solvent evaporation, thus reducing total sample preparation time significantly.

TABLE 5.4 Inter-day precision for phenylpropanolamine in serum

1	2	3	4	Mean (SD)	RSD
Low concentration (spiked: 83.14 ng/ml)					
85.46	86.01	88.69	77.25	84.35 (4.94)	5.86%
High concentration (spiked: 519.60 ng/ml)					
515.65	524.04	517.19	529.81	521.67 (6.54)	1.25%

Although the multiple venipuncture method of blood withdrawal is generally associated with more trauma than withdrawal using butterfly sets, the method was convenient as each subject only had a maximum of 3 blood samples withdrawn in any one day.

5.5.4.2 Clinical Trial

Analysis of the blood samples taken during the phase that each subject took placebo revealed an absence of PPA.HCL in the blood, confirming that each subject took the correct dosage form during the placebo phase. The serum concentrations for each individual subject for the phase of the clinical trial that they were administered active medication are shown in Appendix 14, Tables A14.2 - A14.9. The mean trough level of PPA attained was 122.98 ± 43.76 ng/ml and the average peak PPA level was 255.75 ± 71.08 ng/ml.

The fitted vs observed serum concentration profiles for each subject for the clinical trial are presented in Appendix 14, Figures A14.1 - A14.8. These diagrammatical representations were generated using the PC NONLIN

program discussed in the previous section. The estimated parameters obtained from the last dosing interval of the steady-state data were used to produce the back-ground steady-state profiles onto which individual subject data were overlayed to produce each subject's final serum concentration-time profile.

From these serum concentration-time profiles it can be seen that the experimental data obtained for the subjects were in excellent agreement with the predicted data obtained using the 1BCM model, as the majority of observed data points fell within the predicted steady-state peak and trough levels.

From Figure A14.1, it appears that subject 1 (SS) reached steady-state and complied with the dosing schedule as she exhibited a relatively constant profile for the duration of the PPA phase. Similar profiles are apparent for subjects 4 (Figure A14.4) and 8 (Figure A14.8).

Subject 2's profile (Figure A14.2) reveals conformity with the dosing schedule until the final week (week 5) of the PPA phase, where the peak PPA serum concentration increased dramatically, possibly due to non-compliance with the dosing schedule.

The serum concentration profiles of subject 3 (Figure A14.3), 6 (Figure A14.6) and 7 (Figure A14.7) appeared to be relatively stable during the first two weeks of dosing. However, erratic serum levels were displayed by the former two subjects (3 and 6) from day 7, week 4 until the end of the PPA phase, possibly indicating non-compliance. In addition, these two subjects were administered PPA during the second phase of the trial and appeared to be bored and frustrated at the slow weight loss that they experienced. Subject 7 developed a chest infection during the last two weeks of dosing with PPA and defaulted for the rest of the PPA phase.

As mentioned previously, subject 5 was ill during the 2nd week that she was administered PPA (third week of the PPA phase), and presented considerably irregular serum levels of PPA (Figure A14.5). In particular, no PPA.HCl was present in the two trough serum samples taken during that week. It was uncertain if this was due to concomitant medication (urinary alkaliser)

or patient non-compliance. However, the former reason can possibly be discounted on the basis that urinary alkalization has been shown to increase post-absorptive plasma concentrations of PPA (167).

In controlled clinical trials (and particularly for safety and efficacy trials performed over extended periods of time) it is essential to measure serum drug concentrations in order to monitor compliance once correlated with pharmacodynamic effects. In addition, serum drug concentration levels are useful in determining the dosing regimen required to produce the desired effects.

5.6 IN VITRO DISSOLUTION RATE DETERMINATIONS

It is well established that the determination of dissolution rates plays an important part in the design, evaluation and control of solid dosage forms. It has been stated by Parrott *et al* (326) that "the release of drug from the primary particle and its subsequent availability to the body is governed by the dissolution rate of the particle". Numerous methods to determine *in vitro* dissolution rates of oral, solid dosage forms exist and techniques differ in hydronamic properties, agitating intensities and mechanical destructive forces to the intact dosage form. There are three basic dissolution testing devices: the stirred tank reactor with a mechanical agitator such as Levy's beaker method or the rotating basket method, the rotating vessel reactor such as the rotating flask or the solubility simulator and the stream reactor method such as the column method (327).

In vitro dissolution rate determinations were carried out on two extended-release capsules to determine comparative release rates of the two formulations.

5.6.1 Experimental

5.6.1.1 Chromatographic Methods

The conditions were the same as described in section 5.4.1.3, except that the sensitivity setting of the UV detector was set to 0.5 AUFS instead of 0.005 AUFS and a 10 μ l SSI injector was used in place of the 20 μ l Rheodyne injector.

5.6.1.2 Dosage Form Purity

Two sustained release (SR) forms containing 75 mg PPA.HCl were tested for their dissolution characteristic.

- (i) Product LE - a capsule containing micro-encapsulated particles (the product used for the clinical trials)
- (ii) Product RD - a capsule containing micro-encapsulated particles

The official USP monograph specifications for SR PPA.HCl dosage forms was used for the analysis. For product LE, the accurately weighed contents of the capsule, equivalent to 75 mg of PPA.HCl was transferred to a 100 ml volumetric flask. Fifty millilitres of water was added, mixed and the contents of the flask sonicated for half an hour. Thereafter, the solution was made up to 100 ml with water. Approximately 1.5 ml of this solution was centrifuged for 5 minutes () and 1 ml of this solution plus 1 ml of EPH.Cl solution (530 $\mu\text{g/ml}$) was made to volume in a 10 ml volumetric flask. A 10 μl sample of this filtrate was injected onto the HPLC column. The assay was conducted on six capsules.

5.6.1.3 In Vitro Dissolution Study

A type PTWS dissolution apparatus (Pharmatest, Hainburg, W. Germany) was used for this study. The vessel was mounted in a clear perspex bath, in which water was heated by a pump mounted in such way that the vibrations were not transmitted to the rest of the apparatus. The vessel was covered with a perspex lid containing three apertures, a central one for the shaft and 2 peripheral openings for sampling and fluid replacement. The rotating basket method was used for all dissolution rate determinations.

Each beaker held 1000 ml of the dissolution fluid which was maintained at $37^{\circ}\text{C} \pm 0.5$. One capsule was placed in each of the six dry 40-mesh baskets which were then immersed into the dissolution medium to a depth of 2 cm from the bottom of the vessel. Rotation at 100 rpm was initiated immediately.

For dissolution testing using this apparatus, aliquot withdrawal was achieved with a clean 10 ml syringe, attached to which was a stainless steel cannula. A filter was attached to this cannula during the withdrawal of approximately 2 ml of sample. Thereafter, the filter was removed and the

2 ml sample was inserted into a clean 5 ml vessel. A 250 μ l aliquot of this sample was removed and 10 μ l injected onto the HPLC column, the remainder of the 2 ml sample was returned to the dissolution vessel.

As such small volumes were removed (0.6%), no replacement of dissolution medium was necessary. Sampling times were 1, 2, 4, 6, 8, 10, 12.5, 15, 20, 25, 30 and 45 minutes, and then 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 hours after initiation of rotation. Samples were stored in the refrigerator until analysis.

5.6.1.4 Standard calibrators

Twenty mg of PPA.HCl was accurately weighed into a 50 ml volumetric flask, and made to volume with EPH.HCl (100 μ g/ml). Subsequent dilutions in the concentration range 20 - 120 μ g/ml were made using EPH.HCl (100 μ g/ml) as the diluent. Each standard calibrator was injected onto the HPLC column six times, to monitor stability and reproducibility of the system.

5.6.1.5 Dissolution Media

Simulated intestinal fluid, was evaluated for its effect on the release of PPA.HCl from products LE and RD. Simulated intestinal fluid was prepared according to USP specifications, with the exception that pancreatin was excluded, as follows: 125 ml of monobasic potassium phosphate (6.96g/ 200 ml) was measured into a 57 volumetric flask. One hundred and ninety millilitres of NaOH (1M) was added and the solution diluted to approximately 4000 ml with HPLC-grade water. Twenty five millilitres of EPH.HCl solution (20 mg/ml) was pipetted into the flask and the pH of the solution adjusted to 7.2 with 1 M HCl. The final solution was made up to 57 with water.

5.6.2 Results and Discussion

Analysis of dissolution by HPLC was rapid, accurate and precise. The HPLC column remained stable throughout the analysis and no increase in back-pressure was observed. The PPA.HCl content for Product LE was found to be 94.83% (71.12 mg/capsule) of the label claim of 75 mg/capsule.

The incorporation of the internal standard into the dissolution medium had many associated advantages. The same internal standard solution was used for the standards for the calibration curve and for the dissolution medium.

The presence of the internal standard compensated for the loss in total volume of the dissolution medium due to evaporation during the dissolution test and evaporation from the aliquot removed for analysis. In addition, it has been reported by Dowse (8) that greater accuracy is associated with the incorporation of the internal standard in the dissolution fluid than with the addition of the internal standard following sample withdrawal.

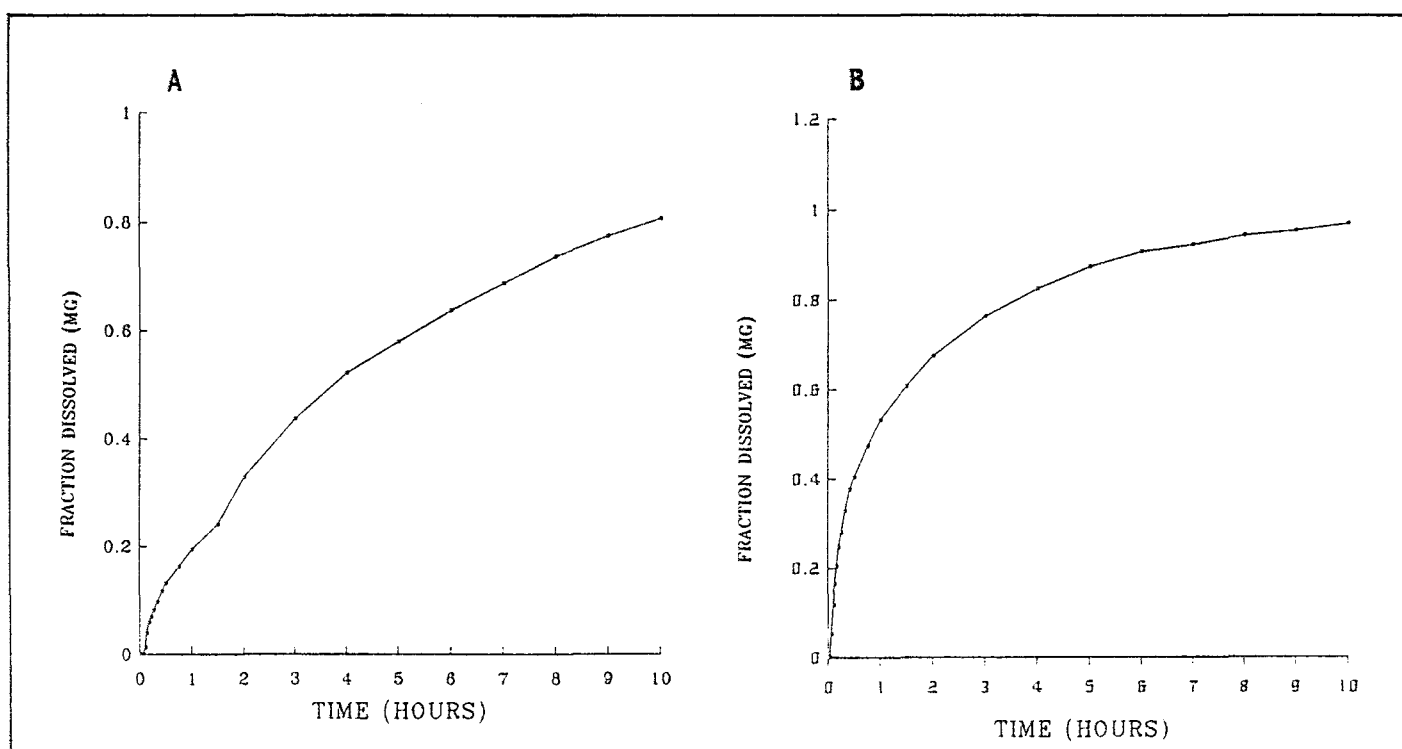
The supplement to the 8th USP (330) gives the following limits for the dissolution profiles of extended-release PPA.HCl capsules:

<u>Time</u>	<u>Hours</u>	<u>Amount Dissolved</u>
0.125 D	1.5	Between 15% and 45%
0.250 D	3.0	Between 40% and 70%
0.500 D	6.0	Not Less Than 70%

where D = Dosing interval (12 hours)

The individual results for the dissolution of PPA.HCl from Products LE and RD are listed in Appendix 15, Tables A15.1 and A15.2 respectively, and the dissolution profiles for product RD and product LE are depicted in Figure 5.5.

FIGURE 5.5 Dissolution profiles for product RD (A) and product LE (B) - (mean for 6 capsules)



It can be seen from Table 5.5 that the release of PPA.HCl from Product LE proceeded more rapidly than for Product RD. Product RD exhibited conformity with the USP limits for rates of release of drug from the dosage form matrix and is a good example of an extended, controlled-release formulation showing linearity within the first three hours. Product LE, on the other hand, did not conform to USP limits, with 60.60% of drug being released in the first 1.5 hours.

TABLE 5.4 Comparative release rates for Product RD and Product LE.

Time (Hrs)	% PPA.HCl dissolved	
	Prod RD $\pm$ SD	Prod LE $\pm$ SD
1.5	24.01 $\pm$ 0.04	60.60 $\pm$ 0.05
3.0	43.64 $\pm$ 0.04	76.30 $\pm$ 0.06
6.0	63.67 $\pm$ 0.04	90.67 $\pm$ 0.05
10.0	80.61 $\pm$ 0.04	96.96 $\pm$ 0.04

CHAPTER 6

CONCLUSIONS

Although extensively used, there is little information in the literature regarding the effects of PPA on appetite and food intake, and no study has been undertaken to determine the global safety and efficacy of PPA as an appetite suppressant over a prolonged period of time, possibly due to methodological and conceptual difficulties. The multi-dimensional approach and standard, validated methods described in this study, whilst certainly being feasible with a few design alterations, revealed certain shortcomings. The major restriction of performing such a clinical trial is that frequent supervision by the trial monitor and an enormous amount of participant effort, motivation and cooperation is required. In addition, the method requires detailed organisation and analysis by clinicians and statisticians and is thus both extremely time-consuming and expensive.

In light of the difficulties encountered in data analysis due to the length of the trial, subject "drop-outs" and hence the cross-over breaking down, it is recommended that a parallel-groups study be performed, if a comprehensive trial is to be undertaken. However, due to the highly subjective character of the variables, it would be wise to increase the number of participating subjects and to establish base-line comparability between subject groups in all parameters under investigation before embarking on the study.

Over the years, the potential for adverse hypertensive and stimulant effects following the use of PPA, has been the topic of sporadic case reports and clinical studies. Whilst some of these reports are anecdotal, others refer to instances where gross overdoses and/or concomitant medications and combination products (including caffeine) were used (100, 103, 107, 108). However, our findings were consistent with other reports and controlled clinical trials in the literature that found no significant stimulant or behavioural reinforcing effects (136, 282) or changes in blood pressure (36, 51, 53, 54, 59, 102) in normal individuals receiving PPA. Although some volunteers reported side-effects, these were considered by the investigator to be minor.

Whilst no absolute statements can be made concerning the efficacy of PPA due to the small number of subjects studied and the limited number of observations, it appeared that treatment with PPA resulted in a significant weight loss, suppression of hunger and appetite and a reduction in salivation, whilst apparently exerting little or no effect on satiety. In a recent study (98) which used a validated 1-week food frequency questionnaire to indirectly monitor intake, treatment with PPA was shown to decrease total food intake, carbohydrate, protein and fat consumption. In the present study, the lack of significant differences in protein and fat intake following treatment with PPA, could have been due to the direct method used to measure dietary intake.

One objective of the study, was to attempt to correlate serum levels of PPA with the subjective and objective variables under consideration. Unfortunately, due to the limited number of observations recorded for the AHQ, SQ, salivation and food intake, it proved impossible to attempt such a correlation of these parameters. Due to large intra-subject variability in responses, and the reality of extraneous environmental influences no correlations of serum levels with BP and the various scales of the ARCI, POMS and VAS data could be found.

Whilst the estimated steady-state pharmacokinetic parameter of k_{el} is in good agreement with those previously reported (171, 325), the rest of the parameters showed discordance with previous results. Numerous reasons are possible and include differences in formulation, dosing interval (12-hourly) and interpersonal variation. Some subjects displayed irregular profiles of drug concentration serum profiles which were difficult to describe and interpret.

Phenylpropanolamine is marketed as a racemic mixture of two enantiomers, and in this study, the pharmacodynamic properties of the racemic mixture were studied. To pursue the possibility of stereoselective differences in safety and efficacy of PPA, further studies could be performed to examine the pharmacodynamic properties of d- and l-norephedrine. In addition, the method of temporal tracking could be used to monitor the safety and efficacy of PPA continually over a period of time. Indeed, a serum concentration-time comparison of the pharmacodynamic effects of PPA could

be performed if blood levels of PPA were monitored simultaneously.

As mentioned in section 3.1, an anorectic agent is seen as efficacious if it reduces hunger and food intake and produces a reduction in body weight. In addition, safety is inferred if the drug does not elevate blood pressure and shows little abuse potential.

The present study demonstrates the utility of the standardised methods and procedures used, and the feasibility of the multidimensional approach for the assessment of the efficacy and safety of PPA as an appetite suppressant. However, in order to validate the data found in this study, it is recommended that a full-scale trial be undertaken, using the design modifications previously discussed.

APPENDIX 1VOLUNTEER INFORMATIONCONSENT TO ACT AS A RESEARCH SUBJECT - STEADY STATE SEVEN DOSE PILOT TRIAL

1. Phenylpropanolamine hydrochloride (PPA. HCl) has been widely used for decades as a nasal decongestant and appetite suppressant. The purpose of this study is to determine the serum concentrations and steady state pharmacokinetics of PPA. HCl following the administration of seven doses of a sustained release capsule containing 75 mg of PPA. HCl, given at 12 hourly intervals.

2. To participate in this trial I must fulfill the following requirements:

- (a) must be in good health - established on the basis of an interview, physical examination, urine and blood analysis.
- (b) must have no prior history of gastrointestinal, cardiovascular, hepatic, renal, respiratory or endocrine disease.
- (c) must not take any medication for one week preceding the trial and for the duration of the trial.
- (d) must not have had any major illnesses for three months preceding the trial.
- (e) must refrain from ingesting alcohol, caffeine or xanthine containing beverages and food for 48 hours prior to and during the trial period (day 1 - day 4). This includes tea, coffee, chocolate and all cola-flavoured drinks.
- (f) must not ingest foods containing tyramine i.e. mature cheese, marmite, bovril, yeast, broad beans, beer, pickled herrings and hung game and foods containing the yellow food colour, tartrazine for 14 days prior to the onset until study completion.
- (g) must refrain from doing any strenuous exercise for 24 hours prior to, and during the trial.
- (h) must follow all instructions concerning my diet before and during the trial.

If I agree to be a subject, the following will occur. I will report to the clinic at the School of Pharmaceutical Sciences at 07h45 and 19h45 each day for three days prior to the trial day (day 4). I will receive one capsule of PPA. HCl with 200 ml of tap water at 08h00 and 20h00. A 10 ml blood sample will be drawn prior to the first and subsequent doses. I will begin fasting at 22h00 on day 3 and report to the clinic at 07h30 on the trial day.

After arrival, a hypodermic needle will be inserted into a suitable arm vein by a registered nurse and a zero-time blood sample collected at 07h45. I will receive a standard breakfast and at 08h00 I will be given the seventh and final dose with 200 ml of water. I will be served a standard lunch at 13h00 and a standard snack at 16h00. I will remain in the clinic for the entire day of the trial (i.e. 07h45 - 20h00).

Blood samples (10 ml) will be collected according to the following schedule : 0,5; 1,0; 2,0; 3,0; 4,0; 5,0; 6,0; 7,0; 8,0; 9,0; 10,0; 11,0; and 12,0 hours after the final dose (a total of 13 samples).

3. The incidence of untoward effects associated with the use of PPA. HCl is low. Phenylpropanolamine hydrochloride has been reported to cause some mild and transient side effects such as headaches, tiredness / lightheadedness, anxiety, insomnia, dry mouth, nausea / vomiting, cramps, heartburn / epigastric pain, frequent urination and in susceptible subjects, to cause an increase in blood pressure, arrhythmias, tachycardia and awareness of heartbeat. The risk of these side effects occurring does increase with the administration of multiple doses.

The insertion of the needle for drawing blood can be painful and a small bruise may develop on my arm and, very rarely a localised infection may occur.

4. These procedures have no direct benefit to me but information may be obtained concerning PPA. HCl concentrations in the human body.

5. This information was explained to me by Miss L. Petrie. I understand that she will answer any questions I may have concerning this investigation. If I have any other questions I may ask Professor Kanfer.

6. I will be paid for participating in this study.

7. Participation in this study is voluntary. I have the right to refuse to participate or may withdraw at any time without jeopardy to my standing whatsoever.

Volunteer Name.....Signature.....Date.....

Witness Name.....Signature.....Date.....

APPENDIX 2VOLUNTEER INFORMATIONCONSENT TO ACT AS A RESEARCH SUBJECT - STEADY STATE PILOT TRIAL

1. Phenylpropanolamine hydrochloride (PPA. HCl) has been widely used for decades as a nasal decongestant and appetite suppressant. The purpose of this study is to evaluate the efficacy of PPA.HCL in terms of the degree of satiety or appetite suppression induced by this agent. The effects of PPA.HCL on changes in body weight, food consumption, blood pressure, skinfold thickness and salivation will be monitored. Adverse drug reactions and changes in psychological mood states will also be assessed. The study will take place for a period of eleven weeks.

WEEK ONE : Baseline evaluation period
 WEEK TWO - FIVE : First phase of the study
 WEEK SIX : Wash-out period
 WEEK SEVEN : Reestablishment of baseline conditions
 WEEK EIGHT - ELEVEN : Second phase of cross-over study

2. To participate in this trial I must fulfill the following requirements:

- (a) be in good health - established on the basis of an interview, physical examination, urine and blood analysis.
- (b) have no prior history of gastrointestinal, cardiovascular, hepatic, renal, respiratory or endocrine disease.
- (c) not take any medication for one week preceding the trial and for the duration of the trial.
- (d) not have had any major illnesses for three months preceding the trial.
- (e) refrain from ingesting alcohol, caffeine or xanthine containing beverages and food for 48 hours prior to and during the trial period. This includes tea, coffee, chocolate and all cola-flavoured drinks.
- (f) not ingest foods containing tyramine i.e. mature cheese, marmite, bovril, yeast, broad beans, beer, pickled herrings and hung game and foods containing the yellow food colour, tartrazine for 14 days prior to the onset until study completion.
- (h) follow all instructions concerning my diet and physical activity before and during the trial.

If I agree to be a subject, the following will occur. I will report to the clinic at the School of Pharmaceutical Sciences at the allocated times on each day of the first and seventh week. I will not receive any medication during these periods, but various tests will be performed according to the experimental schedule to establish my baseline variables. Week six will be a washout period in which I will receive no medication and no tests will be performed on me.

During weeks two to five, and weeks eight to eleven I will report to the clinic at the allocated time each day and after arrival, a hypodermic needle will be inserted into a suitable arm vein by a registered nurse or medical practitioner and a zero-time blood sample collected at 07h45. At 08h00 I will receive one capsule of PPA. HCl or placebo (according to the randomisation schedule) with 200 ml of tap water at 08h00 and at 20h00. A 10 ml blood sample will be drawn prior to the first and subsequent doses of PPA according to the experimental schedule.

It is clear to me that for four weeks I will be taking an active capsule of PPA.HCL and for a further four weeks I will be taking an inactive placebo capsule identical to the PPA.HCL capsule in appearance. I will not be told during which phase I will be receiving the active or the placebo capsule.

Blood samples (10 ml) will be collected according to the following schedule :

Week two (day 1) :	07h50, 12h50 and 19h50
Week two (day 2-3) :	07h50 and 19h50
Week two (day 4) :	07h50 and 12h50
Week two (day 7) :	19h50
Week three, four and five (day 4) :	07h50 and 12h50
Week three, four and five (day 7) :	19h50
Week eight (day 1) :	07h50, 12h50 and 19h50
Week eight (day 2-3) :	07h50 and 19h50
Week eight (day 4) :	07h50 and 12h50
Week eight (day 7) :	19h50
Week nine, ten and eleven (day 4) :	07h50 and 12h50
Week nine, ten and eleven (day 7) :	19h50

A TOTAL OF 38 BLOOD SAMPLES FOR THE ENTIRE TRIAL PERIOD.

Note : The procedures for measuring all of the other variables (i.e blood pressure, skinfold thickness, appetite, food intake and salivation) have been explained to me by Miss L.R. Petrie. The sampling times

for the measurement of all of these variables appear in the daily experimental schedule of which I have a copy.

3. The incidence of untoward effects associated with the use of PPA. HCl is low. Phenylpropanolamine hydrochloride has been reported to cause some mild and transient side effects such as headaches, tiredness / lightheadedness, anxiety, insomnia, dry mouth, nausea / vomiting, cramps, heartburn / epigastric pain, frequent urination and in susceptible subjects, to cause an increase in blood pressure, arrhythmias, tachycardia and awareness of heartbeat. The risk of these side effects occurring does increase with the administration of multiple doses.

The insertion of the needle for drawing blood can be painful and a small bruise may develop on my arm and, very rarely a localised infection may occur.

If I do experience any side-effects, I will report them to Miss L. Petrie. If my blood pressure rises above 10 mmHg (diastolic) or above 30 mmHg (systolic) and is sustained over three consecutive measurements of 30 mins, the medical practitioner may decide to withdraw me from the study, or administer a dose of Adalat (10mg) in order to lower my blood pressure.

4. These procedures have no direct benefit to me but information may be obtained concerning the safety and efficacy of PPA. HCl in humans.

5. This information was explained to me by Miss L. Petrie. I understand that she will answer any questions I may have concerning this investigation. If I have any other questions I may ask Dr A. Kench.

6. I will be paid for participating in this study.

7. Participation in this study is voluntary. I have the right to refuse to participate or may withdraw at any time without jeopardy to my standing whatsoever.

Volunteer Name.....Signature.....Date.....

Supervisor Name.....Signature.....Date.....

Witness Name.....Signature.....Date.....

APPENDIX 3MOOD QUESTIONNAIRESTABLE A3.1

The Addiction Research Centre Inventory (ARCI)

INSTRUCTIONS

These 49 items may or may not describe how you feel. Circle the T next to each item number that does describe how you feel, and circle the F next to each item that does not describe how you feel.

- | | | | |
|---|---|-----|--|
| T | F | 1. | My speech is slurred. |
| T | F | 2. | I am not as active as usual. |
| T | F | 3. | I have a feeling of just dragging along rather than coasting. |
| T | F | 4. | I feel sluggish. |
| T | F | 5. | My head feels heavy. |
| T | F | 6. | I feel like avoiding people although I usually do not feel this way. |
| T | F | 7. | I feel dizzy. |
| T | F | 8. | It seems harder than usual to move around. |
| T | F | 9. | I am moody. |
| T | F | 10. | People might say I am a little moody today. |
| T | F | 11. | I feel drowsy. |
| T | F | 12. | I am full of energy. |
| T | F | 13. | Today I say things in the easiest possible way. |
| T | F | 14. | Things around me seem more pleasing than usual. |
| T | F | 15. | I have a pleasant feeling in my stomach. |
| T | F | 16. | I feel I will lose the contentment that I have now. |
| T | F | 17. | I feel in complete harmony with the world and those around me. |
| T | F | 18. | I can completely appreciate what others are saying when I am in this mood. |
| T | F | 19. | I would be happy all the time if I felt as good as I feel now. |
| T | F | 20. | I feel so good that I know other people can tell it. |
| T | F | 21. | I feel as if something pleasant had just happened to me. |
| T | F | 22. | I would be happy all the time if I felt as I do now. |
| T | F | 23. | I feel more clear headed than dreamy. |
| T | F | 24. | I feel as if I would be more popular with people today. |
| T | F | 25. | I feel a very pleasant emptiness. |
| T | F | 26. | My thoughts come more easily than usual. |
| T | F | 27. | I feel less discouraged than usual. |
| T | F | 28. | I am in the mood to talk about the feelings I have. |
| T | F | 29. | I feel more excited than dreamy. |
| T | F | 30. | Answering these questions was very easy today. |
| T | F | 31. | My memory seems sharper to me than usual. |
| T | F | 32. | I feel as if I could write for hours. |
| T | F | 33. | I feel very patient. |
| T | F | 34. | Some parts of my body are tingling. |
| T | F | 35. | I have a weird feeling. |
| T | F | 36. | My movements seem faster than usual. |
| T | F | 37. | I have better control over myself than usual. |
| T | F | 38. | My movements seem slower than usual. |
| T | F | 39. | I find it hard to keep my mind on a task or job. |
| T | F | 40. | I don't feel like reading anything right now. |
| T | F | 41. | It seems I am spending longer than I should on each of these questions. |
| T | F | 42. | My hand feels clumsy. |
| T | F | 43. | I notice my hand shakes when I write. |
| T | F | 44. | I have a disturbance in my stomach. |
| T | F | 45. | I have an increasing awareness of bodily sensations. |
| T | F | 46. | I feel anxious and upset. |
| T | F | 47. | I have unusual weakness of my muscles. |
| T | F | 48. | I thrill has gone through me one or more times since I started this test. |
| T | F | 49. | My movements are free, relaxed, and pleasurable. |

Name _____

Week _____

Day _____

Time _____

TABLE A3.2

The Profile of Mood States (POMS)

INSTRUCTIONS

Here is a list of words and phrases that describe different feelings people have. Please read each word and decide how much you are feeling that way right now: not at all, a little, moderately, quite a bit, or extremely. Circle a number next to the word to show your answer.

Please be sure to circle ONE number - and ONLY ONE number - next to every word on the sheet. Example: The first word is "Friendly". Consider how friendly you have been feeling. If you have not been feeling friendly at all, circle the number "0" to the left of the word "Friendly":

0 1 2 3 4 Friendly

0 for "not at all"
1 for "a little"
2 for "moderately"
3 for "quite a bit"
4 for "extremely"

0 1 2 3 4 Friendly
0 1 2 3 4 Tense
0 1 2 3 4 Happy
0 1 2 3 4 Angry
0 1 2 3 4 Worn out

0 1 2 3 4 Unhappy
0 1 2 3 4 Confused
0 1 2 3 4 Lively
0 1 2 3 4 Unable to concentrate
0 1 2 3 4 Sorry for things done

0 1 2 3 4 Shaky
0 1 2 3 4 Listless
0 1 2 3 4 Overjoyed
0 1 2 3 4 Peeved
0 1 2 3 4 Agreeable

0 1 2 3 4 Sad
0 1 2 3 4 Active
0 1 2 3 4 On edge
0 1 2 3 4 Grouchy
0 1 2 3 4 Fatigued

0 1 2 3 4 Muddled
0 1 2 3 4 Blue
0 1 2 3 4 Energetic
0 1 2 3 4 Spiteful
0 1 2 3 4 Hopeless

0 1 2 3 4 Satisfied
0 1 2 3 4 Panicky
0 1 2 3 4 Helpful
0 1 2 3 4 Unworthy
0 1 2 3 4 Annoyed

0 1 2 3 4 Cheerful
0 1 2 3 4 Exhausted
0 1 2 3 4 Resentful
0 1 2 3 4 Forgiving
0 1 2 3 4 Discouraged

0 for "not at all"
1 for "a little"
2 for "moderately"
3 for "quite a bit"
4 for "extremely"

0 1 2 3 4 Relaxed
0 1 2 3 4 Bewildered
0 1 2 3 4 Sluggish
0 1 2 3 4 Uneasy
0 1 2 3 4 Kindly

0 1 2 3 4 Lonely
0 1 2 3 4 Miserable
0 1 2 3 4 Efficient
0 1 2 3 4 Bitter
0 1 2 3 4 Pleased

0 1 2 3 4 Alert
0 1 2 3 4 Ready to fight
0 1 2 3 4 Restless
0 1 2 3 4 Good-natured
0 1 2 3 4 Gloomy

0 1 2 3 4 Desperate
0 1 2 3 4 Rebellious
0 1 2 3 4 Nervous
0 1 2 3 4 Helpless
0 1 2 3 4 Weary

0 1 2 3 4 Elated
0 1 2 3 4 Forgetful
0 1 2 3 4 Deceived
0 1 2 3 4 Full of pep
0 1 2 3 4 Warm-hearted

0 1 2 3 4 Carefree
0 1 2 3 4 Furious
0 1 2 3 4 Uncertain about things
0 1 2 3 4 Worthless
0 1 2 3 4 Anxious

0 1 2 3 4 Vigorous
0 1 2 3 4 Terrified
0 1 2 3 4 Good-tempered
0 1 2 3 4 Guilty
0 1 2 3 4 Bushed
0 1 2 3 4 Bad-tempered
0 1 2 3 4 Refreshed

Name _____

Week _____

Day _____

Time _____

TABLE A3.3

Visual Analogue Scales (VAS)

INSTRUCTIONS

On this sheet are a series of lines labelled with a mood or feeling And measuring along a continuum from "NOT AT ALL" (on the left) to "EXTREMELY" (on the right). Please make a mark on each line indicating how you feel RIGHT NOW.

NOT AT ALL	EXTREMELY
Stimulated	
High	
Anxious	
Sedated	
Down	
Hungry	

Name _____

Week _____

Day _____

Time _____

APPENDIX 4HUNGER, APPETITE AND SATIETY QUESTIONNAIRESTABLE A4.1Appetite and Hunger Questionnaire (AHQ)INSTRUCTIONS

The following scales are about hunger and appetite. Each scale has a question that must be answered. To answer, place a mark on the line at a point that you consider to be appropriate to the way you feel at the moment. You must answer all of the questions.

1. How hungry do you feel right now?

NOT AT ALL HUNGRY

AS HUNGRY AS YOU HAVE EVER FELT

2. How strong is your urge to eat?

VERY WEAK

VERY STRONG

3. How preoccupied are you with thoughts of food?

NOT AT ALL

EXTREMELY

4. How much food do you think you could eat right now?

NOTHING AT ALL

A LARGE AMOUNT

TABLE A4.2Bodily Sensations Questionnaire (BSQ)INSTRUCTIONS

The following questionnaire is about hunger and appetite. For each heading circle as many answers that you consider to be appropriate to the way you feel at the moment. You may leave out a section, or answer more than once. At the end add any general comments about your usual feelings of hunger and the desire to eat.

1. GASTRIC SENSATIONS

1. feeling of emptiness
2. rumbling
3. ache
4. pain
5. tenseness
6. nausea
7. no gastric sensations signalling hunger

2. MOUTH AND THROAT SENSATIONS

1. emptiness
2. dryness
3. salivation
4. unpleasant taste or sensation
5. pleasant
6. tightness

3. CEREBRAL SENSATIONS

1. headache
2. dizziness
3. faintness
4. spots before the eyes
5. ringing in the ears

4. GENERAL SENSATIONS

1. weakness
2. tiredness
3. restlessness
4. cold
5. warmth
6. muscular spasms

5. MOOD WHEN EATING

1. nervous
2. irritable
3. tense
4. depressed
5. apathetic
6. cheerful
7. excited
8. calm
9. relaxed
10. contented

TABLE A4.3**Satiety Questionnaire (SQ)**INSTRUCTIONS

The following scales are about satiety. Each scale has a question that must be answered. To answer, place a mark on the line at a point that you consider to be appropriate to the way you feel at the moment. You must answer all of the questions.

1. How satiated / full do you feel right now?

NOT AT ALL FULL

UNCOMFORTABLY FULL

2. How strong is your urge to eat after completion of your meal?

VERY WEAK

VERY STRONG

3. How preoccupied are you with thoughts of food?

NOT AT ALL

EXTREMELY

4. How appealing was the food?

NOT AT ALL

EXTREMELY

5. How did the food taste?

VERY BAD

VERY GOOD

6. How much of your favourite food do you think you eat right now?

NOTHING AT ALL

A LARGE AMOUNT

TABLE A4.4**Food Preference Questionnaire (FPQ)**INSTRUCTIONS

This questionnaire is about food preference. The following is a list of common food commodities. Please indicate your preferences by circling the number next to each food item. You may select as many items as you wish. At the end add any additional comments about your food preferences that you feel may be applicable right now.

1. cheddar cheese
2. dried apples
3. white or brown rice
4. roast leg of lamb
5. doughnut
6. canned tuna fish
7. baked potato
8. cooked halibut fish
9. waffles
10. fried or boiled egg
11. raisin bread
12. kippered herring
13. muffins
14. chicken
15. cane sugar

16. turkey, goose or duck
17. cornflakes
18. honey
19. veal cutlet
20. macaroni
21. fried bacon
22. mince pie
23. plain chocolate
24. dried prunes
25. porterhouse steak
26. fried beef liver
27. canned sardines
28. sturgeon caviar
29. kidney beans
30. pork sausage

COMMENTS

TABLE A5.1.1 Daily Body Mass Measurements [Subject 1 (SS)]

Week	Day	Phase 1 (IM A)	Phase 2 (IM B)
		Mean Mass $\pm$ SD (kg)	Mean Mass $\pm$ SD (kg)
One	1	70.67 $\pm$ 0.115	69.40 $\pm$ 0.000
	2	70.60 $\pm$ 0.000	68.93 $\pm$ 0.115
	3	70.06 $\pm$ 0.115	68.53 $\pm$ 0.115
	4	70.40 $\pm$ 0.000	68.53 $\pm$ 0.115
	5	69.47 $\pm$ 0.115	68.73 $\pm$ 0.115
Two	1	70.20 $\pm$ 0.000	68.87 $\pm$ 0.115
	2	69.80 $\pm$ 0.000	69.40 $\pm$ 0.000
	3	70.00 $\pm$ 0.000	68.93 $\pm$ 0.115
	4	70.20 $\pm$ 0.000	68.33 $\pm$ 0.115
	5	69.67 $\pm$ 0.115	68.67 $\pm$ 0.115
Three	1	69.40 $\pm$ 0.000	69.60 $\pm$ 0.000
	2	69.60 $\pm$ 0.000	69.40 $\pm$ 0.000
	3	69.60 $\pm$ 0.000	68.87 $\pm$ 0.115
	4	69.07 $\pm$ 0.115	68.73 $\pm$ 0.115
	5	68.93 $\pm$ 0.115	68.73 $\pm$ 0.115
Four	1	69.47 $\pm$ 0.115	69.40 $\pm$ 0.000
	2	69.00 $\pm$ 0.000	69.87 $\pm$ 0.115
	3	69.27 $\pm$ 0.115	68.87 $\pm$ 0.115
	4	69.27 $\pm$ 0.115	68.47 $\pm$ 0.115
	5	69.27 $\pm$ 0.231	68.47 $\pm$ 0.115
Five	1	69.33 $\pm$ 0.115	68.73 $\pm$ 0.115
	2	69.40 $\pm$ 0.000	68.80 $\pm$ 0.000
	3	68.67 $\pm$ 0.115	68.27 $\pm$ 0.115
	4	69.20 $\pm$ 0.000	68.27 $\pm$ 0.115
	5	68.80 $\pm$ 0.000	68.60 $\pm$ 0.000

TABLE A5.2.1 Weekly Weight Change and Percentage Weight Change [Subject 1 (SS)]

Week (Day 5 - Day 1)	Weight Change (kg)		Percentage Weight Change (%)	
	Phase 1 (IM A)	Phase 2 (IM B)	Phase 1 (IM A)	Phase 2 (IM B)
1	- 1.2	- 0.67	- 1.7	- 0.97
2	- 0.53	- 0.20	- 0.75	- 0.30
3	- 0.47	- 0.87	- 0.68	- 1.25
4	- 0.20	- 0.93	- 0.30	- 1.34
5	- 0.53	- 0.13	- 0.76	- 0.19
Overall Change*	- 1.40	- 0.27	- 1.99	- 0.39

* Overall Change = Week 5 Day 5 - Week 2 Day 1

TABLE A5.1.2 Daily Body Mass Measurements [Subject 2 (CA)]

Week	Day	Phase 1 (IM A)	Phase 2 (IM B)
		Mean Mass $\pm$ SD (kg)	Mean Mass $\pm$ SD (kg)
One	1	61.80 $\pm$ 0.000	62.06 $\pm$ 0.115
	2	61.60 $\pm$ 0.000	62.73 $\pm$ 0.115
	3	61.40 $\pm$ 0.000	62.80 $\pm$ 0.000
	4	61.33 $\pm$ 0.115	63.00 $\pm$ 0.000
	5	61.47 $\pm$ 0.115	62.60 $\pm$ 0.200
Two	1	61.27 $\pm$ 0.115	63.33 $\pm$ 0.115
	2	60.20 $\pm$ 0.200	63.33 $\pm$ 0.115
	3	60.53 $\pm$ 0.115	63.40 $\pm$ 0.200
	4	60.47 $\pm$ 0.115	62.93 $\pm$ 0.115
	5	60.80 $\pm$ 0.000	63.07 $\pm$ 0.115
Three	1	61.13 $\pm$ 0.115	63.07 $\pm$ 0.115
	2	60.73 $\pm$ 0.115	63.40 $\pm$ 0.000
	3	60.87 $\pm$ 0.115	62.87 $\pm$ 0.115
	4	60.73 $\pm$ 0.115	62.80 $\pm$ 0.000
	5	60.93 $\pm$ 0.115	62.67 $\pm$ 0.115
Four	1	61.00 $\pm$ 0.200	63.33 $\pm$ 0.115
	2	61.33 $\pm$ 0.115	63.47 $\pm$ 0.115
	3	61.40 $\pm$ 0.200	62.53 $\pm$ 0.115
	4	61.33 $\pm$ 0.115	63.07 $\pm$ 0.115
	5	61.20 $\pm$ 0.200	63.80 $\pm$ 0.000
Five	1	60.60 $\pm$ 0.000	63.67 $\pm$ 0.115
	2	60.73 $\pm$ 0.115	64.07 $\pm$ 0.115
	3	60.40 $\pm$ 0.000	63.60 $\pm$ 0.000
	4	60.33 $\pm$ 0.115	63.80 $\pm$ 0.000
	5	60.53 $\pm$ 0.115	63.27 $\pm$ 0.115

TABLE A5.2.2 Weekly Weight Change and Percentage Weight Change [Subject 2 (CA)]

Week (Day 5 - Day 1)	Weight Change (kg)		Percentage Weight Change (%)	
	Phase 1 (IM A)	Phase 2 (IM B)	Phase 1 (IM A)	Phase 2 (IM B)
1	- 0.33	+ 0.54	- 0.53	+ 1.61
2	- 0.47	- 0.26	- 0.77	- 0.41
3	- 0.20	- 0.40	- 0.33	- 0.63
4	+ 0.20	+ 0.47	+ 0.33	+ 0.74
5	- 0.07	- 0.40	- 0.12	- 0.63
Overall Change*	- 0.74	- 0.06	- 1.21	- 0.09

* Overall Change = Week 5 Day 5 - Week 2 Day 1

TABLE A5.1.3

Daily Body Mass Measurements [Subject 3 (LE)]

Week	Day	Phase 1 (IM B)	Phase 2 (IM A)
		Mean Mass $\pm$ SD (kg)	Mean Mass $\pm$ SD (kg)
One	1	77.00 $\pm$ 0.000	76.53 $\pm$ 0.115
	2	77.00 $\pm$ 0.200	75.6 $\pm$ 0.115
	3	77.00 $\pm$ 0.000	76.5 $\pm$ 0.115
	4	76.73 $\pm$ 0.115	76.60 $\pm$ 0.000
	5	76.13 $\pm$ 0.115	76.13 $\pm$ 0.231
Two	1	76.40 $\pm$ 0.200	76.20 $\pm$ 0.000
	2	76.67 $\pm$ 0.115	75.67 $\pm$ 0.115
	3	76.13 $\pm$ 0.115	75.60 $\pm$ 0.000
	4	75.93 $\pm$ 0.115	76.33 $\pm$ 0.115
	5	75.80 $\pm$ 0.200	75.73 $\pm$ 0.115
Three	1	77.20 $\pm$ 0.000	75.20 $\pm$ 0.000
	2	77.07 $\pm$ 0.115	76.27 $\pm$ 0.115
	3	77.33 $\pm$ 0.115	75.33 $\pm$ 0.115
	4	76.80 $\pm$ 0.000	75.33 $\pm$ 0.115
	5	75.80 $\pm$ 0.200	74.60 $\pm$ 0.000
Four	1	76.27 $\pm$ 0.305	74.13 $\pm$ 0.115
	2	77.00 $\pm$ 0.000	74.00 $\pm$ 0.000
	3	77.07 $\pm$ 0.115	73.67 $\pm$ 0.115
	4	76.73 $\pm$ 0.115	73.60 $\pm$ 0.000
	5	76.40 $\pm$ 0.000	74.27 $\pm$ 0.115
Five	1	77.07 $\pm$ 0.115	74.27 $\pm$ 0.115
	2	76.20 $\pm$ 0.000	74.33 $\pm$ 0.115
	3	76.13 $\pm$ 0.115	74.00 $\pm$ 0.000
	4	76.53 $\pm$ 0.115	73.40 $\pm$ 0.000
	5	75.20 $\pm$ 0.000	73.27 $\pm$ 0.115

TABLE A5.2.3

Weekly Weight Change and Percentage Weight Change [Subject 3 (LE)]

Week (Day 5 - Day 1)	Weight Change (kg)		Percentage Weight Change (%)	
	Phase 1 (IM B)	Phase 2 (IM A)	Phase 1 (IM B)	Phase 2 (IM A)
1	- 0.87	- 0.40	- 1.13	- 0.52
2	- 0.60	- .047	- 0.79	- 0.62
3	- 1.40	- 1.67	- 1.81	- 2.19
4	+ 0.13	+ 0.14	+ 0.17	+ 0.19
5	- 1.87	- 1.00	- 2.43	- 1.35
Overall Change*	- 1.20	- 2.93	- 1.57	- 3.85

* Overall Change - Week 5 Day 5 - Week 2 Day 1

TABLE A5.1.4

Daily Body Mass Measurements [Subject 4 (EA)]

Week	Day	Phase 1 (IM B)	Phase 2 (IM A)
		Mean Mass $\pm$ SD (kg)	Mean Mass $\pm$ SD (kg)
One	1	65.73 $\pm$ 0.115	63.93 $\pm$ 0.115
	2	65.67 $\pm$ 0.115	63.73 $\pm$ 0.115
	3	65.87 $\pm$ 0.231	62.73 $\pm$ 0.115
	4	65.67 $\pm$ 0.115	63.73 $\pm$ 0.115
	5	65.60 $\pm$ 0.000	63.00 $\pm$ 0.000
Two	1	65.80 $\pm$ 0.000	62.73 $\pm$ 0.115
	2	65.53 $\pm$ 0.115	62.53 $\pm$ 0.115
	3	65.60 $\pm$ 0.000	62.33 $\pm$ 0.115
	4	65.20 $\pm$ 0.200	62.33 $\pm$ 0.115
	5	65.00 $\pm$ 0.000	61.87 $\pm$ 0.115
Three	1	65.73 $\pm$ 0.115	61.93 $\pm$ 0.115
	2	65.73 $\pm$ 0.115	61.20 $\pm$ 0.000
	3	65.07 $\pm$ 0.115	60.93 $\pm$ 0.115
	4	64.80 $\pm$ 0.000	61.00 $\pm$ 0.000
	5	64.40 $\pm$ 0.000	60.73 $\pm$ 0.115
Four	1	64.80 $\pm$ 0.000	60.93 $\pm$ 0.115
	2	64.47 $\pm$ 0.115	61.13 $\pm$ 0.115
	3	64.07 $\pm$ 0.115	60.53 $\pm$ 0.115
	4	63.60 $\pm$ 0.200	60.20 $\pm$ 0.000
	5	63.87 $\pm$ 0.115	60.13 $\pm$ 0.115
Five	1	64.40 $\pm$ 0.000	60.80 $\pm$ 0.000
	2	63.67 $\pm$ 0.115	61.07 $\pm$ 0.115
	3	63.27 $\pm$ 0.115	60.00 $\pm$ 0.000
	4	62.93 $\pm$ 0.115	60.20 $\pm$ 0.000
	5	63.33 $\pm$ 0.115	59.73 $\pm$ 0.115

TABLE A5.2.4

Weekly Weight Change and Percentage Weight Change [Subject 4 (EA)]

Week (Day 5 - Day 1)	Weight Change (kg)		Percentage Weight Change (%)	
	Phase 1 (IM B)	Phase 2 (IM A)	Phase 1 (IM B)	Phase 2 (IM A)
1	+ 0.07	- 0.93	+ 0.11	- 1.45
2	- 0.80	- 0.86	- 1.22	- 1.37
3	- 1.33	- 1.20	- 2.02	- 1.94
4	- 0.93	- 0.80	- 1.44	- 1.31
5	- 1.07	- 1.07	- 1.66	- 1.66
Overall Change*	- 2.38	- 3.00	- 3.63	- 4.78

* Overall Change - Week 5 Day 5 - Week 2 Day 1

TABLE A5.1.5

Daily Body Mass Measurements [Subject 5 (VM)]

Week	Day	Phase 1 (IM B)	Phase 2 (IM A)
		Mean Mass $\pm$ SD (kg)	Mean Mass $\pm$ SD (kg)
One	1	72.80 $\pm$ 0.000	70.80 $\pm$ 0.000
	2	73.00 $\pm$ 0.200	70.80 $\pm$ 0.000
	3	72.87 $\pm$ 0.115	70.67 $\pm$ 0.115
	4	72.80 $\pm$ 0.200	71.27 $\pm$ 0.115
	5	72.80 $\pm$ 0.000	70.67 $\pm$ 0.115
Two	1	71.93 $\pm$ 0.115	71.53 $\pm$ 0.115
	2	71.40 $\pm$ 0.000	71.20 $\pm$ 0.000
	3	71.27 $\pm$ 0.115	70.80 $\pm$ 0.000
	4	71.60 $\pm$ 0.000	70.80 $\pm$ 0.200
	5	71.80 $\pm$ 0.000	71.00 $\pm$ 0.200
Three	1	71.40 $\pm$ 0.000	70.67 $\pm$ 0.115
	2	71.60 $\pm$ 0.000	70.60 $\pm$ 0.000
	3	71.60 $\pm$ 0.000	70.73 $\pm$ 0.115
	4	71.40 $\pm$ 0.000	71.13 $\pm$ 0.115
	5	71.20 $\pm$ 0.000	70.80 $\pm$ 0.000
Four	1	71.13 $\pm$ 0.115	71.00 $\pm$ 0.200
	2	71.67 $\pm$ 0.115	70.80 $\pm$ 0.200
	3	71.87 $\pm$ 0.115	70.13 $\pm$ 0.115
	4	71.40 $\pm$ 0.000	70.80 $\pm$ 0.200
	5	71.80 $\pm$ 0.000	70.40 $\pm$ 0.000
Five	1	71.47 $\pm$ 0.115	69.73 $\pm$ 0.115
	2	70.40 $\pm$ 0.000	69.60 $\pm$ 0.000
	3	70.33 $\pm$ 0.115	69.47 $\pm$ 0.115
	4	70.87 $\pm$ 0.115	70.07 $\pm$ 0.115
	5	70.67 $\pm$ 0.115	69.53 $\pm$ 0.115

TABLE A5.2.5

Weekly Weight Change and Percentage Weight Change [Subject 5 (VM)]

Week (Day 5 - Day 1)	Weight Change (kg)		Percentage Weight Change (%)	
	Phase 1 (IM B)	Phase 2 (IM A)	Phase 1 (IM B)	Phase 2 (IM A)
1	0.00	- 0.13	0.00	- 0.18
2	- 0.13	- 0.53	- 0.18	- 0.74
3	- 0.20	+ 0.13	- 0.28	+ 0.18
4	+ 0.67	- 0.60	+ 0.94	- 0.85
5	- 0.80	- 0.20	- 1.12	- 0.29
Overall Change*	- 1.26	- 2.00	- 1.75	- 2.80

* Overall Change = Week 5 Day 5 - Week 2 Day 1

TABLE A5.1.6

Daily Body Mass Measurements [Subject 6 (LI)]

Week	Day	Phase 1 (IM B)	Phase 2 (IM A)
		Mean Mass $\pm$ SD (kg)	Mean Mass $\pm$ SD (kg)
One	1	81.20 $\pm$ 0.000	81.60 $\pm$ 0.000
	2	81.53 $\pm$ 0.115	81.47 $\pm$ 0.115
	3	81.47 $\pm$ 0.115	80.40 $\pm$ 0.000
	4	81.69 $\pm$ 0.231	80.60 $\pm$ 0.000
	5	81.20 $\pm$ 0.231	81.93 $\pm$ 0.115
Two	1	81.07 $\pm$ 0.115	82.13 $\pm$ 0.115
	2	80.87 $\pm$ 0.115	81.07 $\pm$ 0.115
	3	81.07 $\pm$ 0.306	80.40 $\pm$ 0.000
	4	80.93 $\pm$ 0.115	80.47 $\pm$ 0.115
	5	81.07 $\pm$ 0.115	80.53 $\pm$ 0.115
Three	1	81.00 $\pm$ 0.346	80.60 $\pm$ 0.000
	2	81.00 $\pm$ 0.346	80.20 $\pm$ 0.000
	3	81.07 $\pm$ 0.115	80.00 $\pm$ 0.000
	4	81.27 $\pm$ 0.231	80.07 $\pm$ 0.115
	5	81.27 $\pm$ 0.115	79.87 $\pm$ 0.115
Four	1	80.73 $\pm$ 0.115	79.93 $\pm$ 0.115
	2	80.73 $\pm$ 0.115	79.53 $\pm$ 0.115
	3	80.33 $\pm$ 0.115	79.47 $\pm$ 0.115
	4	79.87 $\pm$ 0.115	79.20 $\pm$ 0.000
	5	80.67 $\pm$ 0.115	78.47 $\pm$ 0.231
Five	1	81.93 $\pm$ 0.115	78.73 $\pm$ 0.115
	2	81.40 $\pm$ 0.000	79.40 $\pm$ 0.000
	3	80.80 $\pm$ 0.200	79.27 $\pm$ 0.115
	4	80.93 $\pm$ 0.115	79.00 $\pm$ 0.000
	5	81.20 $\pm$ 0.000	78.87 $\pm$ 0.115

TABLE A5.2.6

Weekly Weight Change and Percentage Weight Change [Subject 6 (LI)]

Week (Day 5 - Day 1)	Weight Change (kg)		Percentage Weight Change (%)	
	Phase 1 (IM B)	Phase 2 (IM A)	Phase 1 (IM B)	Phase 2 (IM A)
1	0.00	+ 0.33	0.00	+ 0.40
2	0.00	- 1.60	0.00	- 1.95
3	+ 0.27	- 0.73	+ 0.33	- 0.91
4	- 0.06	- 1.46	- 0.07	- 1.83
5	- 0.73	+ 0.14	- 0.89	+ 0.18
Overall Change*	+ 0.13	- 3.26	+ 0.16	- 3.97

* Overall Change = Week 5 Day 5 - Week 2 Day 1

TABLE A5.1.7

Daily Body Mass Measurements [Subject 7 (EG)]

Week	Day	Phase 1 (TM A)	Phase 2 (TM B)
		Mean Mass $\pm$ SD (kg)	Mean Mass $\pm$ SD (kg)
One	1	62.40 $\pm$ 0.000	60.80 $\pm$ 0.000
	2	62.40 $\pm$ 0.000	60.87 $\pm$ 0.115
	3	62.53 $\pm$ 0.115	60.73 $\pm$ 0.115
	4	62.80 $\pm$ 0.000	60.40 $\pm$ 0.000
	5	62.73 $\pm$ 0.115	60.93 $\pm$ 0.115
Two	1	62.00 $\pm$ 0.200	60.80 $\pm$ 0.000
	2	61.67 $\pm$ 0.115	60.93 $\pm$ 0.115
	3	61.87 $\pm$ 0.115	60.80 $\pm$ 0.000
	4	62.20 $\pm$ 0.000	60.60 $\pm$ 0.000
	5	61.80 $\pm$ 0.000	61.40 $\pm$ 0.000
Three	1	61.93 $\pm$ 0.115	60.93 $\pm$ 0.115
	2	62.00 $\pm$ 0.000	61.20 $\pm$ 0.000
	3	61.60 $\pm$ 0.000	61.13 $\pm$ 0.115
	4	61.40 $\pm$ 0.200	60.075
	5	61.27 $\pm$ 0.115	60.87 $\pm$ 0.115
Four	1		60.60 $\pm$ 0.000
	2		61.07 $\pm$ 0.115
	3		60.33 $\pm$ 0.115
	4		60.67 $\pm$ 0.115
	5		60.53 $\pm$ 0.115
Five	1		60.93 $\pm$ 0.115
	2		60.60 $\pm$ 0.000
	3		61.40 $\pm$ 0.000
	4		60.93 $\pm$ 0.115
	5		60.67 $\pm$ 0.115

TABLE A5.2.7

Weekly Weight Change and Percentage Weight Change [Subject 7 (EG)]

Week (Day 5 - Day 1)	Weight Change (kg)		Percentage Weight Change (%)	
	Phase 1 (TM A)	Phase 2 (TM B)	Phase 1 (TM A)	Phase 2 (TM B)
1	+ 0.33	+ 0.13	+ 0.53	+ 0.21
2	- 0.20	+ 0.60	- 0.32	+ 0.99
3	- 0.66	- 0.06	- 1.07	- 0.1
4		- 0.07		- 0.12
5		- 0.26		- 0.43
Overall Change*	- 0.73	+ 0.07	- 1.18	+ 0.12

* Overall Change = Week 3 Day 5 - Week 2 Day 1

TABLE A5.1.8

Daily Body Mass Measurements [Subject 8 (CV)]

Week	Day	Phase 1 (TM A)	Phase 2 (TM B)
		Mean Mass $\pm$ SD (kg)	Mean Mass $\pm$ SD (kg)
One	1	66.60 $\pm$ 0.000	62.47 $\pm$ 0.115
	2	66.33 $\pm$ 0.115	61.80 $\pm$ 0.000
	3	66.47 $\pm$ 0.115	61.73 $\pm$ 0.115
	4	66.60 $\pm$ 0.200	61.80 $\pm$ 0.000
	5	66.53 $\pm$ 0.115	61.80 $\pm$ 0.000
Two	1	66.27 $\pm$ 0.306	
	2	65.27 $\pm$ 0.115	
	3	65.00 $\pm$ 0.200	
	4	64.53 $\pm$ 0.115	
	5	64.07 $\pm$ 0.115	
Three	1	64.13 $\pm$ 0.115	
	2	64.07 $\pm$ 0.115	
	3	63.60 $\pm$ 0.000	
	4	63.13 $\pm$ 0.115	
	5	62.80 $\pm$ 0.000	
Four	1	63.53 $\pm$ 0.115	
	2	63.00 $\pm$ 0.000	
	3	63.40 $\pm$ 0.000	
	4	63.80 $\pm$ 0.000	
	5	63.40 $\pm$ 0.000	
Five	1	63.00 $\pm$ 0.000	
	2	62.87 $\pm$ 0.115	
	3	62.93 $\pm$ 0.115	
	4	62.60 $\pm$ 0.000	
	5	62.53 $\pm$ 0.115	

TABLE A5.2.8

Weekly Weight Change and Percentage Weight Change [Subject 8 (CV)]

Week (Day 5 - Day 1)	Weight Change (kg)		Percentage Weight Change (%)	
	Phase 1 (TM A)	Phase 2 (TM B)	Phase 1 (TM A)	Phase 2 (TM B)
1	- 0.07	- 0.67	- 0.11	- 1.07
2	- 2.20		- 3.32	
3	- 1.33		- 2.07	
4	- 0.13		- 0.21	
5	- 0.47		- 0.75	
Overall Change*	- 3.74		- 5.64	

* Overall Change = Week 5 Day 5 - Week 2 Day 1

Week	TM A $\pm$ SEM	F Ratio	P	TM B $\pm$ SEM	F Ratio	P
1	69.44 $\pm$ 1.186	0.19	0.9427	69.86 $\pm$ 1.202	0.06	0.8092
2	68.97 $\pm$ 1.223			69.59 $\pm$ 1.146		
3	68.47 $\pm$ 1.210			69.66 $\pm$ 1.172		
4	68.06 $\pm$ 1.152			69.40 $\pm$ 1.166		
5	68.78 $\pm$ 1.250			70.66 $\pm$ 1.195		

n = 65, df = 1,68

TABLE A5.3.1 Average Body Mass per Week (Mean Values for 7 Subjects)

Week	TM A $\pm$ SEM	F	P	TM B $\pm$ SEM	F	P
1	-0.33 $\pm$ 0.22	0.51	0.7267	-0.11 $\pm$ 0.18	0.58	0.4691
2	-0.67 $\pm$ 0.17			-0.20 $\pm$ 0.17		
3	-0.69 $\pm$ 0.23			-0.57 $\pm$ 0.24		
4	-0.45 $\pm$ 0.26			-0.11 $\pm$ 0.28		
5	-0.46 $\pm$ 0.20			-0.83 $\pm$ 0.25		

n = 13, df = 4,31

TABLE A5.3.2 Average Weekly Weight Loss (Mean Values for 7 Subjects)

Week	TM A $\pm$ SEM	F	P	TM B $\pm$ SEM	F	P
1	-0.49 $\pm$ 0.32	0.51	0.7320	-0.02 $\pm$ 0.34	1.01	0.3360
2	-0.93 $\pm$ 0.21			-0.27 $\pm$ 0.26		
3	-0.99 $\pm$ 0.32			-0.82 $\pm$ 0.34		
4	-0.63 $\pm$ 0.35			-0.17 $\pm$ 0.42		
5	-0.68 $\pm$ 0.31			-1.25 $\pm$ 0.28		

n = 13, df = 4,31

TABLE A5.3.3 Average Weekly Percent Weight Loss (Mean Values for 7 Subjects)

Subj	Week	TM A $\pm$ SEM	MRI	F Ratio	P	TM B $\pm$ SEM	MRI	F Ratio	P
1	1	70.24 $\pm$ 0.220	"	12.03 [†]	0.0000	68.82 $\pm$ 0.162	"	26.91 [†]	0.0000
	2	69.97 $\pm$ 0.106	"			68.84 $\pm$ 0.175	"		
	3	69.32 $\pm$ 0.137	"			69.07 $\pm$ 0.182	"		
	4	69.26 $\pm$ 0.075	"			69.02 $\pm$ 0.273	"		
	5	69.08 $\pm$ 0.146	"			68.53 $\pm$ 0.112	"		
2	1	61.52 $\pm$ 0.083	"	15.71 [†]	0.0000	62.64 $\pm$ 0.158	"	39.12 [†]	0.0002
	2	60.65 $\pm$ 0.181	"			63.21 $\pm$ 0.090	"		
	3	60.88 $\pm$ 0.074	"			62.96 $\pm$ 0.127	"		
	4	61.25 $\pm$ 0.071	"			63.24 $\pm$ 0.213	"		
	5	60.52 $\pm$ 0.071	"			63.68 $\pm$ 0.131	"		
3	1	76.29 $\pm$ 0.176	"	33.10 [†]	0.0000	76.77 $\pm$ 0.169	"	3.07	0.0048
	2	75.91 $\pm$ 0.149	"			76.19 $\pm$ 0.158	"		
	3	75.35 $\pm$ 0.268	"			76.84 $\pm$ 0.274	"		
	4	73.94 $\pm$ 0.130	"			76.69 $\pm$ 0.159	"		
	5	73.84 $\pm$ 0.220	"			76.23 $\pm$ 0.306	"		
4	1	63.42 $\pm$ 0.235	"	37.91 [†]	0.0000	65.75 $\pm$ 0.039	"	95.19 [†]	0.0000
	2	62.36 $\pm$ 0.143	"			65.39 $\pm$ 0.106	"		
	3	61.16 $\pm$ 0.207	"			65.15 $\pm$ 0.137	"		
	4	60.58 $\pm$ 0.197	"			64.16 $\pm$ 0.075	"		
	5	60.36 $\pm$ 0.250	"			63.52 $\pm$ 0.146	"		
5	1	70.84 $\pm$ 0.111	"	19.04 [†]	0.0000	72.85 $\pm$ 0.039	"	293.13 [†]	0.0000
	2	71.07 $\pm$ 0.138	"			71.60 $\pm$ 0.122	"		
	3	70.79 $\pm$ 0.092	"			71.44 $\pm$ 0.075	"		
	4	70.63 $\pm$ 0.158	"			71.57 $\pm$ 0.137	"		
	5	69.68 $\pm$ 0.107	"			70.75 $\pm$ 0.205	"		
6	1	81.20 $\pm$ 0.297	"	15.79 [†]	0.0000	81.41 $\pm$ 0.093	"	0.47	0.5185
	2	80.92 $\pm$ 0.325	"			81.00 $\pm$ 0.042	"		
	3	80.15 $\pm$ 0.125	"			81.12 $\pm$ 0.062	"		
	4	79.32 $\pm$ 0.242	"			80.47 $\pm$ 0.166	"		
	5	79.05 $\pm$ 0.124	"			81.25 $\pm$ 0.199	"		

The mean mass for week 1 for both treatments are given in the body of the table. For week 1, n=5 for each subject per phase, df = 1,89. For comparison of the treatment weeks (2-5) with week 1, n = 25, df = 4,23. The *'s in the MRI columns indicate where the differences in weeks occurred. † indicates a P value of less than 0.01

TABLE A5.3.4 Average Weekly Mass per Volunteer

TABLE A6.1

Skinfold Thickness Measurements [Subject 1 (SS)]

Week	Skinfold Thickness Measurement	Phase 1 (TH A)				Phase 2 (TH B)			
		1	2	3	Mean (mm) $\pm$ SD	1	2	3	Mean (mm) $\pm$ SD
1	Triceps	20.0	20.5	19.5	20.0 $\pm$ 0.5				
	Supra-iliac	12.0	12.0	11.5	11.8 $\pm$ 0.3				
	Thigh	42.0	42.0	42.5	42.2 $\pm$ 0.3				
2	Triceps	24.0	24.0	24.5	24.2 $\pm$ 0.3	24.0	24.0	25.0	24.3 $\pm$ 0.6
	Supra-iliac	8.5	8.5	9.0	8.7 $\pm$ 0.3	7.0	7.5	7.5	7.2 $\pm$ 0.3
	Thigh	41.0	40.5	40.5	40.7 $\pm$ 0.3	38.0	38.5	39.0	38.5 $\pm$ 0.5
3	Triceps	24.0	24.0	24.5	24.2 $\pm$ 0.3	25.0	24.5	24.0	24.5 $\pm$ 0.5
	Supra-iliac	10.0	10.5	11.5	10.5 $\pm$ 0.5	8.0	8.0	8.5	8.8 $\pm$ 0.3
	Thigh	41.5	42.0	41.5	41.5 $\pm$ 0.3	37.0	38.0	38.5	37.8 $\pm$ 0.8
4	Triceps								
	Supra-iliac								
	Thigh								
5	Triceps	24.0	24.5	24.5	24.3 $\pm$ 0.3	25.0	24.5	24.5	24.7 $\pm$ 0.3
	Supra-iliac	7.5	7.5	8.0	7.7 $\pm$ 0.3	7.0	7.0	7.5	7.2 $\pm$ 0.3
	Thigh	44.0	43.5	43.0	43.5 $\pm$ 0.5	37.0	37.0	37.5	37.2 $\pm$ 0.3

TABLE A6.2

Skinfold Thickness Measurements [Subject 2 (CA)]

Week	Skinfold Thickness Measurement	Phase 1 (TH A)				Phase 2 (TH B)			
		1	2	3	Mean (mm) $\pm$ SD	1	2	3	Mean (mm) $\pm$ SD
1	Triceps	23.0	23.0	23.0	23.0 $\pm$ 0.0				
	Supra-iliac	19.0	19.0	20.5	19.5 $\pm$ 0.3				
	Thigh	43.0	43.5	44.0	43.5 $\pm$ 0.5				
2	Triceps	24.5	24.5	25.0	24.7 $\pm$ 0.3	25.0	25.0	25.0	25.0 $\pm$ 0.0
	Supra-iliac	20.0	20.0	19.0	19.6 $\pm$ 0.3	20.5	20.5	21.0	20.7 $\pm$ 0.3
	Thigh	43.0	44.0	44.5	43.8 $\pm$ 0.8	42.0	42.0	42.5	42.2 $\pm$ 0.3
3	Triceps	24.5	24.5	25.0	24.7 $\pm$ 0.3	25.0	25.5	25.0	25.2 $\pm$ 0.3
	Supra-iliac	22.5	22.0	22.0	22.2 $\pm$ 0.3	21.5	22.0	22.0	21.8 $\pm$ 0.3
	Thigh	46.0	46.0	46.5	46.2 $\pm$ 0.3	44.0	43.5	43.0	43.5 $\pm$ 0.5
4	Triceps								
	Supra-iliac								
	Thigh								
5	Triceps	24.5	25.0	25.0	24.8 $\pm$ 0.3				
	Supra-iliac	19.0	19.5	20.0	19.5 $\pm$ 0.5				
	Thigh	45.5	45.5	46.0	45.7 $\pm$ 0.3				

TABLE A6.3

Skinfold Thickness Measurements [Subject 3 (LE)]

Week	Skinfold Thickness Measurement	Phase 1 (TH B)				Phase 2 (TH A)			
		1	2	3	Mean (mm) $\pm$ SD	1	2	3	Mean (mm) $\pm$ SD
1	Triceps	24.5	24.5	25.0	24.7 $\pm$ 0.3				
	Supra-iliac	10.0	10.0	9.5	9.8 $\pm$ 0.3				
	Thigh	40.0	40.5	40.5	40.3 $\pm$ 0.3				
2	Triceps	26.0	26.0	25.5	25.8 $\pm$ 0.3	26.0	25.5	25.0	25.5 $\pm$ 0.5
	Supra-iliac	13.5	14.0	14.5	14.0 $\pm$ 0.5	12.5	12.5	13.5	12.8 $\pm$ 0.6
	Thigh	43.0	42.0	43.5	43.2 $\pm$ 0.3	44.0	44.0	44.5	44.3 $\pm$ 0.3
3	Triceps	24.0	24.0	24.5	24.2 $\pm$ 0.3	26.0	25.5	26.0	25.8 $\pm$ 0.3
	Supra-iliac	12.5	12.5	13.0	12.7 $\pm$ 0.3	13.0	13.0	13.5	13.2 $\pm$ 0.3
	Thigh	42.0	42.5	43.0	42.5 $\pm$ 0.5	42.0	43.5	43.0	43.0 $\pm$ 0.5
4	Triceps								
	Supra-iliac								
	Thigh								
5	Triceps					25.5	25.0	26.0	25.5 $\pm$ 0.5
	Supra-iliac					12.5	12.0	11.5	12.0 $\pm$ 0.5
	Thigh					41.5	41.5	41.0	41.3 $\pm$ 0.3

TABLE A6.4

Skinfold Thickness Measurements [Subject 4 (EA)]

Week	Skinfold Thickness Measurement	Phase 1 (TH B)				Phase 2 (TH A)			
		1	2	3	Mean (mm) $\pm$ SD	1	2	3	Mean (mm) $\pm$ SD
1	Triceps	25.0	25.0	25.0	25.0 $\pm$ 0.5				
	Supra-iliac	17.0	17.5	17.5	17.3 $\pm$ 0.3				
	Thigh	36.0	36.5	36.5	36.3 $\pm$ 0.3				
2	Triceps	27.0	27.0	27.5	27.2 $\pm$ 0.3	17.5	16.0	16.5	16.7 $\pm$ 0.8
	Supra-iliac	16.5	16.0	16.0	16.2 $\pm$ 0.3	12.0	12.0	12.5	12.2 $\pm$ 0.3
	Thigh	37.0	38.0	38.0	37.7 $\pm$ 0.6	34.0	34.0	34.5	29.2 $\pm$ 0.3
3	Triceps	19.5	20.0	20.5	20.0 $\pm$ 0.0	15.5	15.5	16.0	15.7 $\pm$ 0.3
	Supra-iliac	15.5	16.0	16.5	16.0 $\pm$ 0.5	11.5	11.5	11.0	11.3 $\pm$ 0.3
	Thigh	37.0	37.0	37.5	37.2 $\pm$ 0.3	34.0	34.0	34.5	34.2 $\pm$ 0.3
4	Triceps								
	Supra-iliac								
	Thigh								
5	Triceps	24.5	24.0	24.5	24.3 $\pm$ 0.3	15.0	15.5	15.5	15.3 $\pm$ 0.3
	Supra-iliac	16.0	16.0	16.0	16.0 $\pm$ 0.0	8.5	8.5	9.0	8.8 $\pm$ 0.3
	Thigh	39.0	38.5	39.0	38.8 $\pm$ 0.3	32.0	32.0	32.5	32.2 $\pm$ 0.3

TABLE A6.5

Skinfold Thickness Measurements [Subject 5 (VW)]

Week	Skinfold Thickness Measurement	Phase 1 (TM B)				Phase 2 (TM A)			
		1	2	3	Mean (mm) $\pm$ SD	1	2	3	Mean (mm) $\pm$ SD
1	Triceps	23.0	23.0	22.5	22.8 $\pm$ 0.3				
	Supra-iliac	21.0	21.0	22.0	21.3 $\pm$ 0.6				
	Thigh	37.0	37.0	37.5	37.2 $\pm$ 0.3				
2	Triceps	25.0	25.0	25.0	25.0 $\pm$ 0.0	20.0	20.0	20.5	20.2 $\pm$ 0.3
	Supra-iliac	19.0	19.0	20.0	19.3 $\pm$ 0.6	20.0	20.5	21.0	19.2 $\pm$ 0.3
	Thigh	40.5	41.5	42.0	36.8 $\pm$ 0.3	37.5	38.0	39.0	31.5 $\pm$ 0.5
3	Triceps	25.0	25.0	25.0	25.0 $\pm$ 0.0	20.5	20.0	20.0	20.5 $\pm$ 0.5
	Supra-iliac	19.5	20.0	20.5	20.0 $\pm$ 0.5	20.5	21.0	20.0	17.2 $\pm$ 0.3
	Thigh	34.5	35.0	34.5	34.7 $\pm$ 0.3	30.5	30.5	30.0	30.3 $\pm$ 0.3
4	Triceps								
	Supra-iliac								
	Thigh								
5	Triceps	25.5	25.5	25.0	25.3 $\pm$ 0.3	20.0	20.0	20.5	20.2 $\pm$ 0.3
	Supra-iliac	21.5	21.0	22.0	21.5 $\pm$ 0.3	17.0	18.0	17.5	17.5 $\pm$ 0.5
	Thigh	36.5	36.5	37.0	36.7 $\pm$ 0.3	30.5	30.0	30.0	30.2 $\pm$ 0.3

TABLE A6.6

Skinfold Thickness Measurements [Subject 6 (LI)]

Week	Skinfold Thickness Measurement	Phase 1 (TM B)				Phase 2 (TM A)			
		1	2	3	Mean (mm) $\pm$ SD	1	2	3	Mean (mm) $\pm$ SD
1	Triceps	36.0	36.0	36.5	36.2 $\pm$ 0.3				
	Supra-iliac	27.5	28.0	28.5	28.0 $\pm$ 0.5				
	Thigh	46.5	45.0	46.0	45.8 $\pm$ 0.8				
2	Triceps	34.5	34.5	34.0	34.3 $\pm$ 0.3	35.5	35.5	36.0	35.5 $\pm$ 0.5
	Supra-iliac	26.5	27.0	27.0	26.8 $\pm$ 0.3	24.0	24.5	25.0	24.5 $\pm$ 0.5
	Thigh	47.5	47.0	47.5	47.2 $\pm$ 0.3	43.0	44.0	43.5	43.5 $\pm$ 0.5
3	Triceps					33.0	33.0	33.0	33.0 $\pm$ 0.0
	Supra-iliac					21.5	22.0	23.0	22.2 $\pm$ 0.8
	Thigh					41.0	41.5	41.5	41.3 $\pm$ 0.3
4	Triceps								
	Supra-iliac								
	Thigh								
5	Triceps	35.5	35.0	36.0	35.5 $\pm$ 0.5				
	Supra-iliac	25.5	24.0	25.0	24.8 $\pm$ 0.8				
	Thigh	45.0	44.5	45.0	44.8 $\pm$ 0.3				

TABLE A6.7

Skinfold Thickness Measurements [Subject 7 (EG)]

Week	Skinfold Thickness Measurement	Phase 1 (TM A)				Phase 2 (TM B)			
		1	2	3	Mean (mm) $\pm$ SD	1	2	3	Mean (mm) $\pm$ SD
1	Triceps	24.0	24.0	24.5	24.3 $\pm$ 0.6				
	Supra-iliac	19.0	18.0	18.5	18.5 $\pm$ 0.5				
	Thigh	30.0	30.5	31.0	30.5 $\pm$ 0.5				
2	Triceps	22.0	21.5	22.0	21.8 $\pm$ 0.3	22.5	23.0	23.0	22.8 $\pm$ 0.3
	Supra-iliac	16.5	17.0	17.5	16.5 $\pm$ 0.5	13.5	14.0	14.5	14.0 $\pm$ 0.5
	Thigh	37.5	38.0	38.5	38.0 $\pm$ 0.5	33.5	34.0	34.5	34.0 $\pm$ 0.5
3	Triceps	23.0	23.5	24.0	23.5 $\pm$ 0.5	23.5	24.0	24.0	23.8 $\pm$ 0.8
	Supra-iliac	16.0	16.0	16.5	16.2 $\pm$ 0.3	14.0	14.0	13.5	13.8 $\pm$ 0.3
	Thigh	37.0	37.5	38.0	37.5 $\pm$ 0.5	37.5	37.5	38.0	37.7 $\pm$ 0.3
4	Triceps								
	Supra-iliac								
	Thigh								
5	Triceps					24.0	24.5	24.0	24.2 $\pm$ 0.3
	Supra-iliac					12.5	12.5	12.0	12.3 $\pm$ 0.3
	Thigh					35.0	35.0	34.5	34.8 $\pm$ 0.3

TABLE A6.8

Skinfold Thickness Measurements [Subject 8 (CV)]

Week	Skinfold Thickness Measurement	Phase 1 (TM A)				Phase 2 (TM B)			
		1	2	3	Mean (mm) $\pm$ SD	1	2	3	Mean (mm) $\pm$ SD
1	Triceps	17.5	18.5	18.0	17.7 $\pm$ 0.3				
	Supra-iliac	14.0	14.5	14.5	14.3 $\pm$ 0.3				
	Thigh	29.5	29.5	30.5	29.8 $\pm$ 0.6				
2	Triceps	17.5	17.5	18.0	17.3 $\pm$ 0.3	12.5	12.5	12.0	12.2 $\pm$ 0.3
	Supra-iliac	15.5	15.5	16.0	15.7 $\pm$ 0.3	12.5	12.5	12.0	12.3 $\pm$ 0.3
	Thigh	30.0	30.5	30.5	30.3 $\pm$ 0.3	26.0	26.5	27.0	26.5 $\pm$ 0.5
3	Triceps								
	Supra-iliac								
	Thigh								
4	Triceps								
	Supra-iliac								
	Thigh								
5	Triceps	12.0	12.0	12.5	12.2 $\pm$ 0.3				
	Supra-iliac	12.5	13.0	13.0	12.8 $\pm$ 0.3				
	Thigh	27.5	27.5	27.0	27.3 $\pm$ 0.3				

TABLE A2.1.1

Daily Supine Blood Pressure Measurements [Subject 1 (SS)]

Week	Day	Time	Phase 1 (IM A)		Phase 2 (IM B)	
			Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)	Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)
One	1	07h45	110	68	114	68
	2	07h45	114	66	112	78
	4	07h45	115	67	116	74
		13h00	120	68	114	70
	7	19h45	120	66	122	78
Two	1	07h45	120	75	112	70
		13h00	110	70	110	80
		19h45	110	70	110	72
	2	07h45	112	72	114	76
		19h45	110	80	110	66
	3	07h45	118	70	100	65
		19h45	110	72	108	65
	4	07h45	120	85	112	75
		13h00	120	70	116	74
	7	19h45	108	60	120	70
Three	1	07h45	118	70	114	74
		19h45	114	64	108	68
	2	07h45	116	64	112	74
		19h45	112	62	114	82
	3	07h45	118	72	100	70
		19h45	113	70	102	66
	4	07h45	110	65	112	70
		13h00	108	68	112	70
	7	19h45	110	74	110	70
Four	1	07h45	110	70	112	74
	2	07h45	112	68	110	70
	4	07h45	108	70	102	54
		13h00	108	70	108	68
	7	19h45	108	60	110	70
Five	1	07h45	112	66	112	78
	2	07h45	114	68	110	66
	4	07h45	112	72	108	56
		13h00	110	78	112	88
	7	19h45	100	60	110	70

TABLE A2.1.2

Daily Supine Blood Pressure Measurements [Subject 2 (CA)]

Week	Day	Time	Phase 1 (IM A)		Phase 2 (IM B)	
			Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)	Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)
One	1	07h45	100	60	95	56
	2	07h45	105	65	94	64
	4	07h45	100	56	96	58
		13h00	100	59	104	65
	7	19h45	97	58	92	72
Two	1	07h45	98	58	102	68
		13h00	100	70	90	60
		19h45	100	65	100	68
	2	07h45	100	60	100	58
		19h45	112	65	102	65
	3	07h45	95	60	98	60
		19h45	100	60	98	60
	4	07h45	98	68	100	58
		13h00	95	60	100	70
	7	19h45	88	60	92	64
Three	1	07h45	90	60	96	54
		19h45	96	58	104	64
	2	07h45	103	68	104	64
		19h45	102	66	98	68
	3	07h45	102	70	98	66
		19h45	93	60	100	65
	4	07h45	95	62	108	68
		13h00	88	62	110	60
	7	19h45	108	60	100	64
Four	1	07h45	98	60	100	58
	2	07h45	92	58	100	58
	4	07h45	98	62	80	50
		13h00	92	65	98	68
	7	19h45	98	60	90	60
Five	1	07h45	98	68	88	58
	2	07h45	98	64	98	62
	4	07h45	102	62	100	58
		13h00	90	65	88	60
	7	19h45	92	65	98	70

BLOOD PRESSURE DATA

APPENDIX 7

TABLE A7.1.3

Daily Supine Blood Pressure Measurements [Subject 3 (LE)]

Week	Day	Time	Phase 1 (IM B)		Phase 2 (IM A)	
			Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)	Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)
One	1	07h45	118	78	116	62
	2	07h45	110	72	112	68
	4	07h45	112	64	116	72
		13h00	108	66	116	68
	7	19h45	114	72	112	68
Two	1	07h45	112	74	112	76
		13h00	115	70	110	65
		19h45	110	65	110	72
	2	07h45	120	75	115	70
		19h45	115	70	108	72
	3	07h45	120	70	118	60
		19h45	105	70	120	70
	4	07h45	105	70	108	66
		13h00	114	76	118	70
	7	19h45	116	72	110	65
Three	1	07h45	114	76	112	66
		19h45	112	78	110	70
	2	07h45	118	78	110	76
		19h45	112	74	112	78
	3	07h45	118	75	110	70
		19h45	120	76	108	76
	4	07h45	110	75	110	60
		13h00	102	70	96	60
Four	7	19h45	104	74	112	78
Four	1	07h45	118	72	112	70
	2	07h45	110	74	110	70
	4	07h45	110	70	110	70
		13h00	118	76	110	70
	7	19h45	118	72	116	78
Five	1	07h45	118	72	112	72
	2	07h45	120	66	112	72
	4	07h45	112	68	102	56
		13h00	115	75	120	78
	7	19h45	110	70	100	68

TABLE A7.1.4

Daily Supine Blood Pressure Measurements [Subject 4 (EA)]

Week	Day	Time	Phase 1 (IM B)		Phase 2 (IM A)	
			Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)	Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)
One	1	07h45	110	68	110	64
	2	07h45	116	72	114	68
	4	07h45	114	70	114	77
		13h00	112	68	115	65
	7	19h45	116	68	110	78
Two	1	07h45	115	75	115	72
		13h00	130	80	115	70
		19h45	122	75	122	80
	2	07h45	120	70	120	80
		19h45	125	80	118	78
	3	07h45	125	80	108	70
		19h45	120	82	110	70
	4	07h45	115	75	110	75
		13h00	120	80	100	68
	7	19h45	108	62	120	70
Three	1	07h45	112	80	120	80
		19h45	110	70	106	66
	2	07h45	118	80	114	74
		19h45	116	70	110	78
	3	07h45	118	80	110	74
		19h45	109	70	110	70
	4	07h45	112	75	118	78
		13h00	116	75	110	70
Four	7	19h45	122	84	112	64
Four	1	07h45	116	70	114	74
	2	07h45	104	70	110	70
	4	07h45	112	70	120	80
		13h00	114	72	112	70
	7	19h45	116	70	120	70
Five	1	07h45	110	72	116	78
	2	07h45	105	72	112	74
	4	07h45	110	68	114	78
		13h00	124	82	120	80
	7	19h45	112	70	110	70

TABLE A7.1.5

Daily Supine Blood Pressure Measurements [Subject 5 (VW)]

Week	Day	Time	Phase 1 (IM B)		Phase 2 (IM A)	
			Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)	Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)
One	1	07h45	118	76	112	80
	2	07h45	120	66	112	78
	4	07h45	118	70	118	76
		13h00	118	72	112	70
	7	19h45	122	82	112	74
Two	1	07h45	105	74	120	78
		13h00	110	70	115	75
		19h45	120	80	108	70
	2	07h45	118	70	98	52
		19h45	110	76	90	62
	3	07h45	110	78	116	70
		19h45	112	70	110	70
	4	07h45	110	70	110	80
		13h00	125	85	112	74
	7	19h45	112	74	110	70
Three	1	07h45	112	72	116	72
		19h45	112	72	114	70
	2	07h45	117	69	100	60
		19h45	122	74	108	68
	3	07h45	118	68	110	70
		19h45	100	64	110	70
	4	07h45	105	70	108	74
		13h00	112	72	110	70
	7	19h45	116	70	100	70
Four	1	07h45	110	70	110	68
	2	07h45	105	68	110	60
	4	07h45	120	70	112	78
		13h00	112	75	120	82
	7	19h45	112	70	112	78
Five	1	07h45	116	74	108	70
	2	07h45	114	78	96	62
	4	07h45	115	78	112	68
		13h00	106	70	110	68
	7	19h45	122	80	110	70

TABLE A7.1.6

Daily Supine Blood Pressure Measurements [Subject 6 (LI)]

Week	Day	Time	Phase 1 (IM B)		Phase 2 (IM A)	
			Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)	Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)
One	1	07h45	112	70	104	62
	2	07h45	108	68	100	58
	4	07h45	105	60	100	60
		13h00	109	72	110	70
	7	19h45	105	60	105	64
Two	1	07h45	105	68	98	64
		13h00	98	60	110	78
		19h45	110	70	100	68
	2	07h45	100	60	108	70
		19h45	120	58	112	70
	3	07h45	105	60	102	70
		19h45	100	60	110	68
	4	07h45	100	72	112	76
		13h00	98	62	98	60
	7	19h45	102	65	110	70
Three	1	07h45	104	64	110	82
		19h45	102	64	112	66
	2	07h45	98	58	98	58
		19h45	106	70	92	60
	3	07h45	110	70	88	58
		19h45	112	70	90	60
	4	07h45	105	62	100	70
		13h00	110	68	100	68
	7	19h45	100	60	102	70
Four	1	07h45	92	60	106	66
	2	07h45	108	66	104	64
	4	07h45	104	66	108	62
		13h00	110	68	100	70
	7	19h45	102	65	100	65
Five	1	07h45	102	62	100	62
	2	07h45	102	60	98	54
	4	07h45	105	61	95	58
		13h00	110	72	108	70
	7	19h45	108	60	100	65

TABLE A7.1.7

Daily Supine Blood Pressure Measurements [Subject 7 (EG)]

			Phase 1 (IM A)		Phase 2 (IM B)	
			Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)	Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)
Week	Day	Time				
One	1	07h45	106	66	112	65
	2	07h45	112	62	114	67
	4	07h45	112	64	112	65
		13h00	116	66	106	62
	7	19h45	117	62	112	66
Two	1	07h45	100	70	100	58
		13h00	110	72	108	65
		19h45	110	68	105	65
	2	07h45	105	60	102	62
		19h45	110	70	112	60
	3	07h45	100	62	115	62
		19h45	100	68	110	60
	4	07h45	108	70	110	60
		13h00	110	68	106	64
	7	19h45	110	70	100	60
Three	1	07h45	112	74	110	64
		19h45	118	66	106	68
	2	07h45	112	62	112	64
		19h45	112	66	108	62
	3	07h45	110	72	110	65
		19h45	110	68	110	68
	4	07h45	114	64	110	60
		13h00	110	76	110	70
7	19h45	110	70	120	60	
Four	1	07h45	108	66	110	68
	2	07h45	112	74	110	68
	4	07h45	110	75	114	68
		13h00	112	68	110	70
	7	19h45	110	60	110	70
Five	1	07h45	112	66	114	64
	2	07h45			110	70
	4	07h45			102	68
		13h00			102	70
	7	19h45			110	70

TABLE A7.1.8

Daily Supine Blood Pressure Measurements [Subject 8 (CV)]

Week	Day	Time	Phase 1 (IM A)		Phase 2 (IM B)	
			Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)	Systolic Pressure (mm/Hg)	Diastolic Pressure (mm/Hg)
One	1	07h45	110	78	108	76
	2	07h45	116	68	112	78
	4	07h45	114	74	110	82
		13h00	116	72	114	76
	7	19h45	108	80	110	70
Two	1	07h45	110	75	110	70
		13h00	109	74	116	70
		19h45	100	70	112	70
	2	07h45	110	74		
		19h45	105	70		
	3	07h45	108	74		
		19h45	110	68		
	4	07h45	112	68		
		13h00	107	78		
	7	19h45	105	70		
	Three	1	07h45	103	70	
			19h45	114	75	
		2	07h45	107	78	
			19h45	108	74	
		3	07h45	114	78	
			19h45	100	70	
	4	07h45	112	80		
		13h00	110	72		
		19h45	105	60		
Four	1	07h45	110	72		
	2	07h45	108	68		
	4	07h45	110	74		
		13h00	112	72		
	7	19h45	108	70		
Five	1	07h45	114	76		
	2	07h45	114	64		
	4	07h45	110	70		
		13h00	115	75		
	7	19h45	100	76		

Week	TM A $\pm$ SEM	F Ratio	P	TM B $\pm$ SEM	F Ratio	P
1	110.40 $\pm$ 1.07	1.55	0.1896	110.86 $\pm$ 1.27	0.08	0.7874
2	108.61 $\pm$ 0.93			109.49 $\pm$ 1.32		
3	107.33 $\pm$ 1.30			109.50 $\pm$ 1.01	0.34	0.5020
4	108.00 $\pm$ 1.36			107.37 $\pm$ 1.56		
5	106.10 $\pm$ 1.50			108.67 $\pm$ 1.56		

n = 228, df = 4,225

TABLE A7.2.1 Average Systolic Blood Pressures per Week (Mean Values for 7 Subjects)

Week	TM A $\pm$ SEM	F Ratio	P	TM B $\pm$ SEM	F Ratio	P
1	56.71 $\pm$ 1.03	0.94	0.4391	58.53 $\pm$ 0.99	1.78	0.1862
2	59.17 $\pm$ 0.74			58.77 $\pm$ 0.34		
3	58.21 $\pm$ 0.78			59.60 $\pm$ 0.77	0.57	0.5864
4	58.50 $\pm$ 1.16			57.47 $\pm$ 1.14		
5	58.33 $\pm$ 1.22			59.30 $\pm$ 1.43		

n = 228, df = 4,225

TABLE A7.2.2 Average Diastolic Blood Pressures per Week (Mean Values for 7 Subjects)

APPENDIX 8

ARCI RESPONSE DATA

TABLE AB.1

Addiction Research Centre Inventory Responses [Subject 1 (SS)]

Phase 1 (TM A)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	2	8	1	12	7
		12h50	2	6	1	10	4
		19h50					
	2	07h50	3	3	1	6	1
		19h50	3	3	1	6	1
	3	07h50	3	5	2	7	2
		19h50	3	5	1	7	3
	4	07h50	3	4	1	6	2
		12h50	3	5	1	7	2
	7	19h50					
Two	1	07h50	3	4	1	7	2
		12h50	3	5	1	7	3
		19h50	3	5	1	7	2
	2	07h50	3	4	1	7	2
		19h50	3	4	1	6	1
	3	07h50	3	5	1	6	2
		19h50	3	5	2	5	3
	4	07h50	3	3	3	5	2
		12h50	3	5	1	5	3
	7	19h50	3	4	2	6	2
Three	4	07h50	3	5	1	5	2
		12h50	3	4	1	5	2
	7	19h50	3	4	1	4	2
Four	4	07h50	3	5	2	5	3
		12h50	3	4	1	6	2
	7	19h50	3	4	2	4	1
Five	4	07h50	3	4	2	4	1
		12h50	3	4	1	3	2
	7	19h50	3	4	2	2	1

Phase 2 (TM B)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	3	4	2	4	2
		12h50	3	4	3	1	0
		19h50					
	2	07h50	3	4	3	2	1
		19h50	3	4	1	2	1
	3	07h50	3	4	3	0	1
		19h50	3	4	2	1	1
	4	07h50	3	4	2	1	1
		12h50	3	4	2	5	1
	7	19h50	3	4	3	1	0
Two	1	07h50	3	4	3	1	1
		12h50	3	4	2	2	2
		19h50	3	4	2	2	2
	2	07h50	3	4	1	2	1
		19h50	3	4	2	3	1
	3	07h50	3	4	2	1	1
		19h50	3	4	2	2	1
	4	07h50	3	3	2	1	1
		12h50	4	4	3	1	2
	7	19h50	3	4	3	1	1
Three	4	07h50	3	4	3	1	1
		12h50	3	4	3	2	1
	7	19h50	3	4	3	1	1
Four	4	07h50	3	4	3	0	1
		12h50	3	4	4	1	0
	7	19h50					
Five	4	07h50	3	4	3	1	1
		12h50	3	4	4	0	0
	7	19h50					

TABLE A8.2

Addiction Research Centre Inventory Responses [Subject 2 (CA)]

Phase 1 (TH A)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	3	3	10	2	2
		12h50	8	1	9	1	0
		19h50					
	2	07h50	1	8	1	12	6
		19h50	11	1	5	3	0
	3	07h50	12	1	5	3	0
		19h50	5	6	3	6	3
	4	07h50	4	8	4	9	6
		12h50	11	1	7	3	1
7	19h50	13	0	6	1	0	
Two	1	07h50	11	1	5	2	0
		12h50	1	12	1	13	9
		19h50	1	9	2	11	8
	2	07h50	6	2	6	0	0
		19h50	3	3	8	8	3
	3	07h50	1	8	3	9	8
		19h50	1	7	4	4	7
	4	07h50	3	7	3	3	5
		12h50	1	6	4	3	2
7	19h50	2	4	4	6	2	
Three	4	07h50	10	2	6	2	0
		12h50	3	4	6	2	2
		19h50	7	3	3	0	0
Four	4	07h50	10	4	4	2	0
		12h50	7	3	6	1	0
		19h50	9	3	4	1	0
Five	4	07h50	5	4	7	2	1
		12h50					
		19h50					

Phase 2 (TH B)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	11	3	5	2	0
		12h50	11	4	8	2	0
		19h50	9	3	6	2	0
	2	07h50					
		19h50	10	4	4	1	1
	3	07h50	7	5	5	1	0
		19h50	8	3	8	2	0
	4	07h50	5	5	3	2	1
		12h50	6	3	7	2	1
	7	19h50	4	6	3	1	3
Two	1	07h50	8	2	7	0	0
		12h50	7	4	6	0	0
		19h50	3	3	5	1	0
	2	07h50	2	5	4	3	3
		19h50	4	3	1	7	1
	3	07h50	5	3	4	1	0
		19h50	8	4	4	1	0
	4	07h50	10	4	3	0	1
		12h50	7	4	4	0	0
	7	19h50	13	2	6	2	0
Three	4	07h50	7	2	7	1	2
		12h50	6	5	6	2	0
	7	19h50	14	4	9	1	1
Four	4	07h50	11	4	6	1	0
		12h50	13	0	7	1	0
	7	19h50	1	3	3	8	2
Five	4	07h50	2	7	3	9	4
		12h50	3	3	1	9	2
	7	19h50					

TABLE AB.3

Addiction Research Centre Inventory Responses [Subject 3 (LE)]

Phase 1 (IM B)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSO
One	1	07h50	1	6	2	3	3
		12h50	3	6	2	1	3
		19h50	1	6	2	1	3
	2	07h50	2	6	3	1	2
		19h50	2	6	3	1	2
	3	07h50	2	5	3	1	1
		19h50	1	5	4	1	1
	4	07h50	2	5	3	1	1
		12h50	1	6	4	2	3
	7	19h50					
Two	1	07h50	4	6	4	1	1
		12h50	3	5	4	1	0
		19h50	3	6	4	1	1
	2	07h50	3	6	4	1	1
		19h50	1	5	4	1	1
	3	07h50	2	5	4	1	1
		19h50	1	5	4	1	1
	4	07h50	3	5	4	1	0
		12h50	2	5	4	1	0
	7	19h50	1	5	4	1	1
Three	4	07h50	3	5	4	1	0
		12h50	3	5	4	1	1
	7	19h50	2	5	4	1	1
Four	4	07h50	4	4	4	0	0
		12h50	4	4	4	0	0
	7	19h50	3	4	4	0	1
Five	4	07h50	4	4	4	0	0
		12h50	4	4	4	0	0
	7	19h50	4	4	4	0	0

TABLE AB.3

Addiction Research Centre Inventory Responses [Subject 3 (LE)]

Phase 2 (IM A)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSO
One	1	07h50	3	4	4	0	0
		12h50	2	5	4	1	0
		19h50					
	2	07h50	3	5	4	1	0
		19h50	2	5	4	1	1
	3	07h50	2	5	4	1	1
		19h50					
	4	07h50	3	5	4	1	0
		12h50	3	5	4	1	0
	7	19h50	4	4	4	0	0
Two	1	07h50	3	5	4	1	0
		12h50	3	5	4	1	0
		19h50	4	4	4	0	0
	2	07h50	4	4	4	0	0
		19h50	4	4	4	0	0
	3	07h50	4	4	4	0	0
		19h50	3	5	4	1	0
	4	07h50	3	5	4	1	0
		12h50	3	5	4	1	0
	7	19h50	3	5	4	1	0
Three	4	07h50	4	4	4	0	0
		12h50	3	5	4	1	0
	7	19h50	3	5	4	1	0
Four	4	07h50	3	5	4	1	0
		12h50	3	5	4	1	0
	7	19h50					
Five	4	07h50	3	5	4	1	0
		12h50	3	5	4	1	0
	7	19h50	3	5	4	1	0

TABLE AB.4 Addiction Research Centre Inventory Responses [Subject 4 (EA)]

Phase 1 (IM B)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	3	10	4	13	8
		12h50	1	10	2	15	7
		19h50	0	10	2	11	7
	2	07h50	0	11	2	13	7
		19h50	5	8	1	9	5
	3	07h50	10	2	4	2	3
		19h50	2	7	2	13	6
	4	07h50	0	11	2	14	7
		12h50	0	11	2	11	8
	7	19h50					
Two	1	07h50	0	9	2	11	6
		12h50	1	10	4	8	9
		19h50	1	10	2	10	6
	2	07h50	0	11	2	13	8
		19h50	0	10	2	14	8
	3	07h50	0	11	2	12	6
		19h50	0	10	2	12	8
	4	07h50	2	5	5	3	3
		12h50	3	6	4	4	6
	7	19h50	0	11	2	14	9
Three	4	07h50	0	11	2	14	9
		12h50	0	11	2	14	9
	7	19h50	0	11	2	11	6
Four	4	07h50	0	12	2	12	8
		12h50	0	13	3	14	10
	7	19h50	1	10	2	13	7
Five	4	07h50	0	11	2	14	9
		12h50	0	10	2	13	7
	7	19h50	0	10	2	13	8

TABLE AB.4 Addiction Research Centre Inventory Responses [Subject 4 (EA)]

Phase 2 (IM A)

Week	Day	Time	Computed Response Ratings					
			MBG	A	BG	PCAG	LSD	
One	1	07h50	0	11	2	14	8	
		12h50	1	11	3	6	7	
		19h50	0	11	3	11	8	
	2	07h50	0	11	2	14	8	
		19h50						
	3	07h50	9	2	6	7	1	
		19h50	0	10	2	14	8	
	4	07h50	0	11	2	14	8	
		12h50	0	11	2	14	9	
	7	19h50	0	9	2	13	7	
	Two	1	07h50	1	11	2	14	9
12h50			0	9	2	13	7	
19h50			0	10	2	13	8	
2		07h50	0	9	2	14	8	
		19h50	0	10	2	13	7	
3		07h50	0	12	2	15	9	
		19h50	0	10	2	13	7	
4		07h50	0	12	3	14	9	
		12h50	0	10	2	14	8	
7		19h50	0	10	2	13	7	
Three		4	07h50	0	10	2	13	7
			12h50	0	10	3	8	8
		7	19h50	0	11	2	13	7
		Four	4	07h50	0	10	2	13
	12h50							
	7		19h50	0	10	2	13	7
Five	4	07h50	0	10	2	13	8	
		12h50	0	11	2	13	8	
	7	19h50	0	11	2	13	7	

TABLE AB.5

Addiction Research Centre Inventory Responses [Subject 5 (VM)]

Phase 1 (IM U)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	0	7	2	9	5
		12h50	0	10	6	11	8
		19h50					
	2	07h50	1	7	5	9	7
		19h50	0	7	6	9	7
	3	07h50	0	10	6	13	8
		19h50	5	4	3	4	3
	4	07h50	0	7	6	7	7
		12h50	0	9	8	5	7
	7	19h50	4	7	4	5	5
	Two	07h50	0	8	5	12	8
		12h50	0	11	6	12	9
		19h50	0	7	7	7	7
Two	2	07h50	0	9	6	7	7
		19h50	1	6	6	6	7
		07h50	5	4	6	3	7
	3	19h50	4	6	6	6	7
		07h50	0	12	5	15	11
	4	12h50	0	11	6	14	10
		19h50	7	4	6	6	6
	Three	07h50	1	6	7	8	7
		12h50	0	13	5	15	11
	7	19h50	9	1	6	0	0
	Four	07h50	7	5	7	5	5
		12h50	0	12	6	13	10
		19h50					
Five	4	07h50	0	13	6	9	10
		12h50	0	13	6	8	10
		19h50	0	13	5	15	11

TABLE AB.5

Addiction Research Centre Inventory Responses [Subject 5 (VM)]

Phase 2 (IM A)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	0	13	5	15	11
		12h50	0	13	5	15	11
		19h50					
	2	07h50	0	13	4	15	11
		19h50	0	13	4	15	11
	3	07h50	0	13	4	15	11
		19h50	0	13	4	15	11
	4	07h50	0	13	4	15	11
		12h50	0	13	4	15	11
	7	19h50	0	13	4	15	11
	Two	07h50	0	12	4	15	11
		12h50	0	13	4	15	11
		19h50	0	13	4	15	11
Two	2	07h50	0	13	4	15	11
		19h50	0	13	4	15	11
		07h50	0	13	4	15	11
	3	19h50	0	13	4	15	11
		07h50	0	12	4	15	11
	4	12h50	11	1	6	0	0
		19h50	10	1	6	0	0
	Three	07h50	11	1	6	0	0
		12h50	10	2	5	0	0
	7	19h50	0	12	2	15	9
	Four	07h50	0	13	4	15	11
		12h50	0	13	3	15	10
		19h50	0	13	4	15	11
Five	4	07h50	0	13	4	15	11
		12h50	0	13	4	15	11
		19h50					

TABLE A8.6

Addiction Research Centre Inventory Responses [Subject 6 (L1)]

Phase 1 (1H B)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	1	11	2	15	8
		12h50	2	11	3	14	8
		19h50	3	7	3	14	5
	2	07h50	3	10	2	14	7
		19h50	3	8	2	15	7
	3	07h50	3	10	1	15	8
		19h50	1	9	1	15	9
	4	07h50	2	10	1	15	9
		12h50	4	6	4	5	5
	7	19h50	4	1	5	3	0
	Two	07h50	1	9	2	15	9
		12h50	2	11	4	12	8
		19h50	4	5	2	1	2
Two	2	07h50	4	6	2	2	3
		19h50	4	8	2	13	8
	3	07h50	1	9	1	14	9
		19h50	3	10	3	12	8
	4	07h50	4	5	3	4	2
		12h50	3	10	4	14	8
	7	19h50	5	4	3	1	2
	Three	07h50	4	6	3	3	3
		12h50	4	6	4	3	3
		19h50	6	3	4	1	1
Four	4	07h50	4	5	3	2	2
		12h50	3	6	2	4	2
	7	19h50	4	3	4	5	0
Five	4	07h50	4	5	3	0	2
		12h50	3	9	4	4	6
	7	19h50	4	4	4	0	0

TABLE A8.6

Addiction Research Centre Inventory Responses [Subject 6 (L1)]

Phase 2 (1H A)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	5	3	3	1	1
		12h50	5	3	4	0	0
		19h50					
	2	07h50	8	3	3	2	1
		19h50	4	4	4	0	0
	3	07h50	4	4	3	0	1
		19h50	4	4	4	0	0
	4	07h50	4	4	4	1	0
		12h50	4	4	5	0	0
	7	19h50	5	3	4	0	0
	Two	07h50	4	4	4	0	0
		12h50	4	4	4	1	0
		19h50	4	5	4	1	1
Two	2	07h50	4	4	4	0	0
		19h50	4	5	4	0	1
	3	07h50	4	4	4	1	0
		19h50					
	4	07h50	3	7	2	7	4
		12h50	4	4	4	0	0
	7	19h50	4	8	2	13	7
	Three	07h50	4	4	4	3	1
		12h50	4	4	2	5	1
		19h50	4	5	4	1	1
Four	4	07h50	4	5	4	3	2
		12h50	4	4	4	2	0
	7	19h50	4	5	4	1	1
Five	4	07h50	3	8	2	11	9
		12h50	2	8	2	10	7
	7	19h50	4	4	3	1	1

TABLE AB.7

Addiction Research Centre Inventory Responses [Subject 7 (EG)]

Phase 1 (TH A)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSO
One	1	07h50	4	5	3	4	1
		12h50	4	5	3	2	2
		19h50	4	4	3	4	1
	2	07h50	3	6	2	4	2
		19h50	3	6	2	4	2
	3	07h50	3	5	1	4	1
		19h50	4	5	3	3	2
	4	07h50	3	5	2	2	1
		12h50	4	5	3	1	2
	7	19h50					
Two	1	07h50	3	6	3	4	1
		12h50	4	4	3	2	1
		19h50	3	6	3	4	2
	2	07h50	3	6	3	4	2
		19h50	3	6	2	4	2
	3	07h50	3	5	3	3	1
		19h50	3	6	3	4	2
	4	07h50	3	5	3	3	1
		12h50	3	6	3	2	2
	7	19h50	3	5	3	3	0
Three	4	07h50	3	5	4	4	0
		12h50	3	6	4	2	1
	7	19h50	4	5	4	3	0
Four	4	07h50					
		12h50					
	7	19h50					
Five	4	07h50					
		12h50					
	7	19h50					

TABLE AB.7

Addiction Research Centre Inventory Responses [Subject 7 (EG)]

Phase 2 (TH B)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSO
One	1	07h50	3	6	3	3	2
		12h50	3	5	3	3	1
		19h50	3	6	3	3	2
	2	07h50	3	6	3	3	2
		19h50	3	6	3	3	2
	3	07h50	3	6	3	3	2
		19h50	3	5	3	3	1
	4	07h50	3	6	3	3	2
		12h50	3	5	3	3	1
	7	19h50	4	5	3	2	2
Two	1	07h50	3	5	3	3	1
		12h50	3	6	3	2	2
		19h50	3	5	3	3	1
	2	07h50	3	5	3	3	1
		19h50	3	5	3	3	1
	3	07h50	3	5	3	3	1
		19h50	3	5	3	3	1
	4	07h50	3	5	3	3	1
		12h50	3	5	3	3	1
	7	19h50	3	5	3	3	1
Three	4	07h50	3	5	3	3	1
		12h50	3	5	3	3	1
	7	19h50	3	5	3	3	1
Four	4	07h50	3	5	3	3	1
		12h50	3	5	3	3	1
	7	19h50	3	5	3	3	1
Five	4	07h50	3	5	3	3	1
		12h50	3	5	3	3	1
	7	19h50	3	5	3	3	1

TABLE AB.8

Addiction Research Centre Inventory Responses [Subject 8 (CV)]

Phase 1 (IM A)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	3	11	2	14	9
		12h50	1	11	3	13	9
		19h50	4	5	4	7	4
	2	07h50	7	2	4	8	4
		19h50	5	2	6	1	1
	3	07h50	1	10	1	13	9
		19h50	3	2	7	5	3
	4	07h50	1	12	1	13	9
		12h50	1	12	1	11	8
	7	19h50					
Two	1	07h50	6	2	6	4	1
		12h50	12	0	7	1	2
		19h50	4	3	5	6	3
	2	07h50	4	4	4	4	4
		19h50	2	12	1	13	8
	3	07h50	4	10	3	5	5
		19h50	1	12	1	12	8
	4	07h50	1	12	1	13	9
		12h50	1	9	2	11	7
	7	19h50	2	6	3	9	4
Three	4	07h50	0	12	2	12	7
		12h50	0	12	2	13	9
	7	19h50	0	12	2	13	9
Four	4	07h50	3	9	3	3	5
		12h50	3	8	5	5	7
	7	19h50	1	11	1	13	9
Five	4	07h50	0	12	2	12	8
		12h50	0	10	2	13	9
	7	19h50	0	10	2	12	7

TABLE AB.8

Addiction Research Centre Inventory Responses [Subject 8 (CV)]

Phase 2 (IM B)

Week	Day	Time	Computed Response Ratings				
			MBG	A	BG	PCAG	LSD
One	1	07h50	4	4	7	6	2
		12h50	4	8	5	4	4
		19h50	5	2	3	1	2
	2	07h50	1	12	3	8	6
		19h50					
	3	07h50	4	10	4	6	5
		19h50					
	4	07h50	2	11	3	10	7
		12h50	0	11	3	12	9
	7	19h50					
Two	1	07h50	5	3	8	9	3
		12h50	9	1	6	3	2
		19h50	5	6	5	3	3
	2	07h50					
		19h50					
	3	07h50					
		19h50					
	4	07h50					
		12h50					
	7	19h50					
Three	4	07h50					
		12h50					
	7	19h50					
Four	4	07h50					
		12h50					
	7	19h50					
Five	4	07h50					
		12h50					
	7	19h50					

ARCI Scale	Week	TM A $\pm$ SEM	F Ratio	P	TM B $\pm$ SEM	F Ratio	P
PCAG	1	3.23 $\pm$ 0.40	0.92	0.4539	3.06 $\pm$ 0.34	0.10	0.7547
	2	2.69 $\pm$ 0.28			2.94 $\pm$ 0.29		
	3	3.90 $\pm$ 0.69			3.67 $\pm$ 0.73		
	4	3.64 $\pm$ 0.87			4.14 $\pm$ 1.02		
	5	3.00 $\pm$ 0.88			2.13 $\pm$ 0.45		
BG	1	6.36 $\pm$ 0.49	0.50	0.6636	6.41 $\pm$ 0.31	0.01	0.9295
	2	6.56 $\pm$ 0.41			6.09 $\pm$ 0.31		
	3	5.29 $\pm$ 0.65			5.76 $\pm$ 0.68		
	4	6.29 $\pm$ 0.96			5.43 $\pm$ 0.94		
	5	6.79 $\pm$ 0.88			7.38 $\pm$ 0.95		
LSD	1	3.43 $\pm$ 0.23	0.29	0.8867	3.32 $\pm$ 0.22	0.12	0.7360
	2	3.21 $\pm$ 0.17			3.54 $\pm$ 0.18		
	3	3.43 $\pm$ 0.35			4.14 $\pm$ 0.41		
	4	3.36 $\pm$ 0.34			4.07 $\pm$ 0.47		
	5	3.71 $\pm$ 0.97			3.56 $\pm$ 0.35		
HBG	1	6.25 $\pm$ 0.72	0.30	0.5241	5.81 $\pm$ 0.66	0.20	0.6602
	2	6.25 $\pm$ 0.57			4.97 $\pm$ 0.58		
	3	4.14 $\pm$ 0.98			4.24 $\pm$ 1.08		
	4	5.57 $\pm$ 1.54			4.64 $\pm$ 1.32		
	5	7.00 $\pm$ 1.51			5.94 $\pm$ 1.47		
A	1	3.56 $\pm$ 0.52	1.02	0.3998	3.63 $\pm$ 0.37	0.00	0.9742
	2	3.71 $\pm$ 0.48			3.47 $\pm$ 0.41		
	3	2.14 $\pm$ 0.64			2.86 $\pm$ 0.74		
	4	3.15 $\pm$ 1.14			2.64 $\pm$ 0.92		
	5	4.64 $\pm$ 1.13			4.38 $\pm$ 1.06		

The mean responses to each ARCI scale for week 1 for both treatments are given in the body of the table. For week 1, $n = 61$ for each phase, $df = 1,120$. Bold italicised F ratios and P values indicate significance for weeks 1.

For the comparison of the treatment weeks (2-5) with week 1, $n = 177$ for each phase, $df = 4,172$.

TABLE AB.2.1 Average Weekly Responses to the 5 Scales of the ARCI Questionnaire (Mean Values for 7 Subjects)

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	3.00 $\pm$ 0.00	3.06 $\pm$ 0.06	1.00	0.3248
2	4.76 $\pm$ 0.88	7.12 $\pm$ 0.98	3.17	0.0844
3	3.28 $\pm$ 0.11	2.83 $\pm$ 0.25	2.51	0.1226
4	0.06 $\pm$ 0.06	0.47 $\pm$ 0.21	3.50	0.0705
5	2.81 $\pm$ 1.27	1.69 $\pm$ 0.73	0.59	0.4553
6	3.89 $\pm$ 0.14	3.44 $\pm$ 0.28	2.00	0.1664

$n = 16$ for each Test Medication Phase for Subject 5, $df = 1,30$
 $n = 17$ for each Test Medication Phase for Subjects 1, 2, and 4, $df = 1,32$
 $n = 18$ for each Test Medication Phase for Subjects 3 and 6, $df = 1,34$

TABLE AB.2.2 Average "PCAG" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	4.35 $\pm$ 0.15	4.00 $\pm$ 0.00	5.76 [§]	0.0224
2	4.82 $\pm$ 0.71	3.47 $\pm$ 0.37	2.85	0.1011
3	4.72 $\pm$ 0.11	4.89 $\pm$ 0.16	0.75	0.4029
4	10.35 $\pm$ 0.21	9.88 $\pm$ 0.44	0.95	0.3483
5	10.06 $\pm$ 1.22	8.56 $\pm$ 0.93	0.96	0.3456
6	5.00 $\pm$ 0.38	6.67 $\pm$ 0.59	5.67 [§]	0.0230

$n = 16$ for each Test Medication Phase for Subject 5, $df = 1,30$
 $n = 17$ for each Test Medication Phase for Subjects 1, 2, and 4, $df = 1,32$
 $n = 18$ for each Test Medication Phase for Subjects 3 and 6, $df = 1,34$
[§] indicates a P value of between 0.015 and 0.05

TABLE AB.2.3 Average "BG" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	2.12 $\pm$ 0.15	1.06 $\pm$ 0.13	28.48 [†]	0.0000
2	2.76 $\pm$ 0.80	0.82 $\pm$ 0.30	5.14 [§]	0.0303
3	0.00 $\pm$ 0.00	0.50 $\pm$ 0.12	17.00 [†]	0.0002
4	7.71 $\pm$ 0.19	7.24 $\pm$ 0.39	1.19	0.2833
5	8.69 $\pm$ 1.09	7.88 $\pm$ 0.69	0.40	0.5391
6	2.06 $\pm$ 0.74	4.22 $\pm$ 0.77	4.03	0.0533

$n = 16$ for each Test Medication Phase for Subject 5, $df = 1,30$
 $n = 17$ for each Test Medication Phase for Subjects 1, 2, and 4, $df = 1,32$
 $n = 18$ for each Test Medication Phase for Subjects 3 and 6, $df = 1,34$
[§] indicates a P value of between 0.015 and 0.05
[†] indicates a P value of less than 0.01

TABLE AB.2.6 Average "A" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	1.35 $\pm$ 0.15	2.55 $\pm$ 0.19	28.90 [†]	0.0000
2	4.47 $\pm$ 0.45	5.00 $\pm$ 0.49	0.65	0.4364
3	4.00 $\pm$ 0.00	4.00 $\pm$ 0.00	100.0 [†]	0.0000
4	2.12 $\pm$ 0.08	2.41 $\pm$ 0.23	1.48	0.2324
5	4.81 $\pm$ 0.72	5.00 $\pm$ 0.16	2.60	0.1177
6	3.22 $\pm$ 0.25	3.00 $\pm$ 0.23	0.43	0.5232

$n = 16$ for each Test Medication Phase for Subject 5, $df = 1,30$
 $n = 17$ for each Test Medication Phase for Subjects 1, 2, and 4, $df = 1,32$
 $n = 18$ for each Test Medication Phase for Subjects 3 and 6, $df = 1,34$
[†] indicates a P value of less than 0.01

TABLE AB.2.4 Average "LSD" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	5.41 $\pm$ 0.31	1.29 $\pm$ 0.19	129.4 [†]	0.0000
2	4.06 $\pm$ 0.95	2.24 $\pm$ 0.70	2.38	0.1327
3	0.72 $\pm$ 0.11	0.72 $\pm$ 0.11	0.00	1.0000
4	13.06 $\pm$ 0.35	11.24 $\pm$ 0.81	4.31 [§]	0.0461
5	11.94 $\pm$ 1.50	8.75 $\pm$ 1.01	2.93	0.0972
6	3.28 $\pm$ 0.98	5.06 $\pm$ 1.30	2.92	0.0966

$n = 16$ for each Test Medication Phase for Subject 5, $df = 1,30$
 $n = 17$ for each Test Medication Phase for Subjects 1, 2, and 4, $df = 1,32$
 $n = 18$ for each Test Medication Phase for Subjects 3 and 6, $df = 1,34$
[§] indicates a P value of between 0.015 and 0.05
[†] indicates a P value of less than 0.01

TABLE AB.2.5 Average "HBG" Response for each Test Medication Phase per Volunteer

TABLE A9.1

Profile of Mood States Responses [Subject 1 (SS)]

Phase 1 (IM A)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.11	0.00	0.83	2.88	0.00	0.29	3.75	2.67	2.70	2.67
		12h50	0.00	0.00	0.33	3.75	0.00	0.14	3.88	3.17	3.61	3.17
		19h50										
	2	07h50	0.00	0.00	0.33	3.00	0.00	0.00	4.00	3.33	3.00	3.33
		19h50	0.11	0.00	0.33	3.88	0.00	0.00	3.88	3.83	3.99	3.83
	3	07h50	0.00	0.00	0.33	4.00	0.00	0.00	4.00	4.00	4.00	4.00
		19h50	0.11	0.00	0.25	3.00	0.00	0.14	3.13	3.00	2.97	3.00
	4	07h50	0.11	0.00	0.25	3.25	0.00	0.14	3.50	3.50	3.22	3.50
		12h50	0.00	0.00	0.33	3.50	0.00	0.00	3.25	3.50	3.50	3.50
	7	19h50										
Two	1	07h50	0.00	0.00	0.33	3.75	0.00	0.14	3.75	3.50	3.61	3.50
		12h50	0.00	0.00	0.33	3.25	0.00	0.14	3.63	3.50	3.11	3.50
		19h50	0.11	0.00	0.33	3.63	0.00	0.14	3.50	3.00	3.59	3.00
	2	07h50	0.00	0.00	0.25	3.13	0.00	0.14	3.50	3.00	2.98	3.00
		19h50	0.11	0.00	0.33	3.13	0.29	0.14	3.13	3.00	2.81	3.00
	3	07h50	0.00	0.00	0.33	3.25	0.00	0.14	3.38	2.67	3.11	2.67
		19h50	0.00	0.00	0.25	3.25	0.00	0.14	3.38	3.50	3.11	3.50
	4	07h50	0.11	0.00	0.25	3.13	0.43	0.14	3.13	3.33	2.67	3.33
		12h50	0.00	0.00	0.33	3.88	0.00	0.00	4.00	3.67	3.88	3.67
	7	19h50	0.11	0.00	0.33	3.00	1.14	0.14	3.13	3.00	1.83	3.00
Three	4	07h50	0.11	0.00	0.33	3.13	0.00	0.14	3.13	3.00	3.09	3.00
		12h50	0.11	0.00	0.25	3.13	0.00	0.14	3.13	3.00	3.09	3.00
	7	19h50	0.11	0.00	0.25	3.00	0.00	0.14	3.00	3.00	2.97	3.00
Four	4	07h50	0.11	0.00	0.25	3.00	0.00	0.14	3.13	3.17	2.97	3.17
		12h50	0.11	0.00	0.33	3.13	0.00	0.14	2.75	3.00	3.09	3.00
	7	19h50	0.11	0.00	0.25	3.00	0.00	0.14	3.00	2.50	2.97	2.50
Five	4	07h50	0.11	0.00	0.25	3.00	0.00	0.14	3.13	3.00	2.97	3.00
		12h50	0.11	0.00	0.25	3.00	0.00	0.14	3.00	3.00	2.97	3.00
	7	19h50	0.11	0.00	0.25	3.00	0.00	0.14	3.13	2.67	2.97	2.67

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

Phase 2 (IM B)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.11	0.00	0.33	3.25	0.00	0.14	2.88	2.67	3.22	2.67
		12h50	0.11	0.00	0.25	2.63	0.00	0.14	3.00	2.50	2.59	2.50
		19h50										
	2	07h50	0.11	0.00	0.25	3.00	0.00	0.14	3.00	3.00	2.97	3.00
		19h50	0.11	0.00	0.25	3.00	0.00	0.14	2.63	3.00	2.97	3.00
	3	07h50	0.11	0.00	0.25	2.63	0.00	0.14	3.00	2.50	2.59	2.50
		19h50	0.11	0.00	0.33	3.00	0.00	0.14	2.63	3.00	2.97	3.00
	4	07h50	0.11	0.00	0.25	3.00	0.00	0.14	3.00	2.50	2.97	2.50
		12h50	0.11	0.00	0.25	3.00	0.00	0.14	3.13	3.17	2.97	3.17
	7	19h50	0.11	0.00	0.25	3.00	0.00	0.14	2.63	2.50	2.97	2.50
Two	1	07h50	0.11	0.00	0.25	3.00	0.00	0.14	3.00	2.00	2.97	2.00
		12h50	0.11	0.00	0.25	3.00	0.00	0.14	3.13	2.17	2.97	2.17
		19h50	0.11	0.00	0.25	3.00	0.00	0.14	3.00	2.00	2.97	2.00
	2	07h50	0.11	0.00	0.25	2.63	0.00	0.14	3.00	2.00	2.59	2.00
		19h50	0.11	0.00	0.25	2.25	0.00	0.14	2.63	2.00	2.22	2.00
	3	07h50	0.11	0.00	0.25	2.25	0.00	0.14	3.00	2.00	2.22	2.00
		19h50	0.11	0.00	0.25	2.25	0.00	0.57	2.25	2.00	1.79	2.00
	4	07h50	0.11	0.00	0.50	2.25	0.00	0.29	3.00	2.00	2.08	2.00
		12h50	0.11	0.00	0.00	0.88	0.14	0.43	2.63	1.50	0.42	1.50
	7	19h50	0.11	0.13	0.25	3.00	0.00	0.14	2.63	2.00	2.97	1.87
Three	4	07h50	0.11	0.00	0.25	2.63	0.00	0.43	2.63	1.50	2.31	1.50
		12h50	0.11	0.00	0.25	2.63	0.00	0.57	2.75	1.67	2.17	1.67
	7	19h50	0.11	0.00	0.00	1.88	0.00	0.57	2.63	1.50	1.42	1.50
Four	4	07h50	0.11	0.00	0.25	3.00	0.00	0.43	3.00	2.00	2.68	2.00
		12h50	0.11	0.00	0.00	1.50	0.00	0.43	2.63	2.00	1.18	2.00
	7	19h50										
Five	4	07h50	0.11	0.00	0.25	2.13	0.00	0.43	3.00	2.00	1.81	2.00
		12h50	0.11	0.00	0.25	2.63	0.00	0.29	2.25	2.00	2.45	2.00
	7	19h50										

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

POMS RESPONSE DATA

APPENDIX 9

TABLE A9.2

Profile of Mood States Responses [Subject 2 (CA)]

Phase 1 (IM A)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	EIA	ARO	POS
One	1	07h50	0.78	0.93	1.08	2.13	1.71	1.00	2.25	1.17	0.19	0.22
		12h50	2.00	2.60	3.03	1.38	1.43	2.00	1.25	1.33	-0.1	-1.3
		19h50										
	2	07h50	0.11	0.13	0.00	1.75	0.29	0.57	2.38	3.00	1.00	2.87
		19h50	0.67	0.00	0.08	0.50	2.00	1.00	1.13	1.50	-1.8	1.50
	3	07h50	0.78	0.07	0.92	0.50	2.43	1.00	0.88	0.50	-2.2	0.43
		19h50	0.00	0.00	0.00	1.00	1.71	0.43	1.63	1.17	-1.1	1.17
	4	07h50	0.22	0.00	0.00	1.38	0.57	0.29	2.25	2.00	0.74	2.00
		12h50	0.56	0.13	0.33	0.63	0.86	0.71	0.75	0.33	-0.4	0.20
	7	19h50	0.44	0.07	0.67	0.25	1.57	1.00	0.38	0.33	-1.9	0.27
Two	1	07h50	0.89	0.07	0.25	0.75	1.00	1.29	0.88	0.50	-0.6	0.43
		12h50	0.33	0.00	0.00	0.88	0.00	0.43	1.38	1.17	0.78	1.17
		19h50	0.44	0.00	0.00	2.25	0.00	0.14	1.88	2.00	2.55	2.00
	2	07h50	0.56	0.60	1.00	0.63	0.14	0.86	0.75	0.67	0.18	0.07
		19h50	0.56	0.27	0.17	0.25	0.00	1.14	0.50	0.83	-0.3	0.57
	3	07h50	0.44	0.20	0.00	1.38	0.00	0.43	1.13	1.00	1.39	0.80
		19h50	0.33	0.00	0.08	1.38	0.00	0.29	1.25	0.67	1.42	0.67
	4	07h50	0.11	0.27	1.00	0.88	0.00	0.71	0.75	0.67	0.27	0.40
		12h50	0.44	0.00	0.00	1.38	0.00	0.29	1.88	0.83	1.53	0.83
	7	19h50	0.44	0.27	0.00	1.00	0.14	0.43	1.38	1.17	0.87	0.90
Three	4	07h50	0.78	2.33	2.08	0.00	0.86	1.71	0.75	0.17	-1.8	-2.2
		12h50	0.33	0.40	0.50	0.75	0.00	0.57	1.13	0.67	0.51	0.27
	7	19h50	0.89	1.87	1.08	0.50	1.57	0.86	0.88	0.50	-1.0	-1.4
Four	4	07h50	1.56	2.20	1.00	0.38	0.57	2.00	0.75	0.67	-0.6	-1.5
		12h50	0.78	1.80	0.42	0.75	0.29	1.00	1.00	0.67	0.24	-1.1
	7	19h50	0.56	1.33	1.25	1.38	0.14	1.43	1.25	0.67	0.36	-0.7
Five	4	07h50	0.67	1.73	1.42	0.75	0.57	1.57	1.13	0.67	-0.7	-1.1
		12h50										
	7	19h50										

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 EIA: Elation
 ARO: Arousal
 POS: Positive Mood

Phase 2 (IM B)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	EIA	ARO	POS
One	1	07h50	0.78	1.87	2.08	0.50	0.43	1.14	1.00	1.33	-0.3	-0.5
		12h50	1.56	2.67	2.08	1.00	0.43	1.71	1.57	0.50	0.41	-2.2
		19h50	1.22	1.93	1.83	0.13	0.57	2.14	1.00	0.50	-1.4	-1.4
	2	07h50										
		19h50	3.11	3.47	3.25	0.25	1.71	2.43	0.00	0.17	-0.8	-3.3
	3	07h50	1.67	2.13	2.42	0.00	0.71	1.57	0.88	0.67	-0.6	-1.5
		19h50	1.11	1.13	0.75	0.50	0.43	1.71	1.00	0.33	-0.5	-0.8
	4	07h50	1.33	1.20	0.25	0.25	0.14	1.00	2.13	1.00	0.44	-0.2
		12h50	1.33	1.73	1.67	1.13	0.43	1.43	1.75	0.83	0.60	-0.9
	7	19h50	0.22	0.60	0.33	0.50	0.29	1.14	2.00	1.17	-0.7	0.57
Two	1	07h50	1.22	2.07	2.83	0.38	0.86	2.43	0.75	0.33	-1.7	-1.7
		12h50	1.33	1.67	1.83	0.38	0.57	1.71	1.13	0.83	-0.6	-0.8
		19h50	1.11	1.33	1.17	0.25	0.43	2.00	1.25	1.00	-1.1	-0.3
	2	07h50	0.89	0.53	0.08	1.13	0.14	0.43	0.88	1.00	1.44	0.47
		19h50	0.22	0.53	0.08	0.75	0.00	0.57	1.75	1.00	0.40	0.47
	3	07h50	0.22	0.80	0.08	0.63	0.14	1.00	1.13	0.67	-0.3	-0.1
		19h50	0.33	0.80	0.17	0.50	0.14	0.71	1.00	0.83	0.02	0.03
	4	07h50	0.44	0.60	0.00	0.88	0.14	0.86	1.75	1.00	0.32	0.40
		12h50	0.56	0.07	0.00	0.25	0.29	0.86	1.50	0.67	-0.3	0.60
	7	19h50	1.78	1.07	1.92	0.25	2.43	1.14	0.63	0.17	-1.5	-0.9
Three	4	07h50	0.22	0.20	0.00	0.75	0.43	0.43	1.75	1.50	0.12	1.30
		12h50	0.67	0.20	0.00	0.38	0.43	0.57	0.88	0.83	0.04	0.63
	7	19h50	0.89	0.40	0.92	0.00	2.14	1.71	0.38	0.00	-3.0	-0.4
Four	4	07h50	1.78	0.87	0.58	0.13	0.86	1.71	1.25	0.50	-0.7	-1.4
		12h50	1.78	1.67	1.08	0.00	0.71	1.86	0.5	0.00	-0.8	-1.7
	7	19h50	0.22	0.13	0.00	0.75	0.00	0.57	1.50	0.67	0.40	0.53
Five	4	07h50	0.44	0.00	0.00	0.88	0.29	0.29	1.88	2.33	0.75	2.33
		12h50	0.44	0.00	0.00	0.38	0.14	0.57	1.50	0.83	0.11	0.83
	7	19h50										

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 EIA: Elation
 ARO: Arousal
 POS: Positive Mood

TABLE A9.3

Profile of Mood States Responses [Subject 3 (LE)]

Phase 1 (IM B)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	1.33	0.27	0.42	2.88	0.14	0.43	2.63	2.33	3.64	2.07
		12h50	0.44	0.07	0.08	2.13	0.43	0.43	1.88	1.67	1.71	1.60
		19h50	0.11	0.00	0.00	2.63	0.00	0.29	2.25	2.33	2.45	2.33
	2	07h50	0.22	0.00	0.00	1.63	0.14	0.29	1.63	1.67	1.42	1.67
		19h50	0.22	0.00	0.00	2.00	0.00	0.29	1.75	1.00	1.94	1.00
	3	07h50	0.11	0.00	0.00	2.00	0.00	0.29	1.38	1.67	1.83	1.67
		19h50	0.22	0.00	0.00	2.13	0.00	0.29	1.63	2.00	2.06	2.00
	4	07h50	0.22	0.00	0.00	1.63	0.14	0.29	1.25	1.17	1.42	1.17
		12h50	0.33	0.00	0.00	2.00	0.00	0.29	1.13	1.67	2.05	1.67
	7	19h50										
Two	1	07h50	0.33	0.00	0.17	0.75	0.71	0.43	0.50	0.50	-0.1	0.50
		12h50	0.44	0.07	0.00	0.88	0.14	0.43	0.88	0.33	0.75	0.27
		19h50	0.33	0.00	0.00	1.00	0.14	0.43	1.00	0.50	0.76	0.50
	2	07h50	0.22	0.00	0.00	2.25	0.00	0.14	1.75	1.67	2.33	1.67
		19h50	0.22	0.00	0.00	1.63	0.00	0.14	1.5	1.17	1.70	1.17
	3	07h50	0.22	0.00	0.00	1.88	0.00	0.29	1.75	1.50	1.81	1.50
		19h50	0.22	0.00	0.00	1.63	0.00	0.43	1.50	1.67	1.42	1.67
	4	07h50	0.22	0.00	0.00	1.63	0.00	0.29	1.25	1.50	1.56	1.50
		12h50	0.33	0.00	0.08	1.75	0.00	0.29	1.25	1.50	1.80	1.5
	7	19h50	0.22	0.00	0.00	1.38	0.00	0.29	1.25	1.33	1.31	1.33
Three	4	07h50	0.22	0.13	0.00	1.88	0.00	0.29	1.75	1.17	1.81	1.03
		12h50	0.22	0.00	0.00	1.50	0.00	0.43	1.25	1.67	1.29	1.67
	7	19h50	0.33	0.00	0.00	2.00	0.00	0.14	1.88	1.67	2.19	1.67
Four	4	07h50	0.22	0.00	0.00	1.50	0.00	0.43	1.38	1.50	1.29	1.50
		12h50	0.22	0.00	0.00	1.75	0.00	0.29	1.25	1.17	1.69	1.17
	7	19h50	0.22	0.00	0.00	1.50	0.00	0.29	1.50	1.00	1.44	1.00
Five	4	07h50	0.22	0.00	0.00	1.75	0.00	0.29	1.75	1.33	1.69	1.33
		12h50	0.44	0.00	0.00	1.25	0.00	0.29	1.00	1.33	1.41	1.33
	7	19h50	0.22	0.00	0.00	1.63	0.00	0.57	1.25	1.17	1.28	1.17

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

Phase 2 (IM A)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.22	0.00	0.00	1.88	0.00	0.14	1.50	1.00	1.95	1.00
		12h50	0.22	0.00	0.00	1.50	0.00	0.29	1.50	1.67	1.44	1.67
		19h50										
	2	07h50	0.11	0.00	0.00	1.75	0.00	0.14	1.50	1.50	1.72	1.50
		19h50	0.22	0.00	0.00	2.00	0.00	0.29	1.50	1.50	1.94	1.50
	3	07h50	0.22	0.00	0.00	1.75	0.00	0.14	1.38	1.17	1.83	1.17
		19h50										
	4	07h50	0.22	0.00	0.00	1.50	0.00	0.29	1.63	1.17	1.44	1.17
		12h50	0.22	0.00	0.00	1.63	0.00	0.29	1.13	1.33	1.56	1.33
	7	19h50	0.22	0.00	0.00	1.75	0.14	0.57	1.38	1.67	1.26	1.67
Two	1	07h50	0.22	0.00	0.00	1.25	0.00	0.29	0.75	0.83	1.19	0.83
		12h50	0.67	0.00	0.00	1.13	0.14	0.29	0.63	0.33	1.36	0.33
		19h50	0.22	0.00	0.00	1.38	0.00	0.57	1.50	1.00	1.03	1.00
	2	07h50	0.44	0.00	0.00	1.38	0.00	0.29	1.25	0.67	1.53	0.67
		19h50	0.22	0.00	0.00	1.25	0.00	0.29	1.13	1.00	1.88	1.00
	3	07h50	0.22	0.00	0.00	0.63	0.00	0.29	1.25	1.00	0.56	1.00
		19h50										
	4	07h50	0.22	0.00	0.00	0.88	0.00	0.29	1.13	0.83	0.81	0.83
		12h50	0.22	0.00	0.00	1.50	0.00	0.14	1.38	1.33	1.58	1.33
	7	19h50	0.22	0.00	0.00	1.00	0.00	0.29	1.00	0.83	0.94	0.83
Three	4	07h50	0.22	0.00	0.00	1.63	0.00	0.57	1.38	0.67	1.28	0.67
		12h50	0.22	0.00	0.00	1.00	0.00	0.29	1.25	0.50	0.94	0.50
	7	19h50	0.33	0.00	0.00	0.75	0.00	0.14	1.13	0.33	0.94	0.33
Four	4	07h50	0.22	0.00	0.00	1.63	0.00	0.29	1.13	0.67	1.56	0.67
		12h50	0.22	0.00	0.00	0.63	0.00	0.57	1.38	0.50	0.28	0.50
	7	19h50										
Five	4	07h50	0.22	0.00	0.00	1.25	0.00	0.29	1.38	0.83	1.19	0.83
		12h50	0.44	0.00	0.00	0.75	0.00	0.13	1.13	1.17	0.77	1.17
	7	19h50	0.50	0.00	0.00	1.00	0.00	0.67	0.88	0.50	0.83	0.50

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

TABLE A9.4

Profile of Mood States Responses [Subject 4 (EA)]

Phase 1 (IM B)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50										
		12h50										
		19h50										
	2	07h50										
		19h50	0.11	0.07	0.08	1.50	0.86	0.86	1.75	1.17	-0.1	1.10
	3	07h50	0.56	0.27	0.25	1.75	1.14	0.57	1.88	1.50	0.59	1.23
		19h50	0.11	0.00	0.00	0.88	0.71	0.71	2.00	1.17	-0.4	1.17
	4	07h50	0.22	0.00	0.00	2.13	0.00	0.29	1.88	1.50	2.06	1.50
		12h50	0.56	0.00	0.08	1.38	0.00	0.29	2.00	1.17	1.65	1.17
	7	19h50										
Two	1	07h50	0.22	0.07	0.00	1.00	0.00	0.29	2.13	1.17	0.94	1.10
		12h50	0.56	0.00	0.08	0.63	0.00	0.86	1.50	0.83	0.32	0.83
		19h50	0.22	0.00	0.00	1.13	0.00	0.29	1.88	1.33	1.06	1.33
	2	07h50	0.11	0.00	0.00	1.25	0.00	0.29	2.00	1.33	1.08	1.33
		19h50	0.22	0.00	0.00	1.88	0.00	0.29	1.88	1.83	1.81	1.83
	3	07h50	0.22	0.00	0.00	1.75	0.00	0.29	1.88	1.33	1.69	1.33
		19h50	0.11	0.00	0.00	1.25	0.00	0.29	1.88	1.33	1.08	1.33
	4	07h50	0.22	0.00	0.00	1.00	0.14	0.57	1.88	1.33	0.51	1.33
		12h50	0.44	0.27	0.83	0.88	0.14	0.86	0.75	0.50	0.32	0.23
	7	19h50	0.11	0.00	0.08	1.75	0.14	0.43	2.63	1.83	1.29	1.83
Three	4	07h50	0.11	0.00	0.00	1.25	0.00	0.29	2.75	2.33	1.08	2.33
		12h50	0.33	0.00	0.00	1.75	0.00	0.57	2.38	1.67	1.51	1.67
	7	19h50	0.11	0.00	0.00	2.38	0.00	0.29	2.38	1.83	2.20	1.83
Four	4	07h50	0.11	0.00	0.00	2.13	0.00	0.29	2.38	2.67	1.95	2.67
		12h50	0.22	0.00	0.00	1.63	0.00	0.29	1.88	1.67	1.56	1.67
	7	19h50	0.11	0.00	0.00	1.75	0.14	0.29	2.00	1.33	1.43	1.33
Five	4	07h50	0.22	0.00	0.00	1.25	0.00	0.29	1.75	1.33	1.19	1.33
		12h50	0.11	0.00	0.00	2.00	0.00	0.29	2.25	1.33	1.83	1.33
	7	19h50	0.11	0.00	0.00	1.63	0.00	0.29	2.25	1.33	1.45	1.33

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

Phase 2 (IM A)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.11	0.00	0.00	2.13	0.00	0.14	2.13	1.67	2.09	1.67
		12h50	0.22	0.00	0.75	1.63	0.00	0.29	1.13	1.17	1.56	1.17
		19h50	0.11	0.00	0.00	2.00	0.00	0.14	2.25	1.33	1.97	1.33
	2	07h50	0.11	0.00	0.00	1.88	0.00	0.79	2.25	1.50	1.70	1.50
		19h50										
	3	07h50	0.33	0.00	0.00	1.00	1.00	0.29	1.63	0.83	0.05	0.83
		19h50	0.11	0.00	0.00	1.25	0.14	0.29	1.88	1.00	0.93	1.00
	4	07h50	0.22	0.00	0.00	1.63	0.00	0.29	2.25	1.33	1.56	1.33
		12h50	0.22	0.00	0.00	1.88	0.00	0.29	2.38	1.17	1.81	1.17
	7	19h50	0.11	0.00	0.00	1.38	0.00	0.29	2.38	1.50	1.20	1.50
Two	1	07h50	0.22	0.00	0.00	1.38	0.00	0.29	2.25	1.33	1.31	1.33
		12h50	0.22	0.00	0.00	1.38	0.00	0.29	2.00	1.00	1.31	1.00
		19h50	0.11	0.00	0.00	1.88	0.00	0.14	2.38	1.67	1.83	1.67
	2	07h50	0.22	0.00	0.00	1.50	0.00	0.29	2.25	1.33	1.44	1.33
		19h50	0.22	0.00	0.00	2.00	0.00	0.29	2.38	2.17	1.94	2.17
	3	07h50	0.22	0.00	0.00	1.38	0.00	0.29	2.25	1.33	1.31	1.33
		19h50	0.22	0.00	0.00	1.88	0.00	0.29	2.25	1.67	1.81	1.67
	4	07h50	0.11	0.00	0.00	1.63	0.00	0.29	2.25	1.50	1.45	1.50
		12h50	0.11	0.00	0.00	1.88	0.00	0.29	2.25	1.33	1.70	1.33
	7	19h50	0.22	0.00	0.00	2.00	0.00	0.29	2.25	1.50	1.94	1.50
Three	4	07h50	0.22	0.00	0.00	1.63	0.00	0.29	2.25	1.33	1.56	1.33
		12h50	0.22	0.00	0.00	1.63	0.00	0.29	2.25	1.50	1.56	1.50
	7	19h50	0.22	0.07	0.00	1.50	0.00	0.29	2.13	1.33	1.44	1.27
Four	4	07h50	0.11	0.00	0.00	1.75	0.00	0.29	2.13	1.17	1.58	1.17
		12h50										
	7	19h50	0.11	0.00	0.00	1.75	0.00	0.29	2.25	1.67	1.58	1.67
Five	4	07h50	0.22	0.00	0.00	1.75	0.00	0.29	2.38	1.33	1.69	1.33
		12h50	0.22	0.00	0.00	1.63	0.00	0.29	2.25	1.67	1.56	1.67
	7	19h50	0.11	0.00	0.00	1.63	0.00	0.29	2.38	1.33	1.45	1.33

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

TABLE A9.5

Profile of Mood States Responses [Subject 5 (W)]

Phase 1 (IM B)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.90	0.00	0.00	2.88	0.00	0.57	2.00	2.17	3.19	2.17
		12h50	0.13	0.00	0.00	3.13	0.00	0.14	3.13	2.83	3.11	2.83
		19h50										
	2	07h50	0.11	0.00	0.00	2.25	0.00	0.29	2.75	2.50	20.8	2.50
		19h50	0.11	0.00	0.00	2.75	0.00	0.14	2.25	2.83	2.72	2.83
	3	07h50	0.00	0.00	0.00	2.63	0.00	0.57	3.00	2.83	2.05	2.83
		19h50	0.00	0.13	0.00	1.50	0.71	0.43	2.13	2.17	0.36	2.03
	4	07h50	0.11	0.00	0.00	2.38	0.00	0.14	2.63	2.33	2.34	2.33
		12h50	0.00	0.00	0.00	2.13	0.00	0.29	2.25	2.00	1.84	2.00
	7	19h50	0.11	0.20	0.00	1.38	0.29	0.43	1.75	1.83	0.77	1.63
Two	1	07h50	0.11	0.00	0.00	2.88	0.00	0.29	2.50	2.50	2.70	2.50
		12h50	0.11	0.00	0.00	2.75	0.00	0.14	3.00	2.83	2.72	2.83
		19h50	0.11	0.00	0.00	2.38	0.00	0.29	2.38	2.50	2.20	2.50
	2	07h50	0.11	0.00	0.00	2.13	0.00	0.14	2.75	2.33	2.09	2.33
		19h50	0.11	0.00	0.17	1.38	0.00	0.29	1.88	2.00	1.20	2.00
	3	07h50	0.11	0.00	0.00	1.25	0.57	0.29	2.38	1.50	0.50	1.50
		19h50	0.11	0.00	0.00	1.00	0.57	0.29	2.00	1.50	0.25	1.50
	4	07h50	0.11	0.00	0.00	2.38	0.00	0.14	3.13	2.17	2.34	2.17
		12h50	0.00	0.00	0.00	2.63	0.00	0.57	3.63	2.67	2.05	2.67
	7	19h50	0.00	0.00	0.00	1.50	0.71	0.14	2.75	1.83	0.64	1.83
Three	4	07h50	0.00	0.00	0.00	1.75	0.29	0.14	2.75	2.17	1.32	2.17
		12h50	0.00	0.00	0.00	2.13	0.00	0.00	3.63	2.83	2.13	2.83
	7	19h50	0.11	1.20	0.17	0.38	2.14	1.00	1.50	0.83	-2.7	-0.4
Four	4	07h50	0.44	0.00	0.17	2.13	0.43	0.29	2.13	2.17	1.86	2.17
		12h50	0.22	0.00	0.00	1.75	0.00	0.29	2.38	2.00	1.69	2.00
	7	19h50										
Five	4	07h50	0.22	0.00	0.00	1.50	0.57	0.43	2.00	1.33	0.72	1.33
		12h50	0.22	0.00	0.00	1.13	0.14	0.29	2.00	2.00	0.92	2.00
	7	19h50	0.11	0.00	0.00	2.25	0.00	0.14	2.88	2.50	2.22	2.50

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

Phase 2 (IM A)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.11	0.00	0.00	3.00	0.00	0.14	3.00	2.50	2.97	2.50
		12h50	0.11	0.00	0.00	2.75	0.00	0.14	3.00	2.50	2.72	2.50
		19h50										
	2	07h50	0.11	0.00	0.00	3.00	0.00	0.14	2.63	2.50	2.97	2.50
		19h50	0.11	0.00	0.00	2.63	0.00	0.14	3.00	2.50	2.59	2.50
	3	07h50	0.11	0.00	0.00	3.00	0.00	0.14	2.63	2.50	2.97	2.50
		19h50	0.11	0.00	0.00	2.63	0.00	0.14	3.00	2.50	2.59	2.50
	4	07h50	0.11	0.00	0.00	2.63	0.00	0.14	3.00	2.50	2.59	2.50
		12h50	0.11	0.00	0.00	3.00	0.00	0.14	3.00	2.50	2.97	2.50
	7	19h50	0.11	0.00	0.00	2.63	0.00	0.14	3.00	2.50	2.59	2.50
Two	1	07h50	0.11	0.00	0.00	2.63	0.00	0.14	3.00	2.50	2.59	2.50
		12h50	0.11	0.00	0.00	2.50	0.00	0.14	3.00	2.33	2.47	2.33
		19h50	0.11	0.00	0.00	2.50	0.00	0.29	2.75	2.00	2.33	2.00
	2	07h50	0.11	0.00	0.00	2.50	0.00	0.14	2.63	2.50	2.47	2.50
		19h50	0.11	0.00	0.00	1.50	2.14	0.14	3.13	1.50	-0.7	1.50
	3	07h50	0.11	0.00	0.00	3.00	0.00	0.14	3.00	2.33	2.97	2.33
		19h50	0.00	0.00	0.17	1.75	1.14	0.29	1.88	1.17	-0.6	1.17
	4	07h50	0.11	0.00	0.00	2.38	0.00	0.29	2.25	1.83	2.20	1.83
		12h50	0.56	0.00	0.00	0.50	2.43	0.86	1.50	0.67	-2.2	0.67
	7	19h50	0.11	0.00	0.00	0.88	1.14	0.43	3.00	1.33	-0.6	1.33
Three	4	07h50	0.11	0.00	0.33	0.88	3.43	0.43	3.00	0.83	-2.9	0.83
		12h50	0.11	0.00	0.33	0.63	3.43	0.43	3.00	1.50	-3.1	1.50
	7	19h50	0.11	0.20	0.00	2.38	0.29	0.14	3.25	2.17	2.06	1.97
Four	4	07h50	0.11	0.00	0.00	3.25	0.00	0.14	3.13	2.83	3.22	2.83
		12h50	0.11	0.00	0.00	2.63	0.00	0.14	3.00	2.50	2.59	2.50
	7	19h50	0.11	0.00	0.00	3.00	0.00	0.14	3.00	2.67	2.97	2.67
Five	4	07h50	0.11	0.00	0.00	3.25	0.00	0.14	3.13	2.50	3.13	2.50
		12h50	0.11	0.20	0.00	3.00	0.00	0.14	3.00	2.50	2.97	2.30
	7	19h50										

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

TABLE A9.6

Profile of Mood States Responses [Subject 6 (L1)]

Phase 1 (IM B)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.44	0.00	0.00	1.13	0.14	0.29	2.38	1.50	1.41	1.50
		12h50	0.22	0.00	0.17	1.50	0.00	0.29	2.13	1.33	1.44	1.33
		19h50	0.44	0.00	0.08	1.00	0.57	0.57	1.75	1.17	0.30	1.17
	2	07h50	0.33	0.00	0.08	1.25	0.14	0.29	1.88	1.00	1.16	1.00
		19h50	0.22	0.00	0.08	0.75	0.00	0.43	1.63	0.83	0.54	0.83
	3	07h50	0.33	0.00	0.08	1.25	0.00	0.29	2.25	0.83	1.30	0.83
		19h50	0.22	0.00	0.08	1.00	0.00	0.29	2.00	1.33	0.94	1.33
	4	07h50	0.22	0.00	0.17	1.25	0.00	0.43	1.50	0.83	1.04	0.83
		12h50	0.44	0.00	0.08	0.88	0.00	0.43	1.25	0.67	0.89	0.67
	7	19h50	0.33	0.00	0.00	0.50	0.29	0.57	1.00	0.33	0.00	0.33
Two	1	07h50	0.33	0.00	0.08	1.00	0.00	0.43	1.50	1.00	0.91	1.00
		12h50	0.33	0.00	0.08	1.00	0.00	0.43	1.25	0.67	0.91	0.67
		19h50	0.33	0.00	0.08	0.38	0.00	0.43	0.88	0.33	0.28	0.33
	2	07h50	0.33	0.00	0.08	0.88	0.00	0.43	1.63	0.50	0.78	0.50
		19h50	0.33	0.00	0.08	0.75	0.00	0.43	0.75	0.33	0.66	0.33
	3	07h50	0.33	0.00	0.08	1.00	0.00	0.43	1.13	0.50	0.91	0.50
		19h50	0.33	0.00	0.08	0.75	0.00	0.43	0.88	0.50	0.66	0.50
	4	07h50	0.44	0.00	0.08	0.38	0.00	0.43	1.00	0.17	0.39	0.17
		12h50	0.33	0.00	0.08	0.88	0.00	0.43	1.25	0.67	0.78	0.67
	7	19h50	0.33	0.07	0.00	0.00	0.00	0.43	0.88	0.17	-0.1	0.10
Three	4	07h50	0.44	0.00	0.17	0.88	0.00	0.43	1.38	0.50	0.89	0.50
		12h50	0.33	0.00	0.08	0.63	0.00	0.29	1.00	0.67	0.67	0.67
	7	19h50	0.67	0.40	0.25	0.00	0.43	0.57	0.13	0.00	-0.3	-0.4
Four	4	07h50	0.44	0.00	0.08	0.38	0.14	0.43	1.25	0.17	0.25	0.17
		12h50	0.44	0.00	0.08	0.50	0.00	0.43	1.50	0.50	0.52	0.50
	7	19h50	0.33	0.00	0.08	0.50	0.00	0.43	1.00	0.33	0.41	0.33
Five	4	07h50	0.33	0.00	0.08	0.63	0.00	0.43	0.88	0.50	0.53	0.50
		12h50	0.44	0.00	0.00	0.63	0.00	0.43	1.00	0.33	0.64	0.33
	7	19h50	0.33	0.00	0.08	0.63	0.00	0.43	1.00	0.17	0.51	0.17

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

Phase 2 (IM A)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.22	0.00	0.08	0.38	0.14	0.43	1.13	0.33	0.21	0.33
		12h50	0.33	0.00	0.08	0.38	0.00	0.43	1.00	0.50	0.28	0.50
		19h50	0.44	0.00	0.08	0.25	0.14	0.43	0.88	0.33	0.12	0.33
	2	07h50	0.44	0.00	0.00	0.13	0.14	0.43	0.88	0.17	0.00	0.17
		19h50										
	3	07h50	0.44	0.00	0.08	0.13	0.17	0.43	1.13	0.33	0.00	0.33
		19h50	0.44	0.00	0.08	0.38	0.14	0.43	1.00	0.17	0.25	0.17
	4	07h50	0.44	0.00	0.08	0.38	0.00	0.57	1.13	0.50	0.25	0.50
		12h50	0.44	0.00	0.08	0.50	0.14	0.57	1.00	0.17	0.23	0.17
	7	19h50	0.56	0.00	0.08	0.13	0.14	0.43	0.75	0.33	0.11	0.33
Two	1	07h50	0.56	0.00	0.08	0.50	0.14	0.57	1.00	0.33	0.34	0.33
		12h50	0.67	0.00	0.17	0.38	0.00	0.43	1.00	0.00	0.61	0.00
		19h50	0.67	0.00	0.17	0.50	0.33	0.43	1.13	0.33	0.41	0.33
	2	07h50	0.67	0.00	0.17	0.38	0.14	0.43	1.13	0.17	0.47	0.17
		19h50	0.56	0.00	0.17	0.50	0.14	0.43	1.13	0.33	0.48	0.33
	3	07h50	0.78	0.00	0.17	0.25	0.14	0.43	1.00	0.17	0.46	0.17
		19h50										
	4	07h50	0.67	0.00	0.17	0.50	0.00	0.43	1.00	0.50	0.24	0.50
		12h50	0.44	0.00	0.08	0.50	0.00	0.57	1.13	0.33	0.37	0.33
	7	19h50	0.22	0.00	0.08	0.50	0.00	0.43	1.50	0.67	0.29	0.67
Three	4	07h50	0.33	0.00	0.17	0.63	0.00	0.43	1.50	0.83	0.53	0.83
		12h50	0.33	0.00	0.08	0.38	0.00	0.43	1.25	0.67	0.28	0.67
	7	19h50	0.33	0.00	0.08	0.38	0.00	0.43	0.88	0.50	0.28	0.50
Four	4	07h50	0.33	0.00	0.08	0.50	0.00	0.43	1.13	0.17	0.41	0.17
		12h50	0.56	0.00	0.08	0.50	0.00	0.43	1.00	0.33	0.63	0.33
	7	19h50	0.44	0.00	0.17	0.50	0.14	0.43	0.88	0.50	0.37	0.50
Five	4	07h50	0.44	0.00	0.17	0.63	0.00	0.57	1.13	0.33	0.50	0.33
		12h50	0.33	0.00	0.08	0.50	0.00	0.43	1.13	0.50	0.41	0.50
	7	19h50	0.44	0.00	0.17	0.50	0.00	0.43	1.00	0.33	0.52	0.33

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

TABLE A9.7

Profile of Mood States Responses [Subject 7 (EG)]

Phase 1 (TM A)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.22	0.00	0.00	1.13	0.00	0.57	2.00	1.33	0.78	1.33
		12h50	0.33	0.00	0.00	0.63	0.00	0.43	1.88	0.67	0.53	0.67
		19h50	0.11	0.00	0.00	0.88	0.00	0.29	2.00	1.33	0.70	1.33
	2	07h50	0.22	0.00	0.00	1.00	0.00	0.29	1.75	1.33	0.94	1.33
		19h50	0.22	0.00	0.00	0.75	0.00	0.43	1.50	1.17	0.54	1.17
	3	07h50	0.22	0.00	0.00	0.88	0.00	0.57	1.63	1.00	0.53	1.00
		19h50	0.22	0.00	0.00	0.63	0.00	0.43	2.00	1.00	0.42	1.00
	4	07h50	0.22	0.00	0.00	0.75	0.00	0.57	1.50	1.00	0.40	1.00
		12h50	0.33	0.00	0.00	0.63	0.00	0.43	1.50	0.50	0.53	0.50
	7	19h50										
Two	1	07h50	0.33	0.00	0.00	0.63	0.00	0.43	1.38	0.50	0.53	0.50
		12h50	0.33	0.00	0.00	0.50	0.00	0.43	1.63	0.83	0.41	0.83
		19h50	0.33	0.00	0.00	0.75	0.00	0.43	1.38	1.17	0.66	1.17
	2	07h50	0.33	0.00	0.00	0.63	0.00	0.57	1.38	0.83	0.39	0.83
		19h50	0.33	0.00	0.00	0.63	0.00	0.43	1.50	0.67	0.53	0.67
	3	07h50	0.22	0.00	0.00	0.75	0.00	0.57	1.13	0.83	0.40	0.83
		19h50	0.33	0.00	0.00	0.25	0.00	0.57	1.38	0.67	0.01	0.67
	4	07h50	0.33	0.00	0.00	0.38	0.00	0.43	1.63	1.00	0.28	1.00
		12h50	0.33	0.00	0.00	0.38	0.00	0.43	1.25	0.50	0.28	0.50
	7	19h50	0.22	0.00	0.00	0.75	0.00	0.43	1.25	0.83	0.54	0.83
Three	4	07h50	0.22	0.00	0.00	0.63	0.00	0.43	1.50	0.50	0.42	0.50
		12h50	0.33	0.00	0.00	0.50	0.00	0.43	1.63	0.67	0.41	0.67
	7	19h50	0.33	0.00	0.00	0.63	0.00	0.43	1.50	0.83	0.53	0.83
Four	4	07h50										
		12h50										
	7	19h50										
Five	4	07h50										
		12h50										
	7	19h50										

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

Phase 2 (TM B)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.33	0.00	0.00	0.75	0.00	0.43	1.38	0.67	0.66	0.67
		12h50	0.22	0.00	0.00	0.75	0.00	0.43	1.63	0.83	0.54	0.83
		19h50	0.22	0.00	0.00	0.63	0.00	0.43	1.75	0.67	0.42	0.67
	2	07h50	0.22	0.00	0.00	0.75	0.00	0.43	1.50	0.67	0.54	0.67
		19h50	0.33	0.00	0.00	0.75	0.00	0.43	1.50	1.17	0.66	1.17
	3	07h50	0.22	0.00	0.00	0.50	0.00	0.43	1.63	0.83	0.29	0.83
		19h50	0.22	0.00	0.00	0.75	0.00	0.43	1.50	0.67	0.54	0.67
	4	07h50	0.33	0.00	0.00	0.63	0.00	0.57	1.75	0.67	0.39	0.67
		12h50	0.33	0.00	0.00	0.63	0.00	0.43	1.63	0.83	0.53	0.83
	7	19h50	0.33	0.00	0.00	0.75	0.00	0.43	1.63	1.17	0.66	1.17
Two	1	07h50	0.33	0.00	0.00	0.75	0.00	0.43	1.88	1.00	0.66	1.00
		12h50	0.22	0.00	0.00	0.63	0.00	0.43	1.63	0.83	0.42	0.83
		19h50	0.33	0.00	0.00	0.50	0.00	0.43	1.50	0.83	0.41	0.83
	2	07h50	0.33	0.00	0.00	0.63	0.00	0.43	1.50	1.00	0.53	1.00
		19h50	0.22	0.00	0.00	0.63	0.00	0.57	1.63	0.83	0.28	0.83
	3	07h50	0.33	0.00	0.00	0.50	0.00	0.43	1.38	0.83	0.41	0.83
		19h50										
	4	07h50	0.33	0.00	0.00	0.63	0.00	0.43	1.63	0.67	0.53	0.67
		12h50	0.33	0.00	0.00	0.50	0.00	0.43	1.75	0.67	0.41	0.67
	7	19h50	0.33	0.00	0.00	0.50	0.00	0.43	1.75	0.83	0.41	0.83
Three	4	07h50	0.33	0.00	0.00	0.50	0.00	0.43	1.63	0.83	0.41	0.83
		12h50	0.33	0.00	0.00	0.38	0.00	0.43	1.75	1.00	0.28	1.00
	7	19h50	0.33	0.00	0.00	0.88	0.00	0.43	1.38	0.50	0.78	0.50
Four	4	07h50	0.33	0.00	0.00	0.38	0.00	0.43	1.75	0.83	0.28	0.83
		12h50	0.33	0.00	0.00	0.63	0.00	0.43	1.63	0.67	0.53	0.67
	7	19h50	0.22	0.00	0.00	0.63	0.00	0.71	1.63	0.67	0.13	0.67
Five	4	07h50	0.33	0.00	0.00	0.50	0.00	0.71	1.75	0.67	0.20	0.67
		12h50	0.33	0.00	0.00	0.38	0.00	0.43	1.50	0.50	0.28	0.50
	7	19h50	0.33	0.00	0.00	0.38	0.00	0.57	1.75	0.50	0.14	0.50

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

TABLE A9.8

Profile of Mood States Responses [Subject 8 (CV)]

Phase 1 (IM A)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.56	0.00	0.00	1.25	0.86	0.57	2.13	1.00	0.38	1.00
		12h50	0.22	0.00	0.00	2.00	0.00	0.29	2.00	1.00	1.94	1.00
		19h50	0.67	0.00	0.00	0.50	0.57	0.43	1.63	0.67	0.17	0.67
	2	07h50	0.44	0.00	0.00	0.75	0.00	0.57	1.63	0.83	0.62	0.83
		19h50	1.00	0.00	0.00	0.00	0.29	0.71	1.00	0.17	0.00	0.17
	3	07h50	0.33	0.00	0.00	1.50	0.00	0.57	2.00	1.17	1.26	1.17
		19h50	0.89	0.00	0.00	0.63	0.29	0.71	1.50	0.50	0.51	0.50
	4	07h50	0.22	0.00	0.00	2.00	0.00	0.43	2.63	2.00	1.79	2.00
		12h50	0.22	0.00	0.00	1.50	0.00	0.57	1.75	0.83	1.15	0.83
	7	19h50										
Two	1	07h50	0.22	0.00	0.00	1.50	0.29	0.57	2.00	1.17	0.87	1.17
		12h50	0.89	0.13	0.00	0.13	0.86	0.86	0.63	0.17	-0.7	0.83
		19h50	0.78	0.07	0.00	0.38	0.57	0.43	1.63	0.50	0.15	0.43
	2	07h50	0.44	0.07	0.08	0.75	0.14	0.57	1.38	0.50	0.48	0.43
		19h50	0.33	0.00	0.00	0.75	0.00	0.43	1.63	0.50	0.66	0.50
	3	07h50			0.33	1.75	0.00		1.75	1.33	1.75	
		19h50	0.22	0.00	0.00	0.88	0.00	0.29	2.00	1.00	0.81	1.00
	4	07h50	0.44	0.00	0.00	1.50	0.00	0.29	1.75	1.17	1.66	1.17
		12h50	0.56	0.13	0.08	1.13	0.14	0.57	2.00	0.50	0.97	0.37
	7	19h50	0.22	0.00	0.00	0.63	0.00	0.43	2.00	0.67	0.42	0.67
Three	4	07h50	0.11	0.00	0.00	1.00	0.00	0.14	2.13	1.83	0.97	1.83
		12h50	0.22	0.00	0.00	1.00	0.00	0.29	2.25	1.67	0.94	1.67
	7	19h50	0.25	0.14	0.00	1.63	0.00	0.57	2.25	1.17	1.30	1.02
Four	4	07h50	0.22	0.00	0.00	1.00	0.00	0.43	1.63	0.83	0.79	0.83
		12h50	1.22	0.13	0.50	2.13	0.29	0.43	1.25	0.50	2.63	0.37
	7	19h50	0.33	0.00	0.00	1.25	0.00	0.43	2.00	1.50	1.16	1.50
Five	4	07h50	0.44	0.00	0.00	2.00	0.00	0.14	2.38	1.83	2.30	1.83
		12h50	0.11	0.00	0.00	1.75	0.00	0.14	2.13	2.00	1.72	2.00
	7	19h50	0.22	0.00	0.00	1.63	0.00	0.14	2.25	1.83	1.82	1.83

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

Phase 2 (IM B)

Week	Day	Time	Computed Response Ratings									
			ANX	DEP	ANG	VIG	FAT	CON	FRI	ELA	ARO	POS
One	1	07h50	0.89	0.53	0.17	1.00	0.14	0.43	1.88	0.33	1.32	-0.2
		12h50	1.00	0.33	0.08	0.88	0.14	0.57	1.13	0.17	1.16	-0.2
		19h50	0.33	0.20	0.08	0.50	0.14	0.43	1.00	0.50	0.26	0.30
	2	07h50	0.67	0.13	0.17	0.75	0.00	0.43	1.88	0.50	0.99	0.37
		19h50										
	3	07h50	0.56	0.13	0.17	1.00	0.00	0.43	1.25	0.33	1.13	0.20
		19h50										
	4	07h50	0.44	0.07	0.08	0.38	0.00	0.57	1.25	0.33	0.25	0.27
		12h50	0.22	0.00	0.00	1.38	0.00	0.43	2.00	0.67	1.17	0.67
	7	19h50										
Two	1	07h50	0.33	0.07	0.00	0.88	0.14	0.43	1.13	0.33	0.64	0.27
		12h50	0.44	0.13	0.08	0.63	0.57	0.43	1.13	0.17	0.07	0.63
		19h50	0.78	0.47	0.08	1.00	0.86	0.71	1.63	0.50	0.21	0.83
	2	07h50										
		19h50										
	3	07h50										
		19h50										
	4	07h50										
		12h50										
	7	19h50										
Three	4	07h50										
		12h50										
	7	19h50										
Four	4	07h50										
		12h50										
	7	19h50										
Five	4	07h50										
		12h50										
	7	19h50										

KEY TO THE ABBREVIATIONS USED:

ANX: Anxiety
 DEP: Depression
 ANG: Anger
 VIG: Vigour
 FAT: Fatigue
 CON: Confusion
 FRI: Friendliness
 ELA: Elation
 ARO: Arousal
 POS: Positive Mood

POMS Scale	Weeks	TM A $\pm$ SEM	MRT	F	P	TM B $\pm$ SEM	F	P
Anxiety	1	0.25 $\pm$ 0.04				0.42 $\pm$ 0.07	<i>4.00[§]</i>	<i>0.0477</i>
	2	0.29 $\pm$ 0.03				0.32 $\pm$ 0.04		
	3	0.29 $\pm$ 0.04		0.34	0.8510	0.29 $\pm$ 0.05	1.06	0.3768
	4	0.35 $\pm$ 0.10				0.42 $\pm$ 0.11		
	5	0.28 $\pm$ 0.05				0.27 $\pm$ 0.03		
Depression	1	0.06 $\pm$ 0.05	*			0.29 $\pm$ 0.09	<i>4.75[§]</i>	<i>0.0313</i>
	2	0.02 $\pm$ 0.01	*			0.15 $\pm$ 0.05		
	3	0.23 $\pm$ 0.14	*	2.77 [§]	0.0288	0.12 $\pm$ 0.06	1.38	0.2417
	4	0.33 $\pm$ 0.18	*			0.19 $\pm$ 0.13		
	5	0.13 $\pm$ 0.12	*			0.00 $\pm$ 0.00		
Anger	1	0.18 $\pm$ 0.06				0.31 $\pm$ 0.09	<i>1.54</i>	<i>0.2171</i>
	2	0.10 $\pm$ 0.02				0.19 $\pm$ 0.06		
	3	0.26 $\pm$ 0.11		0.95	0.4383	0.10 $\pm$ 0.05	1.59	0.1786
	4	0.24 $\pm$ 0.09				0.12 $\pm$ 0.06		
	5	0.17 $\pm$ 0.09				0.04 $\pm$ 0.02		
Vigour	1	1.65 $\pm$ 0.14				1.57 $\pm$ 0.12	<i>0.17</i>	<i>0.6845</i>
	2	1.49 $\pm$ 0.12				1.29 $\pm$ 0.10		
	3	1.22 $\pm$ 0.21		0.92	0.4559	1.26 $\pm$ 0.19	1.37	0.2471
	4	1.73 $\pm$ 0.28				1.18 $\pm$ 0.19		
	5	1.71 $\pm$ 0.27				1.24 $\pm$ 0.16		
Fatigue	1	0.24 $\pm$ 0.07				0.18 $\pm$ 0.04	<i>0.62</i>	<i>0.4395</i>
	2	0.16 $\pm$ 0.06				0.13 $\pm$ 0.04		
	3	0.46 $\pm$ 0.23		1.73	0.1452	0.28 $\pm$ 0.14	1.14	0.3395
	4	0.07 $\pm$ 0.04				0.12 $\pm$ 0.06		
	5	0.04 $\pm$ 0.04				0.06 $\pm$ 0.03		
Confusion	1	0.37 $\pm$ 0.04				0.53 $\pm$ 0.06	<i>4.51[§]</i>	<i>0.0356</i>
	2	0.36 $\pm$ 0.03				0.47 $\pm$ 0.05		
	3	0.43 $\pm$ 0.08		0.78	0.5405	0.47 $\pm$ 0.08	0.52	0.7202
	4	0.50 $\pm$ 0.13				0.54 $\pm$ 0.10		
	5	0.40 $\pm$ 0.09				0.39 $\pm$ 0.03		
Friendliness	1	2.01 $\pm$ 0.12				1.95 $\pm$ 0.09	<i>0.22</i>	<i>0.6474</i>
	2	1.90 $\pm$ 0.11				1.79 $\pm$ 0.09		
	3	1.90 $\pm$ 0.19		0.15	0.9608	1.83 $\pm$ 0.19	0.62	0.6525
	4	1.93 $\pm$ 0.24				1.71 $\pm$ 0.14		
	5	2.01 $\pm$ 0.24				1.77 $\pm$ 0.14		
Elation	1	1.57 $\pm$ 0.13				1.52 $\pm$ 0.11	<i>0.07</i>	<i>0.7975</i>
	2	1.38 $\pm$ 0.12				1.25 $\pm$ 0.08		
	3	1.17 $\pm$ 0.20		0.72	0.5787	1.25 $\pm$ 0.16	1.64	0.1670
	4	1.48 $\pm$ 0.28				1.15 $\pm$ 0.18		
	5	1.49 $\pm$ 0.26				1.24 $\pm$ 0.16		
Arousal	1	1.30 $\pm$ 0.18				1.28 $\pm$ 0.16	<i>0.01</i>	<i>0.9465</i>
	2	1.26 $\pm$ 0.15				1.01 $\pm$ 0.13		
	3	0.62 $\pm$ 0.37		1.49	0.2079	0.79 $\pm$ 0.31	0.97	0.4262
	4	1.51 $\pm$ 0.33				0.94 $\pm$ 0.21		
	5	1.55 $\pm$ 0.31				1.05 $\pm$ 0.17		
Positive Mood	1	1.50 $\pm$ 0.14				1.23 $\pm$ 0.17	<i>0.154</i>	<i>0.2178</i>
	2	1.36 $\pm$ 0.12				1.09 $\pm$ 0.11		
	3	0.94 $\pm$ 0.27		1.12	0.3492	1.13 $\pm$ 0.19	0.33	0.8567
	4	1.15 $\pm$ 0.38				0.96 $\pm$ 0.26		
	5	1.36 $\pm$ 0.30				1.24 $\pm$ 0.16		

The mean responses to each of the POMS scales for week 1 for both treatments are given in the body of the table. For week 1, $n = 61$ for each phase, $df = 1,120$. Bold italicised F ratios and P values indicate significance for weeks 1.
 For the comparison of the treatment weeks (2-5) with week 1, $n = 177$ for each phase, $df = 4,172$.
 The *'s in the MRT column indicates where the differences in the weeks occurred.
 § indicates a P value of between 0.015 and 0.05

TABLE A9.2.1 Average Weekly Responses to the 10 Scales of the POMS Questionnaire (Mean Values for 7 Subjects)

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	0.07 $\pm$ 0.01	0.11 $\pm$ 0.00	8.73 [†]	0.0058
2	0.59 $\pm$ 0.08	0.83 $\pm$ 0.14	2.15	0.1528
3	0.20 $\pm$ 0.03	0.27 $\pm$ 0.02	0.37	0.5561
4	0.19 $\pm$ 0.01	0.20 $\pm$ 0.03	0.32	0.5802
5	0.14 $\pm$ 1.02	0.12 $\pm$ 0.03	0.12	0.7315
6	0.49 $\pm$ 0.04	0.38 $\pm$ 0.02	6.12 [§]	0.0186

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
§ indicates a P value of between 0.015 and 0.05
† indicates a P value of less than 0.01

TABLE A9.2.2 Average "Anxiety" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	0.00 $\pm$ 0.00	0.01 $\pm$ 0.01	1.00	0.3248
2	0.78 $\pm$ 0.21	0.82 $\pm$ 0.16	0.02	0.8971
3	0.00 $\pm$ 0.00	0.01 $\pm$ 0.01	1.89	0.1778
4	0.00 $\pm$ 0.00	0.02 $\pm$ 0.02	0.91	0.3564
5	0.02 $\pm$ 0.02	0.07 $\pm$ 0.07	0.42	0.5270
6	0.00 $\pm$ 0.00	0.03 $\pm$ 0.02	1.35	0.2531

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34

TABLE A9.2.3 Average "Depression" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	0.29 $\pm$ 0.01	0.22 $\pm$ 0.03	5.53 [§]	0.0250
2	0.60 $\pm$ 0.15	0.63 $\pm$ 0.21	0.01	0.9122
3	0.00 $\pm$ 0.00	0.01 $\pm$ 0.01	11.89	0.1786
4	0.00 $\pm$ 0.00	0.06 $\pm$ 0.05	1.45	0.2376
5	0.05 $\pm$ 0.03	0.03 $\pm$ 0.02	0.37	0.5531
6	0.13 $\pm$ 0.01	0.09 $\pm$ 0.01	6.76 [§]	0.0137

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
§ indicates a P value of between 0.015 and 0.05

TABLE A9.2.4 Average "Anger" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	3.22 $\pm$ 0.07	2.40 $\pm$ 0.14	46.8 [†]	0.0000
2	0.90 $\pm$ 0.13	0.49 $\pm$ 0.08	7.30 [§]	0.0109
3	1.12 $\pm$ 0.08	1.55 $\pm$ 0.10	12.0 [†]	0.0015
4	1.67 $\pm$ 0.05	1.48 $\pm$ 0.11	2.55	0.1198
5	2.12 $\pm$ 0.23	1.85 $\pm$ 0.16	0.94	0.3491
6	0.47 $\pm$ 0.02	0.60 $\pm$ 0.07	2.94	0.0957

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
§ indicates a P value of between 0.015 and 0.05
† indicates a P value of less than 0.01

TABLE A9.2.5 Average "Vigour" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	0.11 $\pm$ 0.07	0.01 $\pm$ 0.01	1.99	0.1676
2	0.31 $\pm$ 0.11	0.59 $\pm$ 0.17	1.89	0.1785
3	0.01 $\pm$ 0.01	0.06 $\pm$ 0.04	1.35	0.2535
4	0.00 $\pm$ 0.00	0.03 $\pm$ 0.01	4.86 [§]	0.0344
5	0.78 $\pm$ 0.29	0.30 $\pm$ 0.12	2.27	0.1409
6	0.06 $\pm$ 0.02	0.03 $\pm$ 0.02	0.63	0.4405

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
§ indicates a P value of between 0.015 and 0.05

TABLE A9.2.6 Average "Fatigue" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	0.13 $\pm$ 0.01	0.32 $\pm$ 0.04	19.0 [†]	0.0001
2	0.89 $\pm$ 0.14	1.11 $\pm$ 0.16	1.09	0.3047
3	0.35 $\pm$ 0.04	0.32 $\pm$ 0.03	0.42	0.5267
4	0.28 $\pm$ 0.01	0.39 $\pm$ 0.05	5.69 [§]	0.0228
5	0.25 $\pm$ 0.04	0.29 $\pm$ 0.05	0.22	0.6482
6	0.45 $\pm$ 0.01	0.43 $\pm$ 0.01	1.89	0.1780

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
§ indicates a P value of between 0.015 and 0.05
† indicates a P value of less than 0.01

TABLE A9.2.7 Average "Confusion" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	3.28 $\pm$ 0.08	2.77 $\pm$ 0.07	25.5 [†]	0.0000
2	1.10 $\pm$ 0.09	1.17 $\pm$ 0.11	0.25	0.6251
3	1.15 $\pm$ 0.06	1.33 $\pm$ 0.09	2.75	0.1069
4	2.25 $\pm$ 0.02	2.03 $\pm$ 0.11	4.19 [§]	0.0486
5	2.81 $\pm$ 0.11	2.53 $\pm$ 0.14	2.47	0.1254
6	1.10 $\pm$ 0.04	1.04 $\pm$ 0.08	0.51	0.4883

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
§ indicates a P value of between 0.015 and 0.05
† indicates a P value of less than 0.01

TABLE A9.2.8 Average "Friendliness" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	3.14 $\pm$ 0.06	1.90 $\pm$ 0.05	224 [†]	0.0000
2	0.79 $\pm$ 0.10	0.78 $\pm$ 0.14	0.00	0.9530
3	0.76 $\pm$ 0.07	1.24 $\pm$ 0.10	14.8 [†]	0.0005
4	1.45 $\pm$ 0.06	1.48 $\pm$ 0.12	0.04	0.8376
5	1.98 $\pm$ 0.16	2.09 $\pm$ 0.17	0.31	0.5904
6	0.39 $\pm$ 0.05	0.39 $\pm$ 0.05	0.00	0.9987

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
† indicates a P value of less than 0.01

TABLE A9.2.9 Average "Elation" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	3.05 $\pm$ 0.11	2.19 $\pm$ 0.17	18.3 [†]	0.0002
2	0.29 $\pm$ 0.26	-0.38 $\pm$ 0.25	3.37	0.0757
3	1.06 $\pm$ 0.09	1.45 $\pm$ 0.14	5.72 [§]	0.0228
4	1.58 $\pm$ 0.05	1.26 $\pm$ 0.13	5.59 [§]	0.0239
5	1.22 $\pm$ 0.53	1.38 $\pm$ 0.30	0.07	0.7939
6	0.45 $\pm$ 0.03	0.52 $\pm$ 0.08	0.70	0.4181

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
§ indicates a P value of between 0.015 and 0.05
† indicates a P value of less than 0.01

TABLE A9.2.10 Average "Arousal" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	3.14 $\pm$ 0.06	1.89 $\pm$ 0.05	228 [†]	0.0000
2	0.10 $\pm$ 0.27	-0.04 $\pm$ 0.26	0.01	0.9068
3	0.76 $\pm$ 0.07	1.22 $\pm$ 0.10	13.6 [†]	0.0008
4	1.45 $\pm$ 0.06	1.46 $\pm$ 0.13	0.01	0.9290
5	1.96 $\pm$ 0.15	2.03 $\pm$ 0.17	0.08	0.7793
6	0.39 $\pm$ 0.05	0.36 $\pm$ 0.06	0.11	0.7474

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
† indicates a P value of less than 0.01

TABLE A9.2.11 Average "Positive Mood" Response for each Test Medication Phase per Volunteer

APPENDIX 10
VAS RESPONSE DATA

TABLE A10.1

Visual Analogue Scales (Subject 1 (SS))

Phase 1 (IM A)

Week	Day	Time	Response ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	10	2	2	2	1	0
		12h50	13	13	12	10	12	12
		19h50						
	2	07h50	7	5	5	4	5	4
		19h50	18	17	16	14	15	15
	3	07h50	3	2	3	2	3	2
		19h50	0	0	0	0	0	0
	4	07h50	2	0	1	1	2	3
		12h50	0	0	0	0	0	19
	7	19h50						
Two	1	07h50	2	1	1	2	1	1
		12h50	0	0	0	0	0	12
		19h50	3	1	3	2	1	2
	2	07h50	2	0	3	2	3	0
		19h50	2	1	2	1	3	3
	3	07h50	1	0	1	2	3	2
		19h50	3	1	1	2	1	2
	4	07h50	1	1	2	13	0	3
		12h50	3	2	3	3	3	51
	7	19h50	1	2	3	2	4	3
Three	4	07h50	2	2	4	2	4	2
		12h50	3	2	2	0	0	56
	7	19h50	2	2	2	2	2	3
Four	4	07h50	2	2	2	2	3	4
		12h50	11	3	3	5	6	41
	7	19h50	6	2	2	2	3	6
Five	4	07h50	2	3	4	4	4	4
		12h50	2	5	5	4	3	42
	7	19h50	3	3	3	3	2	2

Phase 2 (IM B)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	4	2	1	2	1	0
		12h50	9	8	10	5	9	4
		19h50						
	2	07h50	4	5	4	4	5	4
		19h50	8	1	3	4	7	4
	3	07h50	8	5	8	5	7	5
		19h50	5	4	2	5	5	10
	4	07h50	7	6	10	8	8	10
		12h50	2	2	1	0	2	2
	7	19h50	5	5	3	6	4	5
Two	1	07h50	4	4	6	3	6	6
		12h50	2	0	1	0	2	15
		19h50	4	4	7	3	4	6
	2	07h50	3	3	5	5	2	6
		19h50	6	5	5	2	1	5
	3	07h50	3	0	1	1	4	2
		19h50	4	3	7	4	5	13
	4	07h50	7	9	9	10	9	9
		12h50	8	6	9	4	30	30
	7	19h50	2	2	4	2	3	6
Three	4	07h50	4	2	2	4	15	3
		12h50	6	7	8	8	17	8
	7	19h50	11	13	7	6	7	9
Four	4	07h50	9	4	9	5	8	3
		12h50	10	5	8	5	11	3
	7	19h50	4	2	4	6	5	9
Five	4	07h50	4	2	4	6	5	9
		12h50	6	3	2	4	5	5
	7	19h50						

TABLE A10.2

Visual Analogue Scales [Subject 2 (CA)]

Phase 1 (IN A)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	44	30	61	43	63	57
		12h50	50	54	47	44	72	60
		19h50						
	2	07h50	60	74	58	59	1	0
		19h50	5	8	1	23	0	1
	3	07h50	28	21	28	20	0	0
		19h50	28	48	51	32	13	0
	4	07h50	45	39	24	27	0	0
		12h50	44	38	8	37	3	79
	7	19h50	0	0	0	0	67	0
	Two	07h50	21	22	9	8	0	76
		12h50	26	55	10	52	69	8
		19h50	34	51	2	30	0	0
Two	2	07h50	9	12	10	8	56	20
		19h50	16	18	15	11	39	0
	3	07h50	14	45	8	8	0	0
		19h50						
	4	07h50	31	32	39	17	38	8
		12h50	30	31	16	44	0	90
	7	19h50	42	39	5	28	0	52
	Three	07h50	1	82	39	4	85	26
		12h50	25	22	45	18	74	14
		19h50	5	4	60	30	75	0
Four	4	07h50	12	11	11	9	85	0
		12h50	16	11	39	14	82	22
	7	19h50	9	8	7	6	64	20
	Five	07h50	2	0	64	21	92	27
		12h50	0	0	0	0	0	0
		19h50						

Phase 2 (IN B)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	20	19	16	14	75	29
		12h50	20	18	17	16	90	100
		19h50	6	7	71	17	92	0
	2	07h50	6	8	72	17	92	0
		19h50	1	20	85	3	96	4
	3	07h50	11	9	75	5	98	0
		19h50	10	9	64	11	76	23
	4	07h50	6	2	79	13	93	2
		12h50	13	10	80	11	94	79
	7	19h50	14	12	12	9	66	58
	Two	07h50	0	0	76	0	87	0
		12h50	9	9	80	20	89	100
		19h50	52	17	60	21	80	0
Two	2	07h50	54	66	13	66	5	0
		19h50	7	53	5	4	3	0
	3	07h50	8	9	7	7	55	0
		19h50	7	61	3	7	46	1
	4	07h50	42	48	9	0	0	0
		12h50	13	32	0	19	0	73
	7	19h50	0	0	72	0	39	0
	Three	07h50	30	44	16	13	0	6
		12h50	17	35	7	4	0	69
		19h50	7	7	5	48	8	38
Four	4	07h50	24	24	60	4	78	20
		12h50	0	0	71	0	99	6
	7	19h50	52	58	25	21	0	36
	Five	07h50	73	76	1	13	0	31
		12h50	59	72	0	10	0	53
		19h50						

TABLE A10.3

Visual Analogue Scales [Subject 3 (LE)]

Phase 1 (TM B)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50						
		12h50	20	20	20	17	16	38
		19h50	25	3	3	5	6	7
	2	07h50						
		19h50						
	3	07h50	20	1	3	3	3	4
		19h50	24	17	7	3	3	13
	4	07h50	19	9	3	3	3	8
		12h50	13	13	4	3	5	33
	7	19h50						
Two	1	07h50	13	3	4	3	5	19
		12h50	7	2	3	2	5	17
		19h50	6	5	4	4	4	2
	2	07h50	4	5	6	2	3	2
		19h50	3	3	2	3	0	2
	3	07h50	6	2	5	3	4	5
		19h50	5	1	3	2	4	0
	4	07h50	7	6	3	4	4	3
		12h50	6	4	3	4	4	4
	7	19h50	18	5	5	3	3	4
Three	4	07h50	5	7	5	9	6	5
		12h50	8	5	5	5	7	42
	7	19h50	8	4	2	5	3	3
Four	4	07h50	9	7	9	7	6	4
		12h50	16	4	3	4	3	33
	7	19h50	8	7	5	4	4	3
Five	4	07h50	4	7	4	4	4	2
		12h50	10	6	7	5	4	73
	7	19h50	7	0	8	7	7	8

Phase 2 (TM A)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	13	7	7	6	4	3
		12h50	10	8	6	9	7	45
		19h50	8	5	5	5	4	4
	2	07h50	8	5	5	4	4	3
		19h50	6	5	4	3	3	2
	3	07h50	10	7	5	4	4	3
		19h50	6	6	5	3	3	2
	4	07h50	10	7	5	4	20	3
		12h50	10	9	9	8	10	43
	7	19h50	9	6	6	4	6	5
Two	1	07h50	7	7	6	6	6	5
		12h50	11	8	9	7	5	48
		19h50	9	7	7	6	6	4
	2	07h50	9	8	7	7	8	6
		19h50	15	11	7	7	9	7
	3	07h50	4	4	7	6	5	6
		19h50	10	11	6	6	5	2
	4	07h50	9	7	6	5	5	7
		12h50	7	6	5	6	5	26
	7	19h50	6	6	4	3	4	3
Three	4	07h50	8	9	8	7	6	6
		12h50	9	7	9	8	7	35
	7	19h50	13	9	10	6	5	4
Four	4	07h50	14	9	8	8	7	7
		12h50	9	5	8	7	10	44
	7	19h50	9	4	7	5	3	3
Five	4	07h50	9	8	9	7	9	8
		12h50	11	9	7	7	7	40
	7	19h50	13	8	9	4	5	5

TABLE A10.4

Visual Analogue Scales [Subject 4 (EA)]

Phase 1 (TM B)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	17	72	42	46	45	61
		12h50	66	61	37	24	4	46
		19h50	30	28	16	54	23	70
	2	07h50	69	70	46	45	23	14
		19h50	41	21	19	18	18	10
	3	07h50	39	33	48	32	32	18
		19h50	33	30	27	28	27	11
	4	07h50	33	33	40	31	25	6
		12h50	34	33	31	33	33	50
	7	19h50						
Two	1	07h50	39	33	31	29	30	30
		12h50	46	30	30	28	28	41
		19h50	33	30	32	30	31	4
	2	07h50	33	31	30	29	38	24
		19h50	30	13	13	9	7	7
	3	07h50	24	18	14	12	11	7
		19h50						
	4	07h50	24	19	16	13	17	14
		12h50	24	19	20	18	17	79
	7	19h50	50	34	36	34	34	46
Three	4	07h50	13	10	18	4	4	4
		12h50	22	13	12	10	12	22
	7	19h50	16	11	12	10	9	9
Four	4	07h50	11	7	8	7	5	5
		12h50	20	12	11	10	10	59
	7	19h50	10	6	5	5	4	3
Five	4	07h50	14	10	11	9	8	9
		12h50	17	11	13	11	12	10
	7	19h50	11	6	6	5	6	5

Phase 2 (TM A)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	10	6	8	6	4	4
		12h50	16	12	12	12	12	10
		19h50	17	17	15	16	12	16
	2	07h50	13	11	9	8	7	5
		19h50						
	3	07h50	18	13	12	8	8	6
		19h50	12	11	10	10	10	8
	4	07h50	9	6	6	6	6	5
		12h50	13	7	8	8	8	15
	7	19h50	11	6	6	5	5	5
Two	1	07h50	11	6	8	9	6	6
		12h50	14	12	12	11	11	20
		19h50	10	5	6	6	6	6
	2	07h50	8	3	3	3	4	6
		19h50	4	1	1	0	0	0
	3	07h50	6	2	2	3	2	2
		19h50	7	4	5	4	3	2
	4	07h50	7	1	1	2	2	3
		12h50	2	2	1	1	2	5
	7	19h50	7	3	4	3	3	3
Three	4	07h50	5	2	2	3	2	1
		12h50	7	3	2	3	4	1
	7	19h50	6	3	2	2	2	4
Four	4	07h50	3	2	2	2	3	2
		12h50						
	7	19h50	4	1	2	2	2	0
Five	4	07h50	5	2	2	1	2	1
		12h50	6	3	3	3	2	1
	7	19h50	6	2	3	2	3	2

TABLE A10.5

Visual Analogue Scales [Subject 5 (VW)]

Phase 1 (TM B)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	70	69	3	8	3	11
		12h50	88	87	31	29	30	98
		19h50						
	2	07h50	64	55	2	0	0	9
		19h50	92	75	3	3	1	94
	3	07h50	84	84	9	8	8	2
		19h50	32	47	3	2	3	0
	4	07h50	58	53	3	2	1	2
		12h50	69	56	4	3	3	96
	7	19h50	44	32	1	0	2	1
Two	1	07h50	61	70	1	2	2	1
		12h50	81	83	2	2	1	96
		19h50	57	49	0	1	1	12
	2	07h50	46	29	2	1	2	2
		19h50	35	30	2	3	2	3
	3	07h50	24	13	3	1	2	2
		19h50	32	10	6	6	6	6
	4	07h50	70	66	0	3	2	0
		12h50	82	81	4	4	3	97
	7	19h50	28	2	2	3	2	4
Three	4	07h50	21	19	5	2	0	2
		12h50	7	9	9	2	1	94
	7	19h50	2	2	4	1	0	0
Four	4	07h50	33	3	4	2	3	3
		12h50	43	19	19	17	20	63
	7	19h50						
Five	4	07h50	28	24	1	0	1	0
		12h50	31	4	2	1	1	28
	7	19h50	32	47	3	0	2	1

Phase 2 (TM A)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	32	30	2	0	0	3
		12h50	35	33	2	1	1	53
		19h50						
	2	07h50	8	24	4	2	2	3
		19h50	14	14	1	0	0	1
	3	07h50	28	27	0	2	3	4
		19h50	4	3	2	3	3	4
	4	07h50	7	2	2	2	1	0
		12h50	19	10	11	3	1	25
	7	19h50	27	3	2	2	1	2
Two	1	07h50	12	4	4	3	1	1
		12h50	14	2	0	1	1	2
		19h50	6	3	3	3	3	1
	2	07h50	7	23	7	5	4	4
		19h50	4	0	0	0	2	1
	3	07h50	5	13	3	3	3	3
		19h50	1	4	0	0	31	3
	4	07h50	4	4	4	2	3	3
		12h50	2	2	2	2	62	2
	7	19h50	3	2	0	2	2	15
Three	4	07h50	0	0	0	2	2	3
		12h50	4	4	3	3	3	42
	7	19h50	1	2	1	2	2	2
Four	4	07h50	2	1	3	1	3	3
		12h50	5	6	5	6	7	23
	7	19h50	2	5	3	2	4	
Five	4	07h50	4	5	4	3	3	3
		12h50	2	3	5	5	6	26
	7	19h50						

TABLE A10.6

Visual Analogue Scales [Subject 6 (L1)]

Phase 1 (TM B)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	47	5	13	2	2	27
		12h50	49	4	5	4	10	63
		19h50	59	58	6	5	11	65
	2	07h50	48	39	11	5	4	29
		19h50	26	5	3	4	5	4
	3	07h50	29	15	21	3	4	6
		19h50	32	25	2	3	2	3
	4	07h50	30	5	5	2	3	4
		12h50	15	8	7	6	5	78
	7	19h50	8	6	5	5	7	7
Two	1	07h50	8	7	7	7	9	27
		12h50	5	6	5	5	6	33
		19h50	5	6	5	6	6	9
	2	07h50	8	8	9	9	10	19
		19h50	6	6	5	5	5	6
	3	07h50	8	8	6	7	7	7
		19h50	5	4	6	5	4	5
	4	07h50	7	5	6	8	7	7
		12h50	4	3	6	4	5	31
	7	19h50	6	5	18	3	27	13
Three	4	07h50	6	5	5	4	25	16
		12h50	4	4	5	4	13	49
	7	19h50	5	4	33	5	35	6
Four	4	07h50	5	5	15	7	16	18
		12h50	8	5	21	3	6	48
		19h50	7	5	6	7	9	9
Five	4	07h50	7	7	7	5	8	9
		12h50	3	5	6	6	7	44
	7	19h50	5	5	4	5	5	5

Phase 2 (TM A)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	5	4	5	4	6	7
		12h50	6	6	15	5	18	36
		19h50	5	6	2	6	23	18
	2	07h50	5	6	20	6	23	18
		19h50	6	6	22	5	24	29
	3	07h50	4	4	16	4	19	23
		19h50	5	4	15	5	9	6
	4	07h50	5	5	18	4	15	20
		12h50	6	5	21	5	15	45
	7	19h50	9	5	32	5	20	5
Two	1	07h50	5	4	28	4	17	3
		12h50	6	7	28	4	23	34
		19h50	6	5	22	5	18	5
	2	07h50	6	5	19	5	22	11
		19h50	5	4	30	4	21	8
	3	07h50	7	6	22	4	10	6
		19h50						
	4	07h50	6	6	6	6	5	7
		12h50	4	5	6	5	5	51
	7	19h50	5	3	3	4	5	6
Three	4	07h50	8	7	7	6	8	31
		12h50	6	4	4	3	3	33
	7	19h50	5	4	4	3	5	6
Four	4	07h50	6	3	4	4	6	7
		12h50	6	5	4	4	4	25
		19h50	7	5	18	3	6	6
Five	4	07h50	4	4	5	6	7	8
		12h50	6	3	5	4	7	36
	7	19h50	4	6	7	5	6	7

TABLE A10.7

Visual Analogue Scales [Subject 7 (EG)]

Phase 1 (TM A)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	29	26	3	0	2	3
		12h50	15	15	16	16	17	12
		19h50	18	15	14	12	11	14
	2	07h50	18	23	0	1	0	2
		19h50	6	11	10	8	7	10
	3	07h50	8	6	6	5	5	7
		19h50	5	10	9	10	9	4
	4	07h50	11	9	9	7	7	7
		12h50	14	14	9	6	13	32
	7	19h50						
Two	1	07h50	5	4	5	4	5	5
		12h50	20	15	17	10	8	25
		19h50	12	12	11	7	6	5
	2	07h50	8	6	8	7	6	10
		19h50	10	11	10	10	10	11
	3	07h50	11	11	8	8	6	3
		19h50	14	14	12	11	7	7
	4	07h50	13	5	2	1	2	4
		12h50	17	6	0	0	0	2
	7	19h50	17	5	4	0	0	3
Three	4	07h50	21	10	1	0	1	2
		12h50	9	11	2	3	4	34
	7	19h50	5	14	0	0	0	0
Four	4	07h50						
		12h50						
	7	19h50						
Five	4	07h50						
		12h50						
	7	19h50						

Phase 2 (TM B)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	27	17	8	2	4	12
		12h50	21	23	4	0	3	35
		19h50	16	12	3	2	2	5
	2	07h50	22	11	6	3	2	8
		19h50	19	5	3	0	0	7
	3	07h50	21	13	2	0	2	5
		19h50	33	21	8	4	4	10
	4	07h50	17	10	6	0	1	5
		12h50	24	17	5	1	6	29
	7	19h50	22	10	7	3	2	8
Two	1	07h50	20	13	7	3	2	6
		12h50	26	12	7	3	2	31
		19h50	25	12	8	4	3	5
	2	07h50	27	17	7	4	2	4
		19h50	19	11	8	3	2	7
	3	07h50	25	12	8	4	5	6
		19h50	16	10	4	1	2	7
	4	07h50	20	10	6	5	2	7
		12h50	27	15	11	7	6	27
	7	19h50	17	7	4	2	4	4
Three	4	07h50	22	15	7	6	4	10
		12h50	28	14	7	4	4	41
	7	19h50	28	16	13	7	5	8
Four	4	07h50	21	14	8	4	0	5
		12h50	18	11	9	3	3	13
	7	19h50	20	13	9	5	3	11
Five	4	07h50	17	14	7	3	0	5
		12h50	24	16	9	4	7	26
	7	19h50	25	19	16	7	11	13

TABLE A10.8

Visual Analogue Scales [Subject 8 (CV)]

Phase 1 (TM A)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	62	65	19	18	19	70
		12h50	64	74	15	14	15	71
		19h50	35	30	18	25	31	25
	2	07h50	45	44	24	29	21	29
		19h50	30	15	41	21	18	17
	3	07h50	70	64	22	11	15	12
		19h50	48	42	56	20	30	72
	4	07h50	78	76	10	5	3	48
		12h50						
	7	19h50						
Two	1	07h50	45	18	60	16	46	15
		12h50	28	18	65	64	67	54
		19h50	21	18	62	43	61	12
	2	07h50	43	43	23	5	58	18
		19h50	45	51	6	5	6	11
	3	07h50	61	60	52	7	23	2
		19h50	45	45	5	16	4	6
	4	07h50	66	71	4	3	4	16
		12h50	64	44	56	16	26	43
	7	19h50	46	54	8	10	10	26
Three	4	07h50	74	73	5	3	4	5
		12h50	76	77	6	7	8	70
	7	19h50	71	70	9	11	10	22
Four	4	07h50	69	57	9	9	10	14
		12h50	77	13	65	14	50	43
	7	19h50	64	35	9	4	4	42
Five	4	07h50	75	76	8	6	7	15
		12h50	70	69	12	8	21	69
	7	19h50	45	43	13	13	15	22

Phase 2 (TM B)

Week	Day	Time	Response Ratings (mm)					
			STIM	HIGH	ANX	SED	DOWN	HUN
One	1	07h50	50	47	62	11	59	43
		12h50	75	50	58	7	61	72
		19h50	25	22	30	10	29	13
	2	07h50						
		19h50	62	26	14	5	3	15
	3	07h50	63	27	68	10	60	12
		19h50						
	4	07h50	58	46	24	6	49	43
		12h50	76	68	48	6	21	76
	7	19h50						
Two	1	07h50	54	46	15	3	12	13
		12h50	34	23	39	7	40	24
		19h50	38	27	34	10	30	42
	2	07h50						
		19h50						
	3	07h50						
		19h50						
	4	07h50						
		12h50						
	7	19h50						
Three	4	07h50						
		12h50						
	7	19h50						
Four	4	07h50						
		12h50						
	7	19h50						
Five	4	07h50						
		12h50						
	7	19h50						

VAS Scale	Weeks	TM A $\pm$ SEM	MRT	F	P	TM B $\pm$ SEM	MRT	F	P
Stimulated	1	15.10 $\pm$ 1.76	*	5.75 [†]	0.0002	30.02 $\pm$ 3.08	*	17.71 [†]	0.0001
	2	9.58 $\pm$ 1.00	*			21.12 $\pm$ 2.46	*		
	3	6.90 $\pm$ 1.36	*			13.14 $\pm$ 1.96	*		
	4	7.56 $\pm$ 1.04	*			15.69 $\pm$ 3.69	*		
	5	5.13 $\pm$ 0.94	*			18.87 $\pm$ 5.42	*		
High	1	13.78 $\pm$ 1.90	*	3.53 [†]	0.0085	23.43 $\pm$ 3.10		7.07 [‡]	0.0090
	2	9.31 $\pm$ 1.45	*			17.28 $\pm$ 2.47			
	3	7.33 $\pm$ 1.68	*			11.95 $\pm$ 2.26			
	4	5.25 $\pm$ 0.80	*			10.38 $\pm$ 3.54			
	5	4.20 $\pm$ 0.74	*			16.93 $\pm$ 6.13			
Anxious	1	12.17 $\pm$ 1.80		1.22	0.3048	18.33 $\pm$ 3.04		3.04	0.0842
	2	7.60 $\pm$ 0.97				12.15 $\pm$ 2.11			
	3	10.00 $\pm$ 3.62				9.14 $\pm$ 1.49			
	4	7.88 $\pm$ 2.32				17.19 $\pm$ 5.07			
	5	8.87 $\pm$ 3.99				5.40 $\pm$ 1.00			
Sedated	1	9.62 $\pm$ 1.59		0.78	0.5411	9.95 $\pm$ 1.65		0.02	0.8883
	2	8.00 $\pm$ 1.62				8.07 $\pm$ 1.32			
	3	5.19 $\pm$ 1.50				7.76 $\pm$ 2.11			
	4	8.56 $\pm$ 3.59				6.69 $\pm$ 1.36			
	5	5.20 $\pm$ 1.24				6.47 $\pm$ 0.90			
Down	1	10.43 $\pm$ 1.96		0.96	0.4330	20.83 $\pm$ 3.98		5.50 [‡]	0.0207
	2	9.22 $\pm$ 1.75				12.28 $\pm$ 2.38			
	3	14.14 $\pm$ 5.86				8.76 $\pm$ 1.98			
	4	18.56 $\pm$ 7.34				17.69 $\pm$ 7.09			
	5	10.60 $\pm$ 5.84				5.20 $\pm$ 0.85			
Hungry	1	13.93 $\pm$ 2.34		0.14	0.9676	23.71 $\pm$ 3.79		4.80 [‡]	0.0304
	2	12.09 $\pm$ 2.35				15.90 $\pm$ 2.89			
	3	14.71 $\pm$ 3.74				21.47 $\pm$ 5.53			
	4	13.38 $\pm$ 3.56				16.81 $\pm$ 4.65			
	5	14.27 $\pm$ 3.99				19.53 $\pm$ 5.61			

The mean responses to each of the VAS scales for week 1 for both treatments are given in the body of the table. For week 1, $n = 58$ for each phase, $df = 1,114$. Bold italicised F ratios and P values indicate significance for weeks 1.

For the comparison of the treatment weeks (2-5) with week 1, $n = 177$ for each phase, $df = 4,177$.

The *'s in the MRT column indicates where the differences in the weeks occurred.

‡ indicates a P value of between 0.015 and 0.05

† indicates a P value of less than 0.01

TABLE A10.2.1 Average Weekly Responses to the 6 Scales of the VAS Questionnaire (Mean Values for 7 Subjects)

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	2.67 $\pm$ 0.57	5.39 $\pm$ 0.63	10.2 [†]	0.0030
2	17.17 $\pm$ 2.99	26.35 $\pm$ 5.85	1.95	0.1721
3	9.63 $\pm$ 0.61	8.32 $\pm$ 0.91	1.43	0.2398
4	6.82 $\pm$ 0.73	24.44 $\pm$ 2.97	34.0 [§]	0.0000
5	4.71 $\pm$ 0.94	40.35 $\pm$ 5.69	38.2 [†]	0.0000
6	5.67 $\pm$ 0.26	6.39 $\pm$ 0.37	2.56	0.1187

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
[†] indicates a P value of less than 0.01

TABLE A10.2.2 Average "Stimulation" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	1.67 $\pm$ 0.29	4.28 $\pm$ 0.74	10.7 [†]	0.0025
2	23.24 $\pm$ 4.23	32.41 $\pm$ 6.43	1.42	0.2422
3	7.74 $\pm$ 0.46	5.32 $\pm$ 0.54	11.8 [†]	0.0015
4	3.47 $\pm$ 0.61	18.06 $\pm$ 2.46	33.2 [†]	0.0000
5	4.76 $\pm$ 1.42	30.59 $\pm$ 6.89	13.5 [†]	0.0009
6	4.78 $\pm$ 0.30	5.94 $\pm$ 0.35	6.50 [§]	0.0155

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
[§] indicates a P value of between 0.015 and 0.05
[†] indicates a P value of less than 0.01

TABLE A10.2.3 Average "High" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	2.39 $\pm$ 0.29	5.61 $\pm$ 0.59	23.6 [†]	0.0000
2	22.35 $\pm$ 5.03	30.18 $\pm$ 7.61	0.74	0.4068
3	7.53 $\pm$ 0.33	4.84 $\pm$ 0.43	24.8 [†]	0.0000
4	3.53 $\pm$ 0.69	18.41 $\pm$ 2.43	34.7 [†]	0.0000
5	2.76 $\pm$ 0.54	4.12 $\pm$ 1.08	1.25	0.2722
6	12.33 $\pm$ 2.34	9.56 $\pm$ 1.78	0.89	0.3616

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
[†] indicates a P value of less than 0.01

TABLE A10.2.4 Average "Anxious" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	2.78 $\pm$ 0.67	4.44 $\pm$ 0.57	3.61	0.0660
2	25.94 $\pm$ 5.59	14.88 $\pm$ 4.35	2.44	0.1283
3	6.37 $\pm$ 0.28	4.63 $\pm$ 0.43	11.6 [†]	0.0016
4	3.53 $\pm$ 0.68	15.71 $\pm$ 2.51	21.9 [†]	0.0000
5	2.65 $\pm$ 0.40	3.47 $\pm$ 0.98	0.61	0.4501
6	4.39 $\pm$ 0.23	5.89 $\pm$ 0.37	11.9 [†]	0.0015

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
[†] indicates a P value of less than 0.01

TABLE A10.2.5 Average "Sedated" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	2.44 $\pm$ 0.39	8.11 $\pm$ 1.63	11.4 [†]	0.0019
2	44.71 $\pm$ 8.96	31.94 $\pm$ 9.60	0.95	0.3486
3	6.47 $\pm$ 0.43	4.58 $\pm$ 0.39	10.6 [†]	0.0024
4	3.76 $\pm$ 0.64	16.29 $\pm$ 2.75	19.7 [†]	0.0001
5	8.29 $\pm$ 3.75	3.35 $\pm$ 1.15	1.58	0.2172
6	9.89 $\pm$ 1.62	11.89 $\pm$ 2.07	0.58	0.4600

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
[†] indicates a P value of less than 0.01

TABLE A10.2.6 Average "Down" Response for each Test Medication Phase per Volunteer

Subject	TM A $\pm$ SEM	TM B $\pm$ SEM	F	P
1	16.50 $\pm$ 5.60	7.61 $\pm$ 1.48	2.36	0.1340
2	21.35 $\pm$ 6.59	25.53 $\pm$ 7.71	0.17	0.6878
3	14.26 $\pm$ 3.59	12.47 $\pm$ 4.27	0.10	0.7537
4	4.00 $\pm$ 1.11	19.12 $\pm$ 4.92	9.0 [†]	0.0052
5	8.41 $\pm$ 2.86	24.59 $\pm$ 9.07	2.89	0.0987
6	16.11 $\pm$ 3.44	20.009 $\pm$ 3.55	0.62	0.4457

n = 16 for each Test Medication Phase for Subject 5, df = 1,30
n = 17 for each Test Medication Phase for Subjects 1, 2, and 4, df = 1,32
n = 18 for each Test Medication Phase for Subjects 3 and 6, df = 1,34
[†] indicates a P value of less than 0.01

TABLE A10.2.7 Average "Hungry" Response for each Test Medication Phase per Volunteer

TABLE A11.1.1 Pre-Meal Hunger and Appetite Questionnaires (AHQ) Data [Subject 1 (SS)]

Phase 1 (IM A)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	39	40	14	36
	4	28	22	17	27
Two	1	21	7	1	28
	4	45	46	15	72
Three	4	32	54	28	54
Four	4	34	29	20	33
Five	4	45	52	43	51

Phase 2 (IM B)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	39	28	29	38
	4	48	59	35	58
Two	1	59	58	47	59
	4	67	65	58	58
Three	4	45	58	35	47
Four	4	39	41	28	49
Five	4	67	72	26	61

TABLE A11.1.2 Pre-Meal Hunger and Appetite Questionnaires (AHQ) Data [Subject 2 (CA)]

Phase 1 (IM A)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	55	69	75	68
	4	59	66	81	66
Two	1	20	17	9	22
	4	62	69	56	63
Three	4	3	2	5	3
Four	4	19	15	18	17
Five	4				

Phase 2 (IM B)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	89	78	87	91
	4	61	62	70	62
Two	1	78	81	79	97
	4	53	61	45	62
Three	4	4	6	41	51
Four	4	38	35	38	43
Five	4	7	18	20	37

TABLE A11.2.1 Post-Meal Satiety Questionnaires (SQ) Data [Subject 1 (SS)]

Phase 1 (IM A)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	47	0	0	38	60	61
	4	48	0	1	69	74	5
Two	1	46	1	2	21	41	25
	4	56	5	5	77	70	5
Three	4	55	17	5	60	70	26
Four	4	69	8	13	56	61	23
Five	4	65	28	15	47	53	28

Phase 2 (IM B)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1						
	4	62	21	27	53	66	27
Two	1	70	14	4	66	74	28
	4	59	20	8	56	68	25
Three	4	55	21	42	64	66	27
Four	4	53	9	6	34	37	25
Five	4	66	11	5	76	72	25

TABLE A11.2.2 Post-Meal Satiety Questionnaires (SQ) Data [Subject 2 (CA)]

Phase 1 (IM A)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	61	19	56	60	60	55
	4	20	4	6	73	73	25
Two	1	62	20	0	0	0	8
	4	70	0	0	90	82	0
Three	4	98	0	0	44	36	2
Four	4	78	0	0	80	79	2
Five	4						

Phase 2 (IM B)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1						
	4	77	0	0	88	90	2
Two	1	77	20	6	90	67	36
	4	70	0	0	50	50	24
Three	4	76	6	0	61	55	17
Four	4	6	14	20	0	0	100
Five	4						

TABLE A11.1.3

Pre-Meal Hunger and Appetite Questionnaires (AIQ) Data [Subject 3 (LE)]

Phase 1 (IM B)

Week	Day	Response Ratings (mm) on AIQ			
		Question 1	Question 2	Question 3	Question 4
One	1	63	70	55	63
	4	40	44	49	50
Two	1	26	16	24	36
	4	28	24	20	37
Three	4	47	42	44	45
Four	4	54	56	61	64
Five	4	47	39	31	28

Phase 2 (IM A)

Week	Day	Response Ratings (mm) on AIQ			
		Question 1	Question 2	Question 3	Question 4
One	1	55	54	49	50
	4	39	38	42	40
Two	1	49	46	49	61
	4	31	29	31	41
Three	4	48	44	31	49
Four	4	30	19	21	35
Five	4	40	31	30	36

TABLE A11.1.4

Pre-Meal Hunger and Appetite Questionnaires (AIQ) Data [Subject 4 (EA)]

Phase 1 (IM B)

Week	Day	Response Ratings (mm) on AIQ			
		Question 1	Question 2	Question 3	Question 4
One	1	47	53	58	59
	4	28	34	41	40
Two	1	37	36	38	40
	4	37	42	28	69
Three	4	25	27	30	18
Four	4	81	46	47	69
Five	4	20	20	22	20

Phase 2 (IM A)

Week	Day	Response Ratings (mm) on AIQ			
		Question 1	Question 2	Question 3	Question 4
One	1	47	52	35	36
	4	11	14	15	14
Two	1	9	14	17	22
	4	4	4	4	12
Three	4	13	6	4	12
Four	4				
Five	4	8	4	4	1

TABLE A11.2.3

Post-Meal Satiety Questionnaires (SQ) Data [Subject 3 (LE)]

Phase 1 (IM B)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	55	22	26	22	28	38
	4	65	18	9	31	39	16
Two	1	46	24	19	22	22	25
	4	45	12	11	28	29	20
Three	4	56	19	15	32	34	24
Four	4	61	16	14	29	26	15
Five	4	66	17	12	35	34	22

Phase 2 (IM A)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	68	13	14	44	41	22
	4	57	20	20	15	15	24
Two	1	71	18	15	33	32	31
	4	57	18	16	39	36	20
Three	4	60	19	18	18	29	39
Four	4	58	19	19	40	41	22
Five	4	65	17	14	14	11	26

TABLE A11.2.4

Post-Meal Satiety Questionnaires (SQ) Data [Subject 4 (EA)]

Phase 1 (IM B)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	43	31	32	34	35	42
	4	12	7	8	31	36	34
Two	1	63	33	33	32	35	47
	4	56	21	35	70	69	29
Three	4	44	33	29	58	62	43
Four	4	57	29	27	59	60	29
Five	4	27	12	13	50	56	27

Phase 2 (IM A)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	64	24	24	51	60	16
	4	47	21	20	53	57	26
Two	1	36	26	26	47	50	26
	4	27	15	12	43	49	18
Three	4	34	10	10	30	33	7
Four	4						
Five	4	41	5	5	24	28	6

TABLE A11.1.5 Pre-Meal Hunger and Appetite Questionnaires (AHQ) Data [Subject 5 (VW)]

Phase 1 (TM B)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	70	79	81	72
	4	87	89	91	79
Two	1	58	59	35	61
	4	52	63	66	69
Three	4	97	98	96	98
Four	4	42	47	49	49
Five	4	20	22	20	18

Phase 2 (TM A)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	55	57	58	53
	4	18	19	20	18
Two	1	26	26	28	25
	4				
Three	4	33	35	41	45
Four	4	12	10	11	9
Five	4	16	16	18	15

TABLE A11.1.6 Pre-Meal Hunger and Appetite Questionnaires (AHQ) Data [Subject 6 (LI)]

Phase 1 (TM B)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	76	65	63	62
	4	55	56	61	63
Two	1	10	19	19	19
	4	34	30	31	29
Three	4	32	39	45	49
Four	4	41	48	25	25
Five	4	30	28	23	38

Phase 2 (TM A)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	36	38	47	47
	4	36	42	47	50
Two	1	25	35	40	45
	4	48	51	55	52
Three	4	48	51	55	52
Four	4	18	16	19	20
Five	4	26	30	28	29

TABLE A11.2.5

Post-Meal Satiety Questionnaires (SQ) Data [Subject 5 (VW)]

Phase 1 (TM B)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	74	2	6	62	64	7
	4	72	2	2	60	58	2
Two	1	75	2	1	0	0	0
	4	80	1	0	74	72	0
Three	4	90	0	3	18	30	2
Four	4	77	1	0	30	28	3
Five	4	67	2	0	34	34	0

Phase 2 (TM A)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1						
	4	74	4	6	38	38	2
Two	1	99	1	0	17	24	2
	4						
Three	4	75	4	0	26	45	2
Four	4	72	2	2	0	0	2
Five	4	88	2	2	27	30	3

TABLE A11.2.6

Post-Meal Satiety Questionnaires (SQ) Data [Subject 6 (LI)]

Phase 1 (TM B)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	53	21	21	29	50	80
	4	48	22	9	17	40	33
Two	1	38	21	18	4	30	29
	4	47	13	11	12	14	31
Three	4	62	25	18	23	47	46
Four	4	57	22	27	35	54	50
Five	4	51	17	17	50	40	45

Phase 2 (TM A)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	62	24	17	50	50	29
	4	57	31	24	38	48	82
Two	1	42	26	32	31	40	71
	4	29	22	27	50	52	77
Three	4	47	18	17	31	38	51
Four	4	52	18	16	17	32	56
Five	4	50	24	12	56	52	52

TABLE A11.1.7 Pre-Meal Hunger and Appetite Questionnaires (AHQ) Data [Subject 7 (EG)]

Phase 1 (TM A)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	24	29	25	35
	4	60	49	31	35
Two	1	25	17	16	23
	4	38	39	30	36
Three	4	46	47	34	49
Four	4				
Five	4				

Phase 2 (TM B)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	50	46	27	45
	4	35	28	22	36
Two	1	30	32	27	32
	4	32	30	25	27
Three	4	45	41	34	48
Four	4	27	29	24	33
Five	4	26	30	12	26

TABLE A11.1.8 Pre-Meal Hunger and Appetite Questionnaires (AHQ) Data [Subject 8 (CV)]

Phase 1 (TM A)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	51	42	30	38
	4	59	69	71	71
Two	1	26	22	28	45
	4	35	36	29	40
Three	4	55	66	67	66
Four	4	60	57	62	58
Five	4	59	60	55	60

Phase 2 (TM B)

Week	Day	Response Ratings (mm) on AHQ			
		Question 1	Question 2	Question 3	Question 4
One	1	75	64	66	63
	4	63	47	49	65
Two	1	34	31	33	35
	4				
Three	4				
Four	4				
Five	4				

TABLE A11.2.7 Post-Meal Satiety Questionnaires (SQ) Data [Subject 7 (EG)]

Phase 1 (TM A)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	74	2	3	12	27	14
	4	65	10	19	35	29	6
Two	1	85	18	12	16	24	13
	4	3	5	2	47	39	6
Three	4	60	10	0	40	36	10
Four	4						
Five	4						

Phase 2 (TM B)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	64	15	9	27	30	26
	4	71	20	12	30	39	5
Two	1	28	12	5	18	26	10
	4	42	19	74	31	31	18
Three	4	46	26	12	27	28	12
Four	4	44	22	14	27	25	19
Five	4	49	42	28	29	34	15

TABLE A11.2.8 Post-Meal Satiety Questionnaires (SQ) Data [Subject 8 (CV)]

Phase 1 (TM A)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	66	18	15	74	74	25
	4	79	44	26	68	80	51
Two	1	68	19	17	78	80	20
	4	62	27	18	39	40	31
Three	4	70	15	16	70	70	21
Four	4	64	22	25	79	76	27
Five	4	68	20	22	70	69	24

Phase 2 (TM B)

Week	Day	Response Ratings (mm) on SQ					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
One	1	64	17	17	68	66	35
	4	75	20	25	75	82	54
Two	1	70	26	17	37	47	28
	4						
Three	4						
Four	4						
Five	4						

TABLE A11.1.9 Bodily Sensations Questionnaire (BSQ) data [Subject 1 (SS)]

WEEK	PHASE ONE (TM A)					PHASE TWO (TM B)							
	1	2	3	4	5	1	2	3	4	5			
DAY	1	4	1	4	4	4	1	4	1	4	4	4	4
GASTRIC													
1. feeling of emptiness	*		*	*	*		*	*	*				
2. rumbling													
3. ache													
4. pain													
5. tenseness													
6. nausea													
7. no gastric sensations	*	*				*	*				*	*	
MOUTH AND THROAT													
1. emptiness			*	*									
2. dryness													
3. salivation						*	*	*	*	*	*	*	*
4. unpleasant taste/sensation	*	*											
5. pleasant					*								
6. tightness													
CEREBRAL													
1. headache													
2. dizziness													
3. faintness													
4. spots before the eyes													
5. ringing in the ears													
GENERAL													
1. weakness													
2. tiredness													
3. restlessness			*	*	*	*	*	*	*	*	*	*	*
4. cold													
5. warmth	*	*	*	*	*	*	*	*	*	*	*	*	*
6. muscular spasms													
MOOD WHEN HUNGRY													
1. nervous													
2. irritable													
3. tense													
4. depressed													
5. apathetic													
6. cheerful	*												
7. excited													
8. calm						*							
9. relaxed			*	*	*	*	*	*	*	*	*	*	*
10. contented		*	*	*	*	*	*	*	*	*	*	*	*

TABLE A11.2.9 Food Preference Questionnaire (FPQ) Data [Subject 1 (SS)]

WEEK	Day	Number of Items Chosen on FPQ					
		Total Number Chosen		High Protein		High Carbohydrate	
		Ph1 (TM A)	Ph2 (TM B)	Ph1 (TM A)	Ph2 (TM B)	Ph1 (TM A)	Ph2 (TM B)
One	1	13		7	*	6	
	4	13	6	7	2	6	4
Two	1	10	6	6	3	4	3
	4	11	5	6	2	5	3
Three	4	10	5	6	2	4	3
Four	4	9	5	4	3	5	2
Five	4	10	5	5	2	5	3

TABLE A11.1.10 Bodily Sensations Questionnaire (BSQ) data [Subject 2 (CA)]

WEEK	PHASE ONE (TM A)					PHASE TWO (TM B)						
	1	2	3	4	5	1	2	3	4	5		
DAY	1	4	1	4	4	4	1	4	1	4	4	4
GASTRIC												
1. feeling of emptiness	*	*		*			*		*			
2. rumbling		*		*			*	*	*			
3. ache		*					*	*				
4. pain							*					
5. tenseness												
6. nausea						*					*	*
7. no gastric sensations			*			*					*	*
MOUTH AND THROAT												
1. emptiness	*	*		*			*					*
2. dryness							*	*				*
3. salivation	*	*		*			*		*	*	*	*
4. unpleasant taste/sensation	*	*		*			*	*	*	*	*	*
5. pleasant						*					*	*
6. tightness							*					
CEREBRAL												
1. headache		*					*				*	*
2. dizziness							*					
3. faintness							*				*	*
4. spots before the eyes							*				*	*
5. ringing in the ears							*				*	*
GENERAL												
1. weakness	*	*		*							*	*
2. tiredness												
3. restlessness			*		*		*					
4. cold							*					
5. warmth												
6. muscular spasms												
MOOD WHEN HUNGRY												
1. nervous												
2. irritable												
3. tense												
4. depressed												
5. apathetic												
6. cheerful	*						*					
7. excited			*	*			*					
8. calm		*	*	*			*	*		*	*	*
9. relaxed		*	*	*			*	*		*	*	*
10. contented		*	*	*	*	*	*	*	*	*	*	*

TABLE A11.2.10 Food Preference Questionnaire (FPQ) Data [Subject 2 (CA)]

WEEK	Day	Number of Items Chosen on FPQ					
		Total Number Chosen		High Protein		High Carbohydrate	
		Ph1 (TM A)	Ph2 (TM B)	Ph1 (TM A)	Ph2 (TM B)	Ph1 (TM A)	Ph2 (TM B)
One	1	9		3		6	
	4	11	0	4	0	7	0
Two	1	11	6	4	1	7	5
	4	12	2	5	0	7	2
Three	4	14	7	6	5	8	2
Four	4	12	5	5	2	7	3
Five	4		4		1		3

TABLE A11.1.11 Bodily Sensations Questionnaire (BSQ) data [Subject 3 (LE)]

WEEK	PHASE ONE (TM B)					PHASE TWO (TM A)							
	1	2	3	4	5	1	2	3	4	5			
DAY	1	4	1	4	4	4	1	4	1	4	4	4	4
GASTRIC													
1. feeling of emptiness	*	*	*		*	*	*				*		*
2. rumbling													
3. ache													
4. pain													
5. tenseness													
6. nausea									*		*	*	
7. no gastric sensations						*							
MOUTH AND THROAT													
1. emptiness	*		*	*		*	*	*			*	*	*
2. dryness		*		*	*							*	*
3. salivation													
4. unpleasant taste/sensation													
5. pleasant													
6. tightness													
CEREBRAL													
1. headache	*				*								
2. dizziness										*			
3. faintness													
4. spots before the eyes													
5. ringing in the ears													
GENERAL													
1. weakness													
2. tiredness													
3. restlessness	*	*		*	*	*	*	*			*		
4. cold													
5. warmth												*	
6. muscular spasms													
MOOD WHEN HUNGRY													
1. nervous													
2. irritable													
3. tense													
4. depressed													
5. apathetic													
6. cheerful	*												
7. excited													
8. calm		*	*	*	*	*	*	*	*	*	*	*	*
9. relaxed						*	*			*	*	*	*
10. contented													

TABLE A11.2.11 Food Preference Questionnaire (FPQ) Data [Subject 3 (LE)]

WEEK	Day	Number of Items Chosen on FPQ					
		Total Number Chosen		High Protein		High Carbohydrate	
		Ph1 (TM B)	Ph2 (TM A)	Ph1 (TM B)	Ph2 (TM A)	Ph1 (TM B)	Ph2 (TM A)
One	1	14	8	7	5	7	3
	4	10	7	5	5	5	2
Two	1	9	7	5	5	4	2
	4	9	6	5	5	4	1
Three	4	9	5	6	5	3	0
Four	4	9	6	6	4	3	2
Five	4	8	2	6	2	2	0

TABLE A11.1.12 Bodily Sensations Questionnaire (BSQ) data [Subject 4 (EA)]

	PHASE ONE (TM B)						PHASE TWO (TM A)															
	WEEK		1		2		3		4		5		1		2		3		4		5	
DAY	1	4	1	4	4	4	4	1	4	1	4	4	4	4	1	4	1	4	4	4	4	
GASTRIC																						
1. feeling of emptiness	*					*	*	*	*	*	*		*					*			*	
2. rumbling																						
3. ache																						
4. pain																						
5. tenseness																						
6. nausea																						
7. no gastric sensations					*												*	*				
MOUTH AND THROAT																						
1. emptiness																						
2. dryness		*	*		*	*						*	*								*	
3. salivation	*			*																		
4. unpleasant taste/sensation																						
5. pleasant								*	*	*	*											
6. tightness																						
CEREBRAL																						
1. headache																						
2. dizziness																						
3. faintness																						
4. spots before the eyes																						
5. ringing in the ears																						
GENERAL																						
1. weakness																						
2. tiredness																						
3. restlessness																						
4. cold																						
5. warmth																						
6. muscular spasms																						
MOOD WHEN HUNGRY																						
1. nervous																						
2. irritable																						
3. tense																						
4. depressed																						
5. apathetic																						
6. cheerful																						
7. excited																						
8. calm			*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	
9. relaxed																						
10. contented	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	

TABLE A11.2.12 Food Preference Questionnaire (FPQ) Data [Subject 4 (EA)]

WEEK	Day	Number of Items Chosen on FPQ					
		Total Number Chosen		High Protein		High Carbohydrate	
		Ph1 (TM B)	Ph2 (TM A)	Ph1 (TM B)	Ph2 (TM A)	Ph1 (TM B)	Ph2 (TM A)
One	1	12		7		5	
	4	14		8		6	
Two	1	13	13	8	7	5	6
	4	14	14	8	8	6	6
Three	4	14	0	8	0	6	0
Four	4	15		8		7	
Five	4	0	15	0	8	0	7

TABLE A11.1.13 Bodily Sensations Questionnaire (BSQ) data [Subject 5 (VM)]

	PHASE ONE (TM B)					PHASE TWO (TM A)				
	1	2	3	4	5	1	2	3	4	5
WEEK	1	4	1	4	4	1	4	1	4	4
DAY	1	4	1	4	4	1	4	1	4	4
GASTRIC										
1. feeling of emptiness	*	*	*	*	*	*	*	*	*	*
2. rumbling										
3. ache										
4. pain										
5. tenseness										
6. nausea										
7. no gastric sensations										
MOUTH AND THROAT										
1. emptiness		*	*	*	*					
2. dryness										
3. salivation	*			*	*	*	*	*	*	*
4. unpleasant taste/sensation										
5. pleasant										
6. tightness										
CEREBRAL										
1. headache		*		*	*			*	*	*
2. dizziness								*	*	*
3. faintness								*	*	*
4. spots before the eyes								*	*	*
5. ringing in the ears								*	*	*
GENERAL										
1. weakness								*	*	*
2. tiredness			*	*	*	*	*	*	*	*
3. restlessness			*	*	*	*	*	*	*	*
4. cold			*	*	*	*	*	*	*	*
5. warmth	*	*	*	*	*	*	*	*	*	*
6. muscular spasms										
MOOD WHEN HUNGRY										
1. nervous					*					
2. irritable					*					
3. tense					*					
4. depressed					*					
5. apathetic	*				*	*	*	*	*	*
6. cheerful					*	*	*	*	*	*
7. excited					*	*	*	*	*	*
8. calm		*	*	*	*	*	*	*	*	*
9. relaxed		*	*	*	*	*	*	*	*	*
10. contented		*	*	*	*	*	*	*	*	*

TABLE A11.2.13 Food Preference Questionnaire (FPQ) Data [Subject 5 (VM)]

		Number of Items Chosen on FPQ					
WEEK	Day	Total Number Chosen		High Protein		High Carbohydrate	
		Ph1 (TM B)	Ph2 (TM A)	Ph1 (TM B)	Ph2 (TM A)	Ph1 (TM B)	Ph2 (TM A)
One	1	10		6		4	
	4	11	5	6	6	5	9
Two	1	11	15	6	6	5	9
	4	12		6		6	
Three	4	14	15	7	4	7	11
Four	4	14	16	6	6	8	10
Five	4	18	17	7	5	11	12

TABLE A11.1.14 Bodily Sensations Questionnaire (BSQ) data [Subject 6 (LI)]

	PHASE ONE (TM B)					PHASE TWO (TM A)				
	1	2	3	4	5	1	2	3	4	5
WEEK	1	4	1	4	4	1	4	1	4	4
DAY	1	4	1	4	4	1	4	1	4	4
GASTRIC										
1. feeling of emptiness	*	*	*	*	*	*	*	*	*	*
2. rumbling			*	*	*			*	*	*
3. ache			*	*	*			*	*	*
4. pain			*	*	*			*	*	*
5. tenseness	*	*	*	*	*	*	*	*	*	*
6. nausea			*	*	*			*	*	*
7. no gastric sensations			*	*	*			*	*	*
MOUTH AND THROAT										
1. emptiness		*	*	*	*					
2. dryness		*	*	*	*					
3. salivation	*			*	*	*	*	*	*	*
4. unpleasant taste/sensation	*			*	*	*	*	*	*	*
5. pleasant				*	*					
6. tightness				*	*					
CEREBRAL										
1. headache	*			*	*	*	*	*	*	*
2. dizziness				*	*	*	*	*	*	*
3. faintness				*	*	*	*	*	*	*
4. spots before the eyes				*	*	*	*	*	*	*
5. ringing in the ears				*	*	*	*	*	*	*
GENERAL										
1. weakness				*	*	*	*	*	*	*
2. tiredness				*	*	*	*	*	*	*
3. restlessness				*	*	*	*	*	*	*
4. cold				*	*	*	*	*	*	*
5. warmth	*	*	*	*	*	*	*	*	*	*
6. muscular spasms				*	*	*	*	*	*	*
MOOD WHEN HUNGRY										
1. nervous				*	*	*	*	*	*	*
2. irritable				*	*	*	*	*	*	*
3. tense				*	*	*	*	*	*	*
4. depressed				*	*	*	*	*	*	*
5. apathetic	*	*	*	*	*	*	*	*	*	*
6. cheerful		*	*	*	*	*	*	*	*	*
7. excited		*	*	*	*	*	*	*	*	*
8. calm	*	*	*	*	*	*	*	*	*	*
9. relaxed	*	*	*	*	*	*	*	*	*	*
10. contented	*	*	*	*	*	*	*	*	*	*

TABLE A11.2.14 Food Preference Questionnaire (FPQ) Data [Subject 6 (LI)]

		Number of Items Chosen on FPQ					
WEEK	Day	Total Number Chosen		High Protein		High Carbohydrate	
		Ph1 (TM B)	Ph2 (TM A)	Ph1 (TM B)	Ph2 (TM A)	Ph1 (TM B)	Ph2 (TM A)
One	1	17	11	10	5	7	6
	4	14	10	8	5	6	5
Two	1	12	9	6	5	6	4
	4	13	2	6	0	7	2
Three	4	3	0	1	0	2	0
Four	4	4	3	0	0	4	3
Five	4	4	3	1	0	3	3

TABLE A11.1.15 Bodily Sensations Questionnaire (BSQ) data [Subject 7 (EG)]

		PHASE ONE (TM A)					PHASE TWO (TM B)							
WEEK		1	2	3	4	5	1	2	3	4	5			
DAY		1	4	1	4	4	4	1	4	1	4	4	4	4
GASTRIC														
1. feeling of emptiness		*	*	*	*	*	*	*	*	*	*	*	*	*
2. rumbling		*	*	*	*	*	*	*	*	*	*	*	*	*
3. ache														
4. pain														
5. tenseness														
6. nausea														
7. no gastric sensations														
MOUTH AND THROAT														
1. emptiness		*												
2. dryness														
3. salivation														
4. unpleasant taste/sensation														
5. pleasant														
6. tightness														
CEREBRAL														
1. headache														
2. dizziness														
3. faintness														
4. spots before the eyes														
5. ringing in the ears														
GENERAL														
1. weakness														
2. tiredness														
3. restlessness														
4. cold														
5. warmth														
6. muscular spasms														
MOOD WHEN HUNGRY														
1. nervous														
2. irritable														
3. tense														
4. depressed														
5. apathetic														
6. cheerful														
7. excited														
8. calm		*	*	*	*	*	*	*	*	*	*	*	*	*
9. relaxed														
10. contented														

TABLE A11.2.15 Food Preference Questionnaire (FPQ) Data [Subject 7 (EG)]

		Number of Items Chosen on FPQ					
		Total Number Chosen		High Protein		High Carbohydrate	
WEEK	Day	Ph1 (TM A)	Ph2 (TM B)	Ph1 (TM A)	Ph2 (TM B)	Ph1 (TM A)	Ph2 (TM B)
One	1	19	19	9	10	10	9
	4	20	18	10	9	10	9
Two	1	20	19	10	9	10	10
	4	18	19	9	9	9	10
Three	4	18	19	8	9	10	10
Four	4		18		9		9
Five	4		17		9		8

TABLE A11.1.16 Bodily Sensations Questionnaire (BSQ) data [Subject 8 (CV)]

		PHASE ONE (TM A)					PHASE TWO (TM B)							
WEEK		1	2	3	4	5	1	2	3	4	5			
DAY		1	4	1	4	4	4	1	4	1	4	4	4	4
GASTRIC														
1. feeling of emptiness		*				*	*	*	*	*	*	*	*	*
2. rumbling		*				*	*	*	*	*	*	*	*	*
3. ache		*	*			*	*	*	*	*	*	*	*	*
4. pain														
5. tenseness								*						
6. nausea														
7. no gastric sensations				*										
MOUTH AND THROAT														
1. emptiness				*										
2. dryness				*										
3. salivation		*	*	*	*	*	*	*	*	*	*	*	*	*
4. unpleasant taste/sensation		*	*	*	*	*	*	*	*	*	*	*	*	*
5. pleasant								*		*				
6. tightness														
CEREBRAL														
1. headache														
2. dizziness														
3. faintness														
4. spots before the eyes														
5. ringing in the ears														
GENERAL														
1. weakness				*										
2. tiredness				*				*	*	*	*	*	*	*
3. restlessness						*		*	*	*	*	*	*	*
4. cold														
5. warmth										*				
6. muscular spasms														
MOOD WHEN HUNGRY														
1. nervous				*	*	*	*	*	*	*	*	*	*	*
2. irritable				*	*	*	*	*	*	*	*	*	*	*
3. tense				*	*	*	*	*	*	*	*	*	*	*
4. depressed				*	*	*	*	*	*	*	*	*	*	*
5. apathetic				*	*	*	*	*	*	*	*	*	*	*
6. cheerful		*	*	*	*	*	*	*	*	*	*	*	*	*
7. excited		*	*	*	*	*	*	*	*	*	*	*	*	*
8. calm								*	*	*	*	*	*	*
9. relaxed								*	*	*	*	*	*	*
10. contented								*	*	*	*	*	*	*

TABLE A11.2.16 Food Preference Questionnaire (FPQ) Data [Subject 8 (CV)]

		Number of Items Chosen on FPQ					
		Total Number Chosen		High Protein		High Carbohydrate	
WEEK	Day	Ph1 (TM A)	Ph2 (TM B)	Ph1 (TM A)	Ph2 (TM B)	Ph1 (TM A)	Ph2 (TM B)
One	1	14	3	8	1	6	2
	4	11	1	7	0	4	1
Two	1	3	0	2	0	1	0
	4	4		3		2	
Three	4	1		1		0	
Four	4	1		0		1	
Five	4	1		0		1	

TABLE A11.3.1 Average Responses to the BSQ (mean 6 subjects)

Sensations	No of Subjects		No of Times	
	TM A	TM B	TM A	TM B
Empty (stomach)	5	5	11	12
Rumbling	2	2	3	5
Pain	1	0	1	0
Nausea	2	0	4	0
No sensations	5	6	9	11
Empty (mouth)	1	1	1	1
Dry	4	5	9	9
Salivation	1	2	2	6
Unpleasant	2	2	5	5
Pleasant	2	2	2	3
Headache	1	3	1	5
Dizziness	1	0	1	0
Faintness	1	0	1	0
Ringing in ears	0	1	0	1
Tiredness	2	1	3	2
Restlessness	0	2	0	3
Cold	4	3	7	7
Warmth	1	1	4	2
Irritable	0	1	0	1
Cheerful	1	2	1	2
Excited	1	0	1	0
Calm	4	3	9	10
Relaxed	5	5	16	16
Contented	2	1	4	2

TABLE A12.1.1

Quantity of Each Food Commodity Presented, Remaining and Eaten (g) at the Test Meals [Subject 1 (SS)]

Phase 1 (TM A)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	99.20	197.40	128.10		60.00	17.80
		Amt Remaining	44.30	192.40	19.60		0.00	8.30
		Amt Eaten	54.90	5.00	108.50		60.00	9.50
	4	Amt Presented	76.50	97.20	108.50	44.50	60.00	19.80
		Amt Remaining	18.70	83.70	0.20	18.30	0.00	9.40
		Amt Eaten	57.80	13.50	108.30	26.20	60.00	10.40
2	1	Amt Presented	93.90	125.80	115.30	20.00	60.00	22.80
		Amt Remaining	37.70	123.40	18.00	2.40	30.00	15.70
		Amt Eaten	56.20	2.40	97.30	17.60	30.00	7.10
	4	Amt Presented	104.50	238.80	110.60	22.80	60.00	31.10
		Amt Remaining	13.70	105.80	22.20	3.90	30.00	22.30
		Amt Eaten	90.80	133.00	88.40	18.90	30.00	8.80
3	4	Amt Presented	105.90	216.30	111.50	18.20	60.00	20.50
		Amt Remaining	18.40	94.60	1.00	4.20	15.00	7.50
		Amt Eaten	87.50	121.70	110.50	13.90	45.00	13.00
4	4	Amt Presented	101.90	220.00	97.20	20.70	60.00	18.60
		Amt Remaining	30.00	62.00	8.30	3.40	30.00	8.30
		Amt Eaten	71.90	158.00	88.90	17.30	30.00	10.30
5	4	Amt Presented	96.70	224.70	108.90	19.40	60.00	22.80
		Amt Remaining	36.60	95.50	10.20	3.20	30.00	4.90
		Amt Eaten	60.10	129.20	98.70	16.20	30.00	17.90

Phase 2 (TM B)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	111.10	193.90	94.20	24.00	60.00	17.90
		Amt Remaining	4.30	18.90	15.10	2.10	7.50	3.90
		Amt Eaten	105.80	175.00	79.10	21.90	52.50	14.00
	4	Amt Presented	119.40	231.60	112.20	25.60	60.00	21.80
		Amt Remaining	40.60	30.70	3.80	2.90	30.00	10.20
		Amt Eaten	78.80	200.90	108.40	22.70	30.00	11.60
2	1	Amt Presented	109.10	152.70	107.40	36.60	60.00	19.30
		Amt Remaining	32.00	43.80	3.40	5.10	7.50	8.30
		Amt Eaten	77.10	108.90	104.00	31.50	52.50	11.00
	4	Amt Presented	97.70	234.50	98.60	13.50	60.00	25.50
		Amt Remaining	27.80	40.40	9.30	5.40	15.00	14.90
		Amt Eaten	69.90	194.10	89.30	8.10	45.00	10.60
3	4	Amt Presented	107.60	200.00	85.60	26.60	60.00	16.60
		Amt Remaining	49.50	35.20	5.20	3.10	15.00	8.50
		Amt Eaten	58.10	64.80	80.40	23.50	45.00	8.10
4	4	Amt Presented	105.70	247.20	102.70	34.20	60.00	19.10
		Amt Remaining	31.90	66.30	29.80	11.50	7.50	10.10
		Amt Eaten	73.80	180.90	72.90	22.70	52.50	9.00
5	4	Amt Presented	100.50	226.40	95.00	37.60	60.00	22.80
		Amt Remaining	20.50	72.20	3.00	4.60	0.00	10.90
		Amt Eaten	80.00	154.20	92.00	33.00	60.00	11.90

TABLE A12.2.1

Total Food Intake and Macro-Nutrient Consumption for Test Meals [Subject 1 (SS)]

Phase 1 (TM A)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	502.50	406.50	437.80	567.80	532.40	518.40	532.50
Total Food Remaining (g)	264.60	130.30	227.20	197.90	140.80	142.00	180.40
Total Food Intake (g)	237.90	276.20	210.60	369.90	391.60	376.40	352.10
Total Food Intake (kJ)	2040.39	2324.31	1730.57	2824.59	3060.50	2725.88	2702.63
Corrected (kJ)	2048.51	2331.72	1737.63	2832.19	3068.73	2738.02	2708.00
Total Protein Intake (g)	22.05	23.40	19.67	31.11	31.87	26.95	23.61
Total Protein Intake (kJ)	370.44	393.12	330.46	522.65	535.42	452.76	396.65
Total Carbohydrate Intake (g)	48.99	51.47	32.01	63.65	71.84	69.99	64.32
Total Carbohydrate Intake (kJ)	823.03	846.70	537.77	1069.32	1206.91	1175.83	1080.58
Total Fat Intake (g)	22.62	28.41	23.00	32.81	35.09	29.35	32.56
Total Fat Intake (kJ)	855.04	1073.90	869.40	1240.22	1326.40	1109.43	1230.77
Protein Energy %	18.08	16.86	19.02	18.45	17.45	16.54	14.65
Carbohydrate Energy %	40.18	37.08	30.95	37.76	39.33	42.94	39.90
Fat Energy %	41.74	46.06	50.03	43.79	43.22	40.52	45.45

Phase 1 (TM B)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	500.10	570.60	485.10	529.80	496.40	568.90	524.30
Total Food Remaining (g)	51.80	118.20	110.10	112.80	116.50	157.10	111.20
Total Food Intake (g)	448.30	452.40	385.00	417.00	379.90	411.80	431.10
Total Food Intake (kJ)	3624.64	3151.42	2989.17	2975.60	2688.45	3054.05	3320.99
Corrected (kJ)	3623.50	3170.78	2999.43	2991.54	2705.26	3065.29	3330.98
Total Protein Intake (g)	37.63	30.29	29.80	28.46	24.91	29.63	31.96
Total Protein Intake (kJ)	632.18	508.87	500.64	478.13	418.49	497.78	536.93
Total Carbohydrate Intake (g)	84.23	84.13	71.90	86.45	78.09	84.72	85.20
Total Carbohydrate Intake (kJ)	1415.06	1413.38	1207.92	145.86	1311.91	1423.30	1431.36
Total Fat Intake (g)	41.70	33.03	34.15	28.07	25.79	30.27	36.05
Total Fat Intake (kJ)	1576.26	1248.53	1290.87	1061.05	974.86	1144.21	1362.69
Protein Energy %	17.45	16.05	16.69	15.98	15.47	16.24	16.12
Carbohydrate Energy %	39.05	44.58	40.27	48.55	48.49	46.43	42.97
Fat Energy %	43.50	39.38	43.04	35.47	36.04	37.33	40.91

TABLE A12.1.2

Quantity of Each Food Commodity Presented, Remaining and Eaten (g) at the Test Meals [Subject 2 (CA)]

Phase 1 (TM A)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	100.70	185.60	130.90		60.00	15.70
		Amt Remaining	12.40	1.80	4.20		0.00	4.60
		Amt Eaten	88.30	183.80	126.70		60.00	11.10
4		Amt Presented	90.00	113.50	122.10	28.20	60.00	23.40
		Amt Remaining	4.80	0.40	6.80	12.80	0.00	11.00
		Amt Eaten	85.20	113.10	115.30	15.40	60.00	12.40
2	1	Amt Presented	92.20	125.60	111.70	14.90	60.00	24.50
		Amt Remaining	7.60	8.80	20.90	0.20	0.00	13.00
		Amt Eaten	84.60	116.80	90.80	14.70	60.00	11.50
4		Amt Presented	91.70	272.70	114.00	27.90	60.00	24.00
		Amt Remaining	0.50	4.50	29.40	3.40	0.00	4.40
		Amt Eaten	91.20	268.20	84.60	24.50	60.00	19.60
3	4	Amt Presented	95.70	119.70	118.40	17.20	60.00	22.80
		Amt Remaining	7.90	2.50	115.30	5.30	0.00	6.10
		Amt Eaten	87.80	197.20	3.10	11.90	60.00	16.70
4	4	Amt Presented	114.40	219.90	70.10	26.30	60.00	18.10
		Amt Remaining	18.50	11.70	8.20	4.10	30.00	2.90
		Amt Eaten	95.90	208.20	61.90	22.20	30.00	15.20
5	4	Amt Presented						
		Amt Remaining						
		Amt Eaten						

Phase 2 (TM B)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	103.90	222.80	88.90	31.20	60.00	19.30
		Amt Remaining	4.00	14.40	20.00	4.90	0.00	0.40
		Amt Eaten	99.90	208.40	68.90	26.30	60.00	18.90
4		Amt Presented	105.60	199.40	81.60	32.60	60.00	22.20
		Amt Remaining	0.10	3.70	4.90	6.10	7.50	0.80
		Amt Eaten	105.50	195.70	76.70	26.50	52.50	21.40
2	1	Amt Presented	108.60	204.90	96.60	29.30	60.00	22.40
		Amt Remaining	17.60	3.80	9.40	5.90	0.00	2.00
		Amt Eaten	91.00	201.10	87.20	23.40	60.00	20.40
4		Amt Presented	101.50	245.00	99.20	21.10	60.00	21.30
		Amt Remaining	30.60	5.20	8.50	3.50	0.00	0.40
		Amt Eaten	70.90	239.80	90.70	17.60	60.00	20.90
3	4	Amt Presented	100.00	239.8	86.10	34.90	60.00	20.70
		Amt Remaining	13.00	31.80	13.80	4.80	0.00	3.80
		Amt Eaten	87.00	208.00	72.30	30.10	60.00	16.90
4	4	Amt Presented	100.50	247.80	96.60	53.40	60.00	23.40
		Amt Remaining	28.60	39.40	53.60	10.70	0.00	9.40
		Amt Eaten	71.90	208.40	43.00	42.70	60.00	14.00
5	4	Amt Presented	98.70	261.7	102.80	36.10	60.00	20.40
		Amt Remaining	51.30	13.40	56.10	5.90	0.00	1.80
		Amt Eaten	47.40	248.30	46.70	30.20	60.00	18.60

TABLE A12.2.2

Total Food Intake and Macro-Nutrient Consumption for Test Meals [Subject 2 (CA)]

Phase 1 (TM A)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	492.90	437.20	428.90	590.30	513.80	508.80	
Total Food Remaining (g)	23.00	35.80	153.50	42.40	137.10	75.40	
Total Food Intake (g)	469.90	401.40	270.40	548.10	376.70	433.40	
Total Food Intake (kJ)	3234.69	3055.49	2563.96	4153.20	3358.14	3384.22	
Corrected (kJ)	3250.59	3062.43	2557.59	4159.06	3336.90	3381.88	
Total Protein Intake (g)	33.89	31.90	29.31	37.01	32.08	33.46	
Total Protein Intake (kJ)	569.35	535.92	492.41	621.77	538.94	562.13	
Total Carbohydrate Intake (g)	87.71	72.20	47.35	112.52	81.00	78.45	
Total Carbohydrate Intake (kJ)	1473.53	1212.96	795.48	1890.34	1360.80	1317.96	
Total Fat Intake (g)	31.95	34.75	33.59	43.57	38.02	39.73	
Total Fat Intake (kJ)	1207.71	1313.55	1269.70	1646.95	1437.16	1501.79	
Protein Energy %	17.52	17.50	19.25	14.95	16.15	16.62	
Carbohydrate Energy %	45.33	39.61	31.10	45.45	40.78	38.97	
Fat Energy %	37.15	42.89	49.64	39.60	43.07	44.41	

Phase 1 (TM B)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	526.10	501.40	521.80	548.10	541.50	581.70	579.70
Total Food Remaining (g)	43.70	23.10	38.70	48.20	67.20	141.70	128.50
Total Food Intake (g)	482.40	478.30	483.10	499.90	474.30	440.00	451.20
Total Food Intake (kJ)	3939.44	3977.42	3870.13	3765.03	3739.66	3450.40	3376.50
Corrected (kJ)	3933.72	3968.16	3868.71	3772.56	3740.39	3449.92	3380.87
Total Protein Intake (g)	37.41	38.05	35.46	31.33	34.33	30.03	24.72
Total Protein Intake (kJ)	628.49	639.24	595.73	526.34	576.74	504.50	415.30
Total Carbohydrate Intake (g)	94.95	89.25	96.00	106.13	95.50	91.24	101.53
Total Carbohydrate Intake (kJ)	1595.16	1499.40	1612.80	1782.98	1604.40	1532.83	1705.70
Total Fat Intake (g)	45.24	48.40	43.92	38.71	41.25	37.37	33.33
Total Fat Intake (kJ)	1710.07	1829.52	1660.18	1463.24	1559.25	1412.59	1259.87
Protein Energy %	15.98	16.11	15.40	13.95	15.42	14.62	12.28
Carbohydrate Energy %	40.55	37.79	41.69	47.26	42.89	44.43	50.45
Fat Energy %	43.47	46.10	42.91	38.79	41.69	40.95	37.26

TABLE A12.1.3

Quantity of Each Food Commodity Presented, Remaining and Eaten (g) at the Test Meals [Subject 3 (LE)]

Phase 1 (TM B)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented Amt Remaining Amt Eaten	95.20 34.70 60.50	181.30 85.80 95.50	130.20 21.90 108.30		60.00 30.00 30.00	19.60 15.00 4.60
	4	Amt Presented Amt Remaining Amt Eaten	94.50 19.70 74.80	123.40 60.70 62.70	113.2 0.40 112.80	35.00 18.00 16.90	60.00 30.00 30.00	19.40 15.30 4.10
2	1	Amt Presented Amt Remaining Amt Eaten	109.40 8.60 100.80	133.90 23.90 110.00	122.00 88.50 33.50	24.30 11.80 12.50	60.00 30.00 30.00	20.70 16.10 4.60
	4	Amt Presented Amt Remaining Amt Eaten	99.30 0.00 99.30	182.70 75.20 107.50	126.10 71.70 54.40	15.20 3.70 11.50	60.00 30.00 30.00	16.30 9.00 7.30
3	4	Amt Presented Amt Remaining Amt Eaten	103.80 8.50 95.30	209.50 65.10 144.40	130.90 39.80 91.10	14.30 3.60 10.70	60.00 30.00 30.00	23.10 10.20 12.90
4	4	Amt Presented Amt Remaining Amt Eaten	101.50 14.40 87.10	216.90 96.20 120.70	104.80 76.30 28.50	18.90 2.80 16.10	60.00 30.00 30.00	19.10 10.60 8.50
5	4	Amt Presented Amt Remaining Amt Eaten	112.40 0.70 111.70	257.00 54.40 202.60	102.60 1.20 101.40	24.20 2.90 21.30	60.00 60.00 0.00	20.40 9.00 11.40

Phase 2 (TM A)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented Amt Remaining Amt Eaten	110.10 29.80 80.40	134.10 17.20 116.90	122.70 24.80 97.90	20.40 4.10 16.30	60.00 30.00 30.00	22.30 14.10 8.20
	4	Amt Presented Amt Remaining Amt Eaten	109.60 6.20 103.40	234.20 78.10 156.10	98.00 14.90 83.10	33.20 3.90 29.30	60.00 30.00 30.00	20.10 10.60 9.50
2	1	Amt Presented Amt Remaining Amt Eaten	110.80 34.10 76.70	234.20 98.90 135.30	96.10 17.90 78.20	32.90 4.80 28.10	60.00 60.00 0.00	20.70 12.10 8.60
	4	Amt Presented Amt Remaining Amt Eaten	101.20 30.70 70.50	242.80 112.20 130.60	94.40 32.20 62.20	36.80 3.00 33.80	60.00 60.00 0.00	20.00 10.00 10.00
3	4	Amt Presented Amt Remaining Amt Eaten	98.80 15.60 83.20	225.50 105.50 120.00	88.50 11.60 76.90	39.50 5.70 33.80	60.00 60.00 0.00	18.00 11.50 6.50
4	4	Amt Presented Amt Remaining Amt Eaten	100.30 12.80 87.50	262.60 142.40 120.20	108.30 10.40 97.90	38.90 4.80 34.10	60.00 60.00 0.00	26.70 16.00 10.70
5	4	Amt Presented Amt Remaining Amt Eaten	99.20 21.50 77.70	267.50 157.70 109.80	114.00 9.30 104.70	48.50 5.20 43.30	60.00 60.00 0.00	15.70 4.90 10.80

TABLE A12.2.3

Total Food Intake and Macro-Nutrient Consumption for Test Meals [Subject 3 (LE)]

Phase 1 (TM B)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	486.30	445.50	470.30	499.60	541.60	521.20	576.60
Total Food Remaining (g)	187.40	144.20	178.90	189.60	157.20	230.30	128.20
Total Food Intake (g)	298.90	301.30	291.40	310.00	384.40	290.90	448.40
Total Food Intake (kJ)	1951.32	2140.45	2403.79	2618.75	3017.16	2510.76	3234.77
Corrected (kJ)	1970.21	2155.90	2392.53	2612.78	3019.39	2500.51	2886.83
Total Protein Intake (g)	22.28	25.75	30.79	31.57	32.41	28.24	35.63
Total Protein Intake (kJ)	374.30	432.60	517.27	530.38	544.49	474.43	598.58
Total Carbohydrate Intake (g)	51.84	46.53	43.02	51.48	66.72	50.76	68.21
Total Carbohydrate Intake (kJ)	870.91	781.70	722.74	864.86	1120.90	852.77	1145.93
Total Fat Intake (g)	19.18	24.91	30.49	32.21	35.82	31.04	30.22
Total Fat Intake (kJ)	725.00	941.60	1152.52	1217.54	1354.00	1173.31	1142.32
Protein Energy %	19.00	20.07	21.62	20.30	18.03	18.97	20.73
Carbohydrate Energy %	44.20	36.26	30.21	33.10	37.12	34.10	39.70
Fat Energy %	36.80	43.68	48.17	46.60	44.84	46.92	39.57

Phase 1 (TM A)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	469.70	555.10	554.70	555.20	530.30	596.80	604.90
Total Food Remaining (g)	120.00	143.70	227.80	248.10	209.90	246.40	258.60
Total Food Intake (g)	349.70	411.40	326.90	307.10	320.40	350.40	346.30
Total Food Intake (kJ)	2603.85	3177.73	2343.87	2277.72	2329.85	2587.15	2498.72
Corrected (kJ)	2648.39	3182.38	2352.08	2280.43	2337.42	2594.47	2509.50
Total Protein Intake (g)	30.33	34.83	24.87	22.89	26.21	27.86	25.55
Total Protein Intake (kJ)	509.54	585.14	417.82	384.55	440.33	468.05	429.24
Total Carbohydrate Intake (g)	61.05	68.94	47.68	44.09	43.78	47.26	46.02
Total Carbohydrate Intake (kJ)	1025.64	1158.19	801.02	740.71	735.50	793.97	773.14
Total Fat Intake (g)	29.45	38.07	29.98	30.56	30.73	35.25	34.58
Total Fat Intake (kJ)	1113.21	1439.05	1133.24	1155.17	1161.59	1332.45	1307.12
Protein Energy %	19.24	18.39	17.76	16.86	18.84	18.04	17.10
Carbohydrate Energy %	38.73	36.39	34.06	32.48	31.47	30.60	30.81
Fat Energy %	42.03	45.22	48.18	50.66	49.70	51.36	52.09

TABLE A12.1.4

Quantity of Each Food Commodity Presented, Remaining and Eaten (g) at the Test Meals [Subject 4 (EA)]

Phase 1 (TM B)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	107.00	179.10	122.10		60.00	19.80
		Amt Remaining	41.40	101.30	0.00		30.00	17.50
		Amt Eaten	65.60	77.80	122.10		30.00	2.30
	4	Amt Presented	102.40	114.50	117.60	40.40	60.00	21.30
		Amt Remaining	44.30	60.70	25.80	10.30	60.00	21.30
		Amt Eaten	58.10	53.80	91.80	30.10	0.00	0.00
2	1	Amt Presented	94.90	123.30	118.20	12.10	60.00	24.90
		Amt Remaining	1.10	92.00	42.70	2.90	60.00	24.90
		Amt Eaten	93.80	31.30	75.50	9.20	0.00	0.00
	4	Amt Presented	101.20	247.00	139.50	28.70	60.00	25.20
		Amt Remaining	27.40	137.80	63.40	4.00	60.00	25.20
		Amt Eaten	73.80	109.20	76.10	24.70	0.00	0.00
3	4	Amt Presented	99.10	232.20	133.20	16.10	60.00	17.80
		Amt Remaining	30.60	192.70	0.00	3.20	60.00	17.80
		Amt Eaten	68.50	38.50	133.20	12.90	0.00	0.00
4	4	Amt Presented	102.20	209.20	100.00	23.60	60.00	16.10
		Amt Remaining	44.90	106.60	18.10	3.40	60.00	16.10
		Amt Eaten	57.30	48.60	81.90	20.20	0.00	0.00
5	4	Amt Presented	105.00	210.50	90.20	31.00	60.00	20.60
		Amt Remaining	19.70	138.10	8.50	2.70	60.00	20.60
		Amt Eaten	85.30	72.40	81.70	28.30	0.00	0.00

Phase 2 (TM A)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	110.10	207.30	98.20	31.20	60.00	22.70
		Amt Remaining	24.30	101.00	1.00	1.80	60.00	22.70
		Amt Eaten	85.80	106.30	97.20	29.40	0.00	0.00
	4	Amt Presented	103.40	237.70	87.50	27.10	60.00	22.40
		Amt Remaining	36.20	138.00	14.60	5.30	60.00	22.40
		Amt Eaten	67.20	99.70	72.90	21.80	0.00	0.00
2	1	Amt Presented	109.50	157.30	91.70	26.40	60.00	20.00
		Amt Remaining	45.90	99.80	31.60	6.70	60.00	20.00
		Amt Eaten	63.60	57.50	60.10	19.70	0.00	0.00
	4	Amt Presented	102.20	224.90	98.50	12.00	60.00	20.20
		Amt Remaining	32.00	220.90	0.00	3.10	60.00	20.20
		Amt Eaten	70.20	4.00	98.50	8.90	0.00	0.00
3	4	Amt Presented	92.10	225.00	114.70	30.80	60.00	18.00
		Amt Remaining	42.10	208.70	28.50	4.90	60.00	18.00
		Amt Eaten	50.00	16.30	86.20	25.90	0.00	0.00
4	4	Amt Presented						
		Amt Remaining						
		Amt Eaten						
5	4	Amt Presented	99.20	273.30	83.20	32.70	60.00	15.70
		Amt Remaining	34.50	273.00	3.70	4.70	60.00	15.70
		Amt Eaten	64.70	0.30	79.50	28.00	0.00	0.00

TABLE A12.2.4

Total Food Intake and Macro-Nutrient Consumption for Test Meals [Subject 4 (EA)]

Phase 1 (TM B)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	488.00	456.20	433.40	601.60	558.40	511.10	517.30
Total Food Remaining (g)	190.20	222.40	223.60	317.80	305.30	303.10	249.60
Total Food Intake (g)	297.80	233.80	209.80	283.80	253.10	208.00	267.70
Total Food Intake (kJ)	1922.75	1454.00	1648.97	1880.68	1574.68	1370.69	1907.85
Corrected (kJ)	1945.98	1472.52	1651.73	1897.10	1602.30	1387.00	1920.12
Total Protein Intake (g)	23.63	18.43	26.10	23.41	21.80	17.98	25.66
Total Protein Intake (kJ)	396.98	309.62	438.48	393.29	366.24	302.06	431.09
Total Carbohydrate Intake (g)	50.51	26.56	18.78	40.62	31.68	26.15	32.36
Total Carbohydrate Intake (kJ)	848.57	446.21	315.50	682.42	532.22	439.32	543.65
Total Fat Intake (g)	18.53	18.96	23.75	21.73	18.62	17.08	25.01
Total Fat Intake (kJ)	700.43	716.69	897.75	821.39	703.84	645.62	945.38
Protein Energy %	20.40	21.03	26.55	20.73	22.86	21.78	22.45
Carbohydrate Energy %	43.61	30.30	19.10	35.97	32.22	31.67	28.31
Fat Energy %	36.00	48.67	54.35	43.30	43.93	46.55	49.24

Phase 1 (TM A)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	529.50	538.10	464.90	517.80	540.60		564.10
Total Food Remaining (g)	210.80	276.50	264.00	336.20	362.20		391.60
Total Food Intake (g)	318.70	261.60	200.90	181.60	178.40		172.50
Total Food Intake (kJ)	2123.26	1719.56	1426.13	1307.68	1179.98		1297.01
Corrected (kJ)	2143.13	1735.27	1434.93	1321.24	1196.46		1306.45
Total Protein Intake (g)	26.99	21.40	19.15	20.40	15.65		18.80
Total Protein Intake (kJ)	453.43	359.52	321.72	342.72	262.92		315.84
Total Carbohydrate Intake (g)	43.45	37.61	24.84	17.25	18.87		13.83
Total Carbohydrate Intake (kJ)	729.96	631.85	417.31	289.80	317.02		232.34
Total Fat Intake (g)	25.39	19.68	18.41	18.22	16.31		20.06
Total Fat Intake (kJ)	959.74	743.90	695.90	688.72	616.52		758.27
Protein Energy %	21.16	20.72	22.42	25.94	21.97		24.18
Carbohydrate Energy %	34.06	36.41	29.08	21.93	26.50		17.78
Fat Energy %	44.78	42.87	48.50	52.13	51.53		58.04

TABLE A12.1.5

Quantity of Each Food Commodity Presented, Remaining and Eaten (g) at the Test Meals [Subject 5 (VM)]

Phase 1 (TM B)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented Amt Remaining Amt Eaten	97.70 0.00 97.70	115.80 0.00 115.80	150.10 0.00 151.10		60.00 0.00 60.00	15.00 1.00 14.00
	4	Amt Presented Amt Remaining Amt Eaten	110.90 0.00 110.90	112.10 0.00 112.10	130.80 11.40 119.40	45.50 8.00 37.50	60.00 60.00 0.00	20.50 20.50 0.00
2	1	Amt Presented Amt Remaining Amt Eaten	94.60 15.60 79.00	122.20 24.10 98.10	119.30 11.60 107.70	19.10 7.50 11.60	60.00 0.00 60.00	26.30 14.70 11.60
	4	Amt Presented Amt Remaining Amt Eaten	98.50 5.80 92.70	249.70 108.10 141.60	127.80 33.20 94.60	30.80 7.20 23.60	60.00 30.00 30.00	24.10 14.10 10.00
3	4	Amt Presented Amt Remaining Amt Eaten	93.70 33.00 60.70	218.60 81.50 137.10	105.30 0.00 105.30	15.90 12.10 3.80	60.00 0.00 60.00	26.40 9.80 16.60
4	4	Amt Presented Amt Remaining Amt Eaten	108.20 33.40 74.80	215.40 119.70 95.70	102.10 22.60 79.50	22.70 4.80 17.90	60.00 15.00 45.00	17.40 0.40 17.00
5	4	Amt Presented Amt Remaining Amt Eaten	106.60 48.40 58.20	188.90 154.40 34.50	95.90 13.60 82.30	22.60 3.10 19.50	60.00 30.00 30.00	19.30 2.90 16.40

Phase 2 (TM A)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented Amt Remaining Amt Eaten	105.10 4.30 100.80	199.10 18.90 180.20	97.30 15.10 82.20	28.00 2.10 25.90	60.00 30.00 30.00	19.30 3.70 15.60
	4	Amt Presented Amt Remaining Amt Eaten	119.80 21.20 98.60	241.20 194.40 46.80	97.30 21.20 76.00	40.80 3.70 37.10	60.00 30.00 30.00	21.50 5.90 15.60
2	1	Amt Presented Amt Remaining Amt Eaten	108.70 30.50 78.20	150.00 107.50 42.50	87.50 18.90 68.60	36.10 5.30 30.80	60.00 0.00 60.00	22.40 7.80 14.60
	4	Amt Presented Amt Remaining Amt Eaten						
3	4	Amt Presented Amt Remaining Amt Eaten	109.60 64.60 45.20	215.50 170.10 45.40	89.20 23.50 65.70	35.00 7.70 27.30	60.00 30.00 30.00	19.60 8.50 11.10
4	4	Amt Presented Amt Remaining Amt Eaten	106.40 70.60 35.80	218.10 185.30 32.80	91.90 36.40 55.50	40.30 8.10 32.20	60.00 30.00 30.00	25.80 18.00 7.80
5	4	Amt Presented Amt Remaining Amt Eaten	100.00 73.60 26.40	274.10 254.70 19.40	109.60 53.80 55.80	41.50 8.50 33.00	60.00 30.00 30.00	24.60 17.30 7.30

TABLE A12.2.5

Total Food Intake and Macro-Nutrient Consumption for Test Meals [Subject 5 (VM)]

Phase 1 (TM B)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	478.60	479.80	441.50	590.90	519.90	525.80	493.30
Total Food Remaining (g)	1.00	99.90	73.50	198.40	136.40	195.90	252.40
Total Food Intake (g)	477.60	379.90	368.00	392.50	383.50	329.90	240.90
Total Food Intake (kJ)	3421.12	2500.33	2843.68	2979.41	2969.18	2837.20	2172.05
Corrected (kJ)	3436.40	2518.32	2850.24	2986.96	2978.64	2831.94	2165.48
Total Protein Intake (g)	36.40	33.45	29.83	32.03	26.55	27.36	20.57
Total Protein Intake (kJ)	611.52	561.96	501.44	538.10	446.04	459.65	345.58
Total Carbohydrate Intake (g)	85.91	42.92	67.85	66.97	82.17	60.41	37.88
Total Carbohydrate Intake (kJ)	1443.29	721.06	1139.88	1125.10	1380.46	1014.89	636.38
Total Fat Intake (g)	36.55	32.68	31.99	35.02	30.48	35.91	31.31
Total Fat Intake (kJ)	1381.59	235.30	1209.22	1323.76	1152.14	1357.40	1183.52
Protein Energy %	17.80	22.31	17.58	18.01	14.97	16.23	15.96
Carbohydrate Energy %	42.00	28.63	39.99	37.67	46.34	35.84	29.39
Fat Energy %	40.20	49.05	42.43	44.32	38.68	47.93	54.65

Phase 2 (TM A)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	508.80	580.50	464.70		528.90	542.50	609.80
Total Food Remaining (g)	74.10	276.40	170.00		304.20	348.40	437.90
Total Food Intake (g)	434.70	304.10	294.70		224.70	194.10	171.90
Total Food Intake (kJ)	3421.42	2845.12	2788.52		1885.54	1602.15	1406.89
Corrected (kJ)	3420.90	2830.38	2776.96		1885.85	1604.86	1411.12
Total Protein Intake (g)	34.65	31.08	28.26		17.27	14.46	11.84
Total Protein Intake (kJ)	582.12	522.14	474.77		290.14	242.93	198.91
Total Carbohydrate Intake (g)	74.79	40.51	53.20		38.17	33.48	30.17
Total Carbohydrate Intake (kJ)	1256.47	680.57	893.76		641.26	562.46	506.86
Total Fat Intake (g)	41.86	43.06	37.26		25.25	21.15	18.66
Total Fat Intake (kJ)	1582.31	1627.67	1408.43		954.45	799.47	705.35
Protein Energy %	17.02	18.45	17.10		15.39	15.14	14.10
Carbohydrate Energy %	36.73	24.05	32.18		34.00	35.05	35.92
Fat Energy %	46.25	57.51	50.72		50.61	49.82	50.00

TABLE A12.1.6

Quantity of Each Food Commodity Presented, Remaining and Eaten (g) at the Test Meals [Subject 6 (L1)]

Phase 1 (IM B)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	56.30	191.10	130.30	13.90	60.00	19.20
		Amt Remaining	5.70	1.40	122.50	2.60	30.00	0.20
		Amt Eaten	50.60	189.70	7.80	11.30	30.00	19.00
	4	Amt Presented	108.70	224.30	108.80	34.00	60.00	23.40
		Amt Remaining	25.50	89.00	39.40	4.20	30.00	8.30
		Amt Eaten	83.20	135.30	69.40	29.80	30.00	15.10
2	1	Amt Presented	105.60	242.50	93.30	11.10	60.00	20.80
		Amt Remaining	78.20	110.30	80.90	4.10	30.00	7.70
		Amt Eaten	27.40	132.20	12.40	7.00	30.00	13.10
	4	Amt Presented	117.30	246.20	94.00	35.40	60.00	19.60
		Amt Remaining	106.10	24.30	55.70	13.00	60.00	0.40
		Amt Eaten	11.20	221.90	38.30	22.40	0.00	19.20
3	4	Amt Presented	102.00	186.10	105.60	31.50	60.00	28.20
		Amt Remaining	33.80	62.70	5.00	3.90	30.00	7.60
		Amt Eaten	68.20	123.40	100.60	27.60	30.00	20.60
4	4	Amt Presented	112.00	218.90	98.80	16.60	60.00	19.10
		Amt Remaining	35.50	53.60	51.20	2.00	30.00	0.40
		Amt Eaten	76.50	165.30	47.60	14.60	30.00	18.70
5	4	Amt Presented	106.70	225.30	96.40	29.00	60.00	22.00
		Amt Remaining	38.00	78.90	5.30	4.20	30.00	0.40
		Amt Eaten	68.70	146.40	91.10	24.80	30.00	21.60

Phase 2 (IM A)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	162.20	252.20	83.00	25.00	60.00	18.80
		Amt Remaining	30.30	62.10	49.60	2.10	60.00	0.40
		Amt Eaten	71.90	190.10	33.40	23.90	0.00	18.40
	4	Amt Presented	98.10	258.20	90.40	28.20	60.00	18.90
		Amt Remaining	26.70	118.60	86.70	3.10	60.00	6.50
		Amt Eaten	71.40	139.60	3.70	25.10	0.00	12.40
2	1	Amt Presented	100.00	208.00	97.80	34.10	60.00	20.40
		Amt Remaining	64.30	33.10	90.60	4.10	60.00	9.90
		Amt Eaten	35.70	174.90	7.20	29.60	0.00	10.50
	4	Amt Presented	112.10	220.70	91.90	38.40	60.00	19.30
		Amt Remaining	33.50	179.50	3.30	3.00	60.00	13.90
		Amt Eaten	78.60	41.20	88.60	35.40	0.00	5.40
3	4	Amt Presented	101.00	264.10	87.40	36.20	60.00	24.70
		Amt Remaining	101.00	122.00	1.20	36.20	60.00	9.50
		Amt Eaten	0.00	142.10	86.20	0.00	0.00	15.20
4	4	Amt Presented	99.20	245.30	90.00	38.60	60.00	15.30
		Amt Remaining	71.00	124.40	28.00	11.20	60.00	2.20
		Amt Eaten	28.20	120.90	62.00	27.40	0.00	13.10
5	4	Amt Presented	98.90	229.60	104.70	43.70	60.00	18.20
		Amt Remaining	73.90	113.20	11.70	5.70	45.00	0.50
		Amt Eaten	25.00	116.40	93.00	38.00	15.00	17.70

TABLE A12.2.6

Total Food Intake and Macro-Nutrient Consumption for Test Meals [Subject 6 (L1)]

Phase 1 (IM B)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	470.80	559.20	533.30	572.50	513.40	525.40	539.40
Total Food Remaining (g)	162.40	196.40	311.20	259.5	143.00	172.70	156.80
Total Food Intake (g)	308.40	362.80	222.10	313.00	370.40	352.70	382.60
Total Food Intake (kJ)	2580.97	2956.62	1805.25	2048.89	2956.91	2946.30	3052.11
Corrected (kJ)	2565.86	2952.86	1798.90	2055.31	2957.60	2935.42	3050.93
Total Protein Intake (g)	20.09	28.97	13.02	9.39	25.77	27.13	26.12
Total Protein Intake (kJ)	337.51	486.70	218.74	157.75	432.94	455.78	438.82
Total Carbohydrate Intake (g)	64.69	61.52	50.79	62.91	63.54	65.09	67.71
Total Carbohydrate Intake (kJ)	1086.79	1033.54	853.27	1056.89	1067.47	1093.51	1137.53
Total Fat Intake (g)	30.20	37.90	19.23	22.24	38.55	36.67	39.01
Total Fat Intake (kJ)	1141.56	1432.62	726.89	840.67	1457.19	1286.13	1474.58
Protein Energy %	13.15	16.48	12.16	7.68	14.64	15.53	14.38
Carbohydrate Energy %	42.36	35.00	47.43	51.42	36.09	37.25	37.28
Fat Energy %	44.49	48.52	40.41	40.90	49.27	47.22	48.33

Phase 2 (IM A)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	541.80	553.80	520.30	542.40	573.40	548.40	555.10
Total Food Remaining (g)	204.50	301.60	262.40	293.20	329.90	296.80	250.00
Total Food Intake (g)	337.30	252.20	257.90	249.20	243.50	251.60	305.10
Total Food Intake (kJ)	2676.96	2170.63	1839.56	1920.65	1293.12	1725.18	2143.91
Corrected (kJ)	2665.19	2153.13	1837.22	1926.20	1412.50	1733.34	2156.87
Total Protein Intake (g)	23.66	21.59	13.68	23.59	5.63	12.02	13.52
Total Protein Intake (kJ)	397.49	362.71	229.82	396.31	94.58	201.94	227.14
Total Carbohydrate Intake (g)	54.14	36.62	46.22	25.86	49.85	41.43	53.26
Total Carbohydrate Intake (kJ)	909.55	615.22	776.50	434.45	837.48	696.02	894.77
Total Fat Intake (g)	35.93	31.09	21.99	28.98	12.71	22.10	27.38
Total Fat Intake (kJ)	1358.15	1175.20	831.22	1095.44	480.44	835.38	1034.96
Protein Energy %	14.91	16.85	12.51	20.57	6.70	11.65	10.53
Carbohydrate Energy %	34.13	28.57	42.26	22.55	59.29	40.15	41.48
Fat Energy %	50.96	54.58	45.24	56.87	34.01	48.19	47.98

TABLE A12.1.7

Quantity of Each Food Commodity Presented, Remaining and Eaten (g) at the Test Meals [Subject 7 (EG)]

Phase 1 (TM A)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	123.10	182.90	150.50		60.00	22.20
		Amt Remaining	101.10	182.90	78.00		60.00	15.00
		Amt Eaten	22.00	0.00	72.50		0.00	7.20
	4	Amt Presented	74.70	112.90	99.50	38.00	60.00	19.40
		Amt Remaining	38.90	110.70	23.00	16.40	30.00	15.90
		Amt Eaten	35.80	2.20	76.50	21.60	30.00	3.50
2	1	Amt Presented	97.60	131.10	124.20	32.20	60.00	19.90
		Amt Remaining	41.40	77.50	51.20	8.50	30.00	15.10
		Amt Eaten	56.20	53.60	73.00	23.70	30.00	4.80
	4	Amt Presented	100.40	165.10	120.20	13.90	60.00	20.60
		Amt Remaining	29.00	113.50	40.50	2.10	30.00	14.90
		Amt Eaten	71.41	51.60	79.70	11.80	30.00	5.70
3	4	Amt Presented	103.80	164.40	146.10	16.80	60.00	20.80
		Amt Remaining	72.00	105.50	49.10	7.60	30.00	15.70
		Amt Eaten	31.80	58.90	97.00	9.80	30.00	5.10
4	4	Amt Presented						
		Amt Remaining						
		Amt Eaten						
5	4	Amt Presented						
		Amt Remaining						
		Amt Eaten						

Phase 2 (TM B)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented	100.50	164.10	107.00	21.00	60.00	23.10
		Amt Remaining	39.10	70.00	34.60	1.80	30.00	9.90
		Amt Eaten	61.40	94.10	72.40	19.20	30.00	13.20
	4	Amt Presented	117.50	209.80	92.00	44.80	60.00	24.80
		Amt Remaining	60.30	105.40	24.70	5.50	60.00	14.40
		Amt Eaten	57.20	104.40	67.30	39.30	0.00	10.40
2	1	Amt Presented	119.20	222.60	84.20	34.50	60.00	20.80
		Amt Remaining	70.60	130.90	22.30	9.30	30.00	13.00
		Amt Eaten	48.60	91.70	61.90	25.20	30.00	7.80
	4	Amt Presented	96.60	227.40	102.40	36.00	60.00	18.90
		Amt Remaining	51.80	126.10	20.30	4.40	30.00	8.50
		Amt Eaten	44.80	101.30	82.10	31.60	30.00	10.40
3	4	Amt Presented	106.50	245.70	97.70	35.40	60.00	25.40
		Amt Remaining	51.50	152.20	17.10	4.30	30.00	6.70
		Amt Eaten	55.00	93.50	80.60	31.10	30.00	18.70
4	4	Amt Presented	98.90	244.10	84.40	33.80	60.00	23.20
		Amt Remaining	34.10	165.00	4.70	3.70	30.00	13.90
		Amt Eaten	64.80	79.10	79.70	30.10	30.00	9.30
5	4	Amt Presented	209.90	259.10	96.20	36.30	60.00	18.60
		Amt Remaining	49.10	139.20	10.60	8.20	30.00	7.20
		Amt Eaten	60.80	119.90	85.60	28.10	30.00	1.40

TABLE A12.2.7

Total Food Intake and Macro-Nutrient Consumption for Test Meals [Subject 7 (EG)]

Phase 1 (TM A)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	538.70	404.50	465.00	480.20	511.90		
Total Food Remaining (g)	337.00	234.90	223.70	230.00	279.90		
Total Food Intake (g)	161.70	169.60	241.30	250.20	232.00		
Total Food Intake (kJ)	1404.52	1310.24	1812.58	2020.33	1542.00		
Corrected (kJ)	1412.12	1321.74	1819.35	2025.16	1526.94		
Total Protein Intake (g)	12.78	14.11	20.00	24.02	14.74		
Total Protein Intake (kJ)	214.87	237.05	336.00	403.54	247.63		
Total Carbohydrate Intake (g)	42.15	28.70	38.48	41.49	46.05		
Total Carbohydrate Intake (kJ)	708.12	482.16	646.46	697.03	773.64		
Total Fat Intake (g)	12.94	15.94	22.14	24.46	14.33		
Total Fat Intake (kJ)	489.13	602.53	836.89	924.59	541.67		
Protein Energy %	15.22	17.93	18.47	19.93	15.84		
Carbohydrate Energy %	50.15	36.48	35.53	34.42	49.50		
Fat Energy %	34.46	45.59	46.00	45.66	34.66		

Phase 1 (TM B)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	475.70	548.90	541.30	541.30	570.70	544.40	580.10
Total Food Remaining (g)	185.40	270.30	276.10	241.10	261.80	251.40	244.30
Total Food Intake (g)	290.30	278.60	265.20	300.20	208.90	293.00	335.80
Total Food Intake (kJ)	2352.16	2048.95	2009.87	2192.40	2549.73	2303.51	2507.07
Corrected (kJ)	1352.21	2052.87	2016.88	2230.99	2546.92	2308.63	2516.13
Total Protein Intake (g)	22.46	19.23	19.05	19.00	21.33	23.37	23.43
Total Protein Intake (kJ)	377.33	323.06	320.04	319.20	358.34	392.62	393.62
Total Carbohydrate Intake (g)	51.29	34.48	49.14	55.04	52.85	49.00	60.19
Total Carbohydrate Intake (kJ)	861.67	646.46	825.55	924.67	887.88	823.20	1011.19
Total Fat Intake (g)	29.45	22.86	23.05	25.40	34.41	28.91	29.40
Total Fat Intake (kJ)	1113.21	1983.35	871.29	960.12	1300.70	1092.80	111.32
Protein Energy %	16.04	15.74	15.87	14.48	14.07	17.01	15.64
Carbohydrate Energy %	36.63	31.49	40.93	41.95	34.86	35.66	40.19
Fat Energy %	47.33	52.77	43.20	43.56	51.07	47.34	44.17

TABLE A12.1.8

Quantity of Each Food Commodity Presented, Remaining and Eaten (g) at the Test Meals [Subject 8 (CV)]

Phase 1 (TM A)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented Amt Remaining Amt Eaten	104.20 17.60 86.60	221.20 24.00 187.20	112.20 1.20 111.00	16.30 3.80 12.50	60.00 60.00 0.00	22.30 17.60 4.70
	4	Amt Presented Amt Remaining Amt Eaten	102.20 4.90 97.30	197.70 21.20 176.50	143.20 7.30 135.90	16.00 3.60 12.40	60.00 60.00 0.00	22.10 10.60 11.50
2	1	Amt Presented Amt Remaining Amt Eaten	114.60 49.30 65.30	210.60 135.00 75.60	109.90 0.00 109.90	17.60 1.20 16.40	60.00 30.00 30.00	22.80 11.30 11.50
	4	Amt Presented Amt Remaining Amt Eaten	108.70 29.30 79.40	229.80 141.70 88.10	96.60 5.80 90.80	20.70 4.10 16.60	60.00 30.00 30.00	21.40 10.10 11.30
3	4	Amt Presented Amt Remaining Amt Eaten	105.60 5.60 100.00	284.90 207.50 77.40	98.70 6.30 92.40	18.90 3.30 15.60	60.00 0.00 60.00	24.20 8.10 16.10
4	4	Amt Presented Amt Remaining Amt Eaten	104.10 2.40 101.70	247.80 209.10 38.70	94.10 5.00 89.10	23.40 3.10 20.30	60.00 15.00 45.00	21.10 9.00 12.10
5	4	Amt Presented Amt Remaining Amt Eaten	110.80 27.60 83.20	215.40 152.10 63.30	93.60 3.70 89.90	33.80 5.80 28.00	60.00 30.00 30.00	20.30 12.20 8.10

Phase 2 (TM B)

Week	Day	Measure (g)	Meat	Potato	Vegetable	Gravy	Bread	Margarine
1	1	Amt Presented Amt Remaining Amt Eaten	99.90 30.30 69.60	233.00 62.00 171.00	107.40 49.60 57.80	30.70 3.10 27.60	60.00 30.00 30.00	19.80 13.10 6.70
	4	Amt Presented Amt Remaining Amt Eaten	99.10 8.00 91.10	223.90 122.40 101.50	99.70 5.00 94.70	34.10 6.70 27.40	60.00 0.00 60.00	24.70 13.80 10.90
2	1	Amt Presented Amt Remaining Amt Eaten	100.00 48.10 51.90	239.50 102.70 136.80	101.80 3.00 98.80	31.00 3.70 27.30	60.00 30.00 30.00	18.40 10.30 8.10
	4	Amt Presented Amt Remaining Amt Eaten						
3	4	Amt Presented Amt Remaining Amt Eaten						
4	4	Amt Presented Amt Remaining Amt Eaten						
5	4	Amt Presented Amt Remaining Amt Eaten						

TABLE A12.2.8

Total Food Intake and Macro-Nutrient Consumption for Test Meals [Subject 8 (CV)]

Phase 1 (TM A)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	526.20	541.20	535.50	537.20	592.30	550.50	533.90
Total Food Remaining (g)	124.20	107.60	226.80	221.00	230.80	243.60	231.40
Total Food Intake (g)	402.00	433.60	308.70	316.20	361.50	306.90	302.50
Total Food Intake (kJ)	2574.10	2958.64	2357.34	2539.36	3247.50	2823.23	2452.77
Corrected (kJ)	2602.82	2988.15	2376.96	2550.62	3251.77	2824.12	2462.84
Total Protein Intake (g)	29.12	32.22	23.97	27.26	34.85	33.04	27.83
Total Protein Intake (kJ)	489.22	541.30	402.70	457.97	585.48	555.07	467.54
Total Carbohydrate Intake (g)	65.67	67.46	53.12	53.17	66.12	48.19	46.97
Total Carbohydrate Intake (kJ)	1105.10	1133.33	892.42	893.26	1110.82	809.59	789.10
Total Fat Intake (g)	26.68	34.75	28.62	31.73	41.15	38.61	31.91
Total Fat Intake (kJ)	1008.50	1313.55	1081.84	1199.39	1555.47	1459.46	1205.20
Protein Energy %	18.80	18.11	16.94	17.96	18.00	19.65	18.98
Carbohydrate Energy %	42.46	37.93	37.54	35.02	34.16	28.67	32.04
Fat Energy %	38.75	43.96	45.51	47.02	47.83	51.68	48.98

Phase 1 (TM B)

Measure	Week 1		Week 2		Week 3	Week 4	Week 5
	Day 1	Day 4	Day 1	Day 4	Day 4	Day 4	Day 4
Total Food Presented (g)	550.80	541.50	550.70				
Total Food Remaining (g)	188.10	155.90	197.80				
Total Food Intake (g)	352.70	385.60	352.90				
Total Food Intake (kJ)	2619.78	3164.18	2394.21				
Corrected (kJ)	2625.89	3167.51	2415.55				
Total Protein Intake (g)	26.02	33.45	21.95				
Total Protein Intake (kJ)	437.14	561.96	368.76				
Total Carbohydrate Intake (g)	68.52	72.18	66.55				
Total Carbohydrate Intake (kJ)	1151.14	1212.62	1118.04				
Total Fat Intake (g)	27.54	36.85	24.57				
Total Fat Intake (kJ)	1037.61	1392.93	928.75				
Protein Energy %	16.65	17.74	15.27				
Carbohydrate Energy %	43.84	38.28	46.28				
Fat Energy %	39.51	43.98	38.45				

Measure	Subj	TM A ± SEM	TM B ± SEM	F	P
Total Food Intake (g)	1	372.50 ± 8.18	409.95 ± 10.81	7.63§	0.0328
	2	452.73 ± 50.41	471.40 ± 17.35	0.12	0.7474
	3	331.05 ± 10.38	358.43 ± 36.14	0.53	0.5015
	4	177.50 ± 2.67	268.20 ± 8.87	96.0†	0.0006
	5	221.35 ± 26.74	336.70 ± 34.79	6.91§	0.0391
	6	262.35 ± 14.35	354.68 ± 15.19	19.5†	0.0045
Total Food Intake (kJ)	1	2836.74 ± 81.73	3023.28 ± 128.64	1.50	0.2669
	2	3625.95 ± 266.87	3654.29 ± 102.61	0.01	0.9268
	3	2430.46 ± 73.21	2754.38 ± 119.82	5.34	0.0602
	4	1274.72 ± 39.36	1806.51 ± 102.32	23.5†	0.0083
	5	1919.70 ± 301.91	2740.76 ± 195.03	5.22	0.0624
	6	1807.23 ± 157.50	2749.82 ± 232.85	11.2§	0.0154
Total Protein Intake (g)	1	28.39 ± 1.92	28.74 ± 1.47	0.02	0.8897
	2	34.18 ± 1.48	31.90 ± 1.27	1.38	0.3046
	3	25.63 ± 1.03	31.96 ± 1.52	11.9§	0.0137
	4	18.28 ± 1.40	23.62 ± 1.12	8.91§	0.0405
	5	17.96 ± 3.61	26.23 ± 2.35	4.05	0.0908
	6	13.69 ± 3.72	22.10 ± 4.24	2.22	0.1867
Total Protein Intake (kJ)	1	476.87 ± 32.33	482.83 ± 24.68	0.02	0.8897
	2	574.28 ± 24.67	535.86 ± 21.39	1.38	0.3046
	3	430.54 ± 17.37	536.97 ± 25.51	11.9§	0.0137
	4	307.16 ± 23.44	396.87 ± 18.81	8.91§	0.0405
	5	301.69 ± 60.63	447.34 ± 39.52	4.05	0.0908
	6	229.99 ± 62.45	371.32 ± 71.36	2.22	0.1867
Total Carbohydrate Intake (g)	1	67.45 ± 2.04	83.62 ± 1.88	34.0†	0.0011
	2	90.66 ± 10.96	97.62 ± 4.43	0.35	0.5931
	3	45.29 ± 0.82	59.29 ± 4.73	8.51§	0.0267
	4	16.65 ± 1.49	34.89 ± 2.87	31.8†	0.0049
	5	38.75 ± 5.09	61.86 ± 9.20	4.83	0.0703
	6	42.60 ± 6.11	64.81 ± 1.07	12.8§	0.0116
Total Carbohydrate Intake (kJ)	1	1133.15 ± 34.28	1404.73 ± 31.54	34.0†	0.0011
	2	1523.03 ± 184.07	1640.07 ± 74.38	0.35	0.5931
	3	760.83 ± 13.83	996.12 ± 79.47	8.51§	0.0267
	4	279.72 ± 24.96	586.10 ± 48.27	31.8†	0.0049
	5	651.09 ± 85.46	1039.21 ± 154.57	4.83	0.0703
	6	715.68 ± 102.63	1088.85 ± 17.96	12.8§	0.0116
Total Fat Intake (g)	1	32.45 ± 1.18	30.05 ± 2.20	0.93	0.3821
	2	40.44 ± 1.64	39.11 ± 1.14	0.44	0.5485
	3	32.78 ± 1.24	32.32 ± 1.24	0.07	0.8053
	4	18.20 ± 1.08	21.79 ± 1.84	2.82	0.1686
	5	25.58 ± 4.12	33.18 ± 1.34	3.07	0.1302
	6	22.79 ± 3.67	34.12 ± 3.99	4.36	0.0817
Total Fat Intake (kJ)	1	1226.71 ± 44.62	1135.70 ± 83.19	0.93	0.3821
	2	1528.63 ± 62.03	1478.36 ± 43.01	0.44	0.5485
	3	1239.08 ± 46.90	1221.79 ± 46.69	0.07	0.8053
	4	687.84 ± 40.92	823.54 ± 69.73	2.82	0.1686
	5	966.93 ± 155.87	1254.21 ± 50.75	3.07	0.1302
	6	861.56 ± 138.66	1289.64 ± 150.88	4.36	0.0817

Measure	Subj	TM A ± SEM	TM B ± SEM	F	P
Protein Energy %	1	16.77 ± 0.81	15.95 ± 0.17	0.99	0.3691
	2	15.91 ± 0.48	14.66 ± 0.42	3.61	0.1301
	3	17.71 ± 0.45	19.51 ± 0.62	5.48	0.0578
	4	24.03 ± 1.15	22.01 ± 0.65	2.33	0.2015
	5	14.88 ± 0.39	15.72 ± 0.38	2.35	0.2001
	6	12.36 ± 2.93	13.06 ± 1.81	0.04	0.8489
Carbohydrate Energy %	1	39.98 ± 1.08	46.61 ± 1.31	15.2†	0.0080
	2	41.73 ± 1.93	44.86 ± 1.28	1.82	0.2483
	3	31.34 ± 0.42	36.01 ± 1.50	8.97§	0.0242
	4	22.07 ± 2.52	32.50 ± 2.24	9.58§	0.0364
	5	34.99 ± 0.56	37.19 ± 4.94	0.20	0.6854
	6	40.87 ± 7.05	40.51 ± 3.65	0.00	0.9677
Fat Energy %	1	43.25 ± 1.02	37.44 ± 1.22	13.3§	0.0108
	2	42.36 ± 1.43	40.48 ± 0.87	1.26	0.3242
	3	50.95 ± 0.51	44.48 ± 1.70	13.3§	0.0108
	4	53.90 ± 2.08	45.49 ± 1.88	8.99§	0.0400
	5	50.14 ± 0.24	47.09 ± 4.63	0.44	0.5523
	6	46.76 ± 4.73	46.43 ± 1.89	0.00	0.9507

n = 4, df = 1,6 for subjects 1, 3 and 6
n = 3, df = 1,4 for subjects 2, 4 and 5
§ indicates a P value of between 0.015 and 0.05
† indicates a P value of less than 0.01

TABLE A12.3.1

Total Food Intake and the Elective Consumption of Macro-nutrients per Volunteer

TABLE A13.1 Salivation Data [Subject 1 (SS)]

Phase 1 (TM A)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	1.739 1.423 1.465	1.543 $\pm$ 0.172	0.974 1.266 1.039	1.0780 $\pm$ 0.131
	4	1.681 1.004 1.722	1.469 $\pm$ 0.260	0.9144 1.1807 2.0027	1.3660 $\pm$ 0.570
2	1	1.718 1.027 1.236	0.994 $\pm$ 0.260	0.5085 1.1650 1.0129	0.8954 $\pm$ 0.344
	4	0.983 1.122 1.250	1.118 $\pm$ 0.134	3.0064 1.8880 1.2796	2.0580 $\pm$ 0.880
3	4	1.469 1.384 1.284	1.379 $\pm$ 0.093	2.2016 1.2873 1.4420	1.6436 $\pm$ 0.490
4	4	1.660 1.542 2.985	2.062 $\pm$ 0.801	2.2480 2.7620 3.9391	2.9830 $\pm$ 0.870
5	4	2.156 1.676 2.771	2.201 $\pm$ 0.550	1.6230 1.3753 1.7660	1.5880 $\pm$ 0.1980

Phase 2 (TM B)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	3.085 2.837 2.608	2.483 $\pm$ 0.238	1.679 3.247 4.288	3.071 $\pm$ 1.313
	4	2.879 1.616 3.427	2.650 $\pm$ 0.229	3.624 2.169 4.345	3.379 $\pm$ 1.108
2	1	3.425 2.572 4.498	3.498 $\pm$ 0.965	4.400 2.698 4.056	3.718 $\pm$ 0.900
	4	3.163 1.509 3.758	2.810 $\pm$ 0.166	4.107 3.071 4.077	3.752 $\pm$ 0.590
3	4	4.639 4.874 2.675	4.067 $\pm$ 1.208	3.864 4.241 5.837	4.647 $\pm$ 1.047
4	4	4.519 3.200 4.082	3.934 $\pm$ 0.672	4.980 5.243 4.700	4.974 $\pm$ 0.271
5	4	4.136 4.776 4.594	4.502 $\pm$ 0.330	4.344 3.615 3.978	3.979 $\pm$ 0.365

TABLE A13.2

Salivation Data [Subject 2 (CA)]

Phase 1 (TM A)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	0.847 0.988 0.782	0.782 $\pm$ 0.105	1.184 0.922 1.011	1.034 $\pm$ 0.133
	4	1.366 1.282 1.103	1.240 $\pm$ 0.122	1.248 1.170 1.295	1.238 $\pm$ 0.063
2	1	0.623 1.128 0.74	0.832 $\pm$ 0.264	1.419 1.281 0.832	1.177 $\pm$ 0.307
	4	0.999 0.970 0.631	0.867 $\pm$ 0.204	1.583 1.081 0.981	1.215 $\pm$ 0.322
3	4	0.913 0.570 0.542	0.675 $\pm$ 0.207	0.642 0.693 0.602	0.646 $\pm$ 0.046
4	4	1.161 0.950 0.968	1.029 $\pm$ 0.114	0.981 1.238 1.831	1.350 $\pm$ 0.436
5	4				

Phase 2 (TM B)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	1.494 1.639 1.504	1.546 $\pm$ 0.081	1.492 1.276 1.594	1.454 $\pm$ 0.162
	4	0.961 1.142 1.302	1.135 $\pm$ 0.170	1.463 1.820 1.610	1.631 $\pm$ 0.180
2	1	1.699 1.605 1.083	1.462 $\pm$ 0.322	2.344 1.399 2.069	1.937 $\pm$ 0.486
	4	1.642 1.079 1.368	1.363 $\pm$ 0.282	1.944 1.937 2.051	1.977 $\pm$ 0.064
3	4	0.787 1.490 1.177	1.152 $\pm$ 0.352	1.952 0.992 1.493	1.479 $\pm$ 0.480
4	4	1.387 1.351 0.747	1.161 $\pm$ 0.360	1.856 2.404 2.103	2.121 $\pm$ 0.275
5	4	2.953 1.270 1.023	1.749 $\pm$ 1.050	1.579 1.193 1.536	1.436 $\pm$ 0.212

TABLE A13.3

Salivation Data [Subject 3 (LH)]

Phase 1 (TM B)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	0.832 0.966 0.739	0.846 $\pm$ 0.114	0.629 0.574 0.623	0.069 $\pm$ 0.030
	4	0.700 1.141 0.856	0.899 $\pm$ 0.224	0.661 1.663 0.843	0.890 $\pm$ 0.256
2	1	1.215 0.952 0.833	1.000 $\pm$ 0.196	0.759 0.882 1.682	1.108 $\pm$ 0.502
	4	1.557 1.142 0.839	1.179 $\pm$ 0.361	1.025 0.627 1.685	1.112 $\pm$ 0.534
3	4	0.974 0.809 1.718	1.167 $\pm$ 0.484	1.354 1.156 0.864	1.125 $\pm$ 0.247
4	4	0.591 0.669 0.752	0.670 $\pm$ 0.081	0.796 1.074 1.154	1.008 $\pm$ 0.188
5	4	1.072 1.230 0.970	1.089 $\pm$ 0.133	1.010 1.435 0.608	1.047 $\pm$ 0.415

Phase 2 (TM A)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	0.745 0.595 0.552	0.630 $\pm$ 0.101	1.041 1.260 1.711	1.371 $\pm$ 0.335
	4	1.503 0.485 0.780	0.923 $\pm$ 0.524	1.006 0.619 1.254	0.960 $\pm$ 0.320
2	1	0.740 0.700 0.645	0.695 $\pm$ 0.046	0.886 0.771 0.542	0.733 $\pm$ 0.175
	4	0.598 0.578 0.374	0.517 $\pm$ 0.124	0.701 0.494 0.848	0.681 $\pm$ 0.178
3	4	0.613 0.317 0.508	0.480 $\pm$ 0.150	0.737 0.885 0.885	0.836 $\pm$ 0.086
4	4	1.100 1.021 0.700	0.940 $\pm$ 0.212	1.284 0.964 0.928	1.059 $\pm$ 0.196
5	4	0.624 0.824 0.581	0.676 $\pm$ 0.129	0.783 0.938 0.518	0.746 $\pm$ 0.213

TABLE A13.4

Salivation Data [Subject 4 (EA)]

Phase 1 (TM B)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	0.698 0.680 1.089	0.922 $\pm$ 0.202	1.564 0.625 0.970	1.053 $\pm$ 0.475
	4	0.671 0.688 0.701	0.687 $\pm$ 0.015	0.378 0.602 0.714	0.565 $\pm$ 0.171
2	1	0.675 0.587 0.338	0.533 $\pm$ 0.175	0.689 0.532 0.551	0.591 $\pm$ 0.086
	4	0.587 0.524 0.407	0.506 $\pm$ 0.092	0.567 0.589 0.601	0.585 $\pm$ 0.017
3	4	0.445 0.442 0.515	0.468 $\pm$ 0.041	0.268 0.770 0.899	0.646 $\pm$ 0.333
4	4	0.339 0.749 0.525	0.538 $\pm$ 0.205	0.482 0.575 0.601	0.553 $\pm$ 0.063
5	4	0.743 0.308 0.536	0.529 $\pm$ 0.217	0.566 0.700 0.525	0.597 $\pm$ 0.092

Phase 2 (TM A)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	0.473 0.626 0.830	0.643 $\pm$ 0.179	0.768 0.660 0.539	0.655 $\pm$ 0.115
	4	0.597 0.523 0.522	0.547 $\pm$ 0.043	0.617 0.735 0.614	0.655 $\pm$ 0.069
2	1	0.476 0.419 0.270	0.388 $\pm$ 0.107	0.648 0.452 0.417	0.505 $\pm$ 0.124
	4	0.255 0.395 0.265	0.305 $\pm$ 0.080	0.427 0.222 0.575	0.408 $\pm$ 0.177
3	4	0.349 0.489 0.430	0.423 $\pm$ 0.070	0.461 0.549 0.843	0.618 $\pm$ 0.200
4	4				
5	4	0.308 0.284 0.222	0.271 $\pm$ 0.045	0.509 0.352 0.463	0.442 $\pm$ 0.081

TABLE A13.5

Salivation Data [Subject 5 (VM)]

Phase 1 (TM B)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	2.596 2.480 2.026	2.368 $\pm$ 0.302	1.899 1.442 2.950	2.097 $\pm$ 0.773
	4	1.595 2.037 1.009	1.547 $\pm$ 0.516	1.226 0.817 1.576	1.206 $\pm$ 0.380
2	1	1.097 1.245 0.835	1.059 $\pm$ 0.208	1.888 1.565 1.826	1.176 $\pm$ 0.171
	4	1.050 1.050 1.087	1.062 $\pm$ 0.021	0.901 1.034 1.073	1.003 $\pm$ 0.090
3	4	1.271 0.934 1.252	1.152 $\pm$ 0.189	1.595 1.790 1.280	1.555 $\pm$ 0.257
4	4	1.446 0.724 0.868	1.013 $\pm$ 0.382	1.351 2.060 0.917	1.443 $\pm$ 0.577
5	4	1.244 1.373 1.429	1.348 $\pm$ 0.095	1.809 2.822 1.885	2.172 $\pm$ 0.564

Phase 2 (TM A)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	0.731 1.151 1.714	1.199 $\pm$ 0.493	1.868 2.275 2.428	2.190 $\pm$ 0.289
	4	1.423 1.236 1.318	1.326 $\pm$ 0.094	2.274 2.031 2.117	2.141 $\pm$ 0.124
2	1	0.938 0.876 1.258	1.024 $\pm$ 0.205	1.309 1.142 0.985	1.145 $\pm$ 0.162
	4				
3	4	0.901 0.964 1.059	0.975 $\pm$ 0.079	1.342 1.812 1.946	1.700 $\pm$ 0.318
4	4	1.278 1.371 1.209	1.286 $\pm$ 0.081	1.102 1.598 1.479	1.393 $\pm$ 0.259
5	4	1.536 2.097 1.282	1.638 $\pm$ 0.417	1.638 2.067 1.736	1.814 $\pm$ 0.225

TABLE A13.6

Salivation Data [Subject 6 (LI)]

Phase 1 (TM B)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	1.199 1.643 1.377	1.406 $\pm$ 0.223	0.700 1.144 1.222	1.020 $\pm$ 0.285
	4	1.541 1.111 1.077	1.243 $\pm$ 0.259	0.505 0.667 0.624	0.599 $\pm$ 0.084
2	1	0.620 0.749 0.509	0.626 $\pm$ 0.120	0.624 0.333 0.609	0.522 $\pm$ 0.164
	4	0.739 1.306 0.856	0.976 $\pm$ 0.300	0.691 0.805 1.063	0.853 $\pm$ 0.191
3	4	0.710 0.970 0.829	0.837 $\pm$ 0.130	1.035 0.527 1.058	0.873 $\pm$ 0.300
4	4	1.068 1.003 1.070	1.047 $\pm$ 0.038	0.729 0.719 0.769	0.739 $\pm$ 0.026
5	4	0.837 0.508 1.594	0.980 $\pm$ 0.557	0.436 0.497 0.556	0.496 $\pm$ 0.060

Phase 2 (TM A)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	1.699 1.266 1.034	1.333 $\pm$ 0.338	1.283 0.736 1.031	1.017 $\pm$ 0.274
	4	1.055 0.579 0.825	0.829 $\pm$ 0.238	0.722 0.607 1.333	0.887 $\pm$ 0.390
2	1	0.566 0.486 0.714	0.589 $\pm$ 0.116	0.988 0.855 1.004	0.949 $\pm$ 0.082
	4	0.596 0.895 0.524	0.672 $\pm$ 0.197	0.561 0.508 0.513	0.528 $\pm$ 0.030
3	4	0.530 1.065 0.492	0.696 $\pm$ 0.320	0.633 0.454 0.673	0.587 $\pm$ 0.117
4	4	0.401 0.374 0.353	0.376 $\pm$ 0.024	0.877 0.516 1.187	0.860 $\pm$ 0.336
5	4	0.896 0.958 0.375	0.743 $\pm$ 0.321	1.294 0.492 0.925	0.904 $\pm$ 0.401

TABLE A13.7

Salivation Data [Subject 7 (EG)]

Phase 1 (TM A)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	3.414 3.435 3.393	3.414 $\pm$ 0.021	2.123 3.466 3.827	3.139 $\pm$ 0.898
	4	4.837 3.965 2.877	3.893 $\pm$ 0.982	2.604 3.678 3.142	3.141 $\pm$ 0.537
2	1	3.625 3.771 3.548	3.648 $\pm$ 0.113	2.945 3.778 3.481	3.401 $\pm$ 0.422
	4	3.764 3.533 3.667	3.655 $\pm$ 0.116	3.983 2.293 2.737	3.004 $\pm$ 0.876
3	4	3.463 4.046 2.955	3.488 $\pm$ 0.546	2.423 3.333 1.839	2.531 $\pm$ 0.753
4	4				
5	4				

Phase 2 (TM B)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	6.275 2.629 3.130	4.011 $\pm$ 1.976	6.109 3.416 3.053	4.103 $\pm$ 1.669
	4	3.671 3.069 3.523	3.388 $\pm$ 0.303	3.450 4.677 3.160	3.562 $\pm$ 0.469
2	1	2.756 3.317 2.327	2.801 $\pm$ 0.496	3.938 3.189 3.726	3.617 $\pm$ 0.386
	4	3.033 1.695 3.132	2.620 $\pm$ 0.802	2.363 3.618 3.546	3.176 $\pm$ 0.704
3	4	3.746 4.350 4.815	4.304 $\pm$ 0.536	3.599 3.121 2.990	3.237 $\pm$ 0.320
4	4	3.291 3.266 3.028	3.195 $\pm$ 0.195	3.717 3.482 3.402	3.534 $\pm$ 0.164
5	4	2.301 3.671 2.922	2.995 $\pm$ 0.643	1.983 2.555 2.093	2.210 $\pm$ 0.303

TABLE A13.8

Salivation Data [Subject 8 (CV)]

Phase 1 (TM A)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	1.872 1.598 1.345	1.605 $\pm$ 0.264	1.311 1.671 1.354	1.446 $\pm$ 0.197
	4	1.371 1.220 1.116	1.236 $\pm$ 0.129	1.493 1.371 1.343	1.402 $\pm$ 0.080
2	1	1.016 0.778 1.029	0.941 $\pm$ 0.142	1.247 0.929 1.786	1.321 $\pm$ 0.434
	4	0.957 1.302 1.043	1.101 $\pm$ 0.180	1.041 0.891 1.221	1.051 $\pm$ 0.165
3	4	1.186 0.741 0.587	0.838 $\pm$ 0.311	0.705 0.544 1.018	0.755 $\pm$ 0.241
4	4	0.972 0.797 0.815	0.861 $\pm$ 0.096	0.782 1.076 1.238	1.032 $\pm$ 0.231
5	4	0.836 0.686 0.921	0.815 $\pm$ 0.119	0.665 0.838 1.245	0.916 $\pm$ 0.298

Phase 2 (TM B)

Week	Day	Baseline Salivation (g/2min)	Mean $\pm$ SD	Stimulus-Induced Salivation (g/2min)	Mean $\pm$ SD
1	1	1.356 1.307 1.209	1.291 $\pm$ 0.075	1.191 0.857 1.551	1.191 $\pm$ 0.347
	4	1.031 1.145 1.083	1.086 $\pm$ 0.057	0.989 0.852 0.888	0.909 $\pm$ 0.071
2	1	0.565 0.908 1.108	0.860 $\pm$ 0.275	0.676 0.662 1.022	0.787 $\pm$ 0.204
	4				
3	4				
4	4				
5	4				

APPENDIX 14
BLOOD LEVEL DATA

TABLE A14.1

Blood Levels of PPA.HCl
reached (Pilot Steady-State
Trial)

Time (Hrs)	PPA Concentration (ng/ml)
12	61.11
36	83.20
48	92.67
60	81.59
0.0	70.58
0.5	140.82
1.0	276.87
2.0	336.52
3.0	297.83
4.0	228.39
5.0	217.48
6.0	168.48
8.0	125.87
9.0	104.97
10.0	97.68
12.0	59.98

TABLE 7.1

Steady-state 1 patient

TABLE A14.2.1

Peak and Trough Blood Levels
of PPA.HCl reached during Multiple
Dosing (Subject 1, Phase 1, [SS])

WEEK	DAY	TIME	SERUM PPA.HCL CONCENTRATION (ng/ml)
Two	1	07h50	0.00
		12h50	174.18
		19h50	72.93
	2	07h50	115.29
		19h50	118.73
	3	07h50	138.06
		19h50	120.79
	4	07h50	147.38
		12h50	282.33
	7	19h50	128.59
Three	4	07h50	129.52
		12h50	263.65
	7	19h50	144.16
Four	4	07h50	
		12h50	248.25
	7	19h50	149.42
Five	4	07h50	135.17
		12h50	239.11
	7	19h50	123.05

TABLE A14.2.2

Peak and Trough Blood Levels
of PPA.HCl reached during Multiple
Dosing (Subject 2, Phase 1, [CA])

WEEK	DAY	TIME	SERUM PPA.HCL CONCENTRATION (ng/ml)
Two	1	07h50	0.00
		12h50	167.53
		19h50	56.07
	2	07h50	81.71
		19h50	63.74
	3	07h50	66.90
		19h50	68.75
	4	07h50	95.78
		12h50	204.66
	7	19h50	80.75
Three	4	07h50	90.22
		12h50	190.54
	7	19h50	79.78
Four	4	07h50	80.82
		12h50	217.96
	7	19h50	106.86
Five	4	07h50	117.86
		12h50	395.45
	7	19h50	

TABLE A14.2.3

Peak and Trough Blood Levels
of PPA.HCl reached during Multiple
Dosing (Subject 3, Phase 2, {LE})

WEEK	DAY	TIME	SERUM PPA.HCL CONCENTRATION (ng/ml)
Two	1	07h50	0.00
		12h50	215.19
		19h50	131.96
	2	07h50	127.16
		19h50	150.06
	3	07h50	112.49
		19h50	130.46
	4	07h50	134.87
		12h50	277.72
	7	19h50	150.76
Three	4	07h50	138.59
		12h50	269.74
	7	19h50	180.14
Four	4	07h50	
		12h50	363.86
	7	19h50	
Five	4	07h50	49.88
		12h50	284.09
	7	19h50	169.61

TABLE A14.2.4

Peak and Trough Blood Levels
of PPA.HCl reached during Multiple
Dosing (Subject 4, Phase 2, {EA})

WEEK	DAY	TIME	SERUM PPA.HCL CONCENTRATION (ng/ml)
Two	1	07h50	0.00
		12h50	150.20
		19h50	57.27
	2	07h50	86.77
		19h50	69.63
	3	07h50	97.29
		19h50	86.57
	4	07h50	89.35
		12h50	236.57
	7	19h50	77.13
Three	4	07h50	96.64
		12h50	216.27
	7	19h50	75.41
Four	4	07h50	85.05
		12h50	
	7	19h50	84.11
Five	4	07h50	94.47
		12h50	242.05
	7	19h50	89.98

TABLE A14.2.5

Peak and Trough Blood Levels
of PPA.HCl reached during Multiple
Dosing (Subject 5, Phase 2, {VH})

WEEK	DAY	TIME	SERUM PPA.HCL CONCENTRATION (ng/ml)
Two	1	07h50	0.00
		12h50	154.76
		19h50	48.07
	2	07h50	74.34
		19h50	53.14
	3	07h50	91.05
		19h50	60.21
	4	07h50	107.28
		12h50	187.93
	7	19h50	
Three	4	07h50	18.13
		12h50	236.52
	7	19h50	18.29
Four	4	07h50	188.03
		12h50	328.50
	7	19h50	0.00
Five	4	07h50	0.00
		12h50	168.02
	7	19h50	59.45

TABLE A14.2.6

Peak and Trough Blood Levels
of PPA.HCl reached during Multiple
Dosing (Subject 6, Phase 2, [L1])

WEEK	DAY	TIME	SERUM PPA.HCL CONCENTRATION (ng/ml)
Two	1	07h50	0.00
		12h50	192.76
		19h50	81.99
	2	07h50	98.25
		19h50	88.38
	3	07h50	115.08
		19h50	
	4	07h50	
		12h50	
	7	19h50	101.46
Three	4	07h50	112.36
		12h50	247.79
	7	19h50	116.28
Four	4	07h50	152.34
		12h50	350.59
	7	19h50	232.16
Five	4	07h50	197.22
		12h50	321.73
	7	19h50	182.84

TABLE A14.2.7

Peak and Trough Blood Levels
of PPA.HCl reached during Multiple
Dosing (Subject 7, Phase 1, [EG])

WEEK	DAY	TIME	SERUM PPA.HCL CONCENTRATION (ng/ml)
Two	1	07h50	0.00
		12h50	185.33
		19h50	66.93
	2	07h50	72.55
		19h50	109.14
	3	07h50	99.97
		19h50	75.26
	4	07h50	104.23
		12h50	329.48
	7	19h50	97.42
	Three 4	07h50	113.55
		12h50	232.50
Four	4	07h50	
		12h50	
	7	19h50	
Five	4	07h50	
		12h50	
	7	19h50	

TABLE A14.2.8

Peak and Trough Blood Levels
of PPA.HCl reached during Multiple
Dosing (Subject 8, Phase 1, [CV])

WEEK	DAY	TIME	SERUM PPA.HCL CONCENTRATION (ng/ml)
Two	1	07h50	0.00
		12h50	178.41
		19h50	118.26
	2	07h50	160.94
		19h50	184.98
	3	07h50	218.57
		19h50	198.40
	4	07h50	219.70
		12h50	344.89
	7	19h50	177.02
	Three 4	07h50	173.67
		12h50	344.26
Four	4	07h50	188.88
		12h50	330.02
	7	19h50	204.70
Five	4	07h50	206.14
		12h50	374.67
	7	19h50	145.78

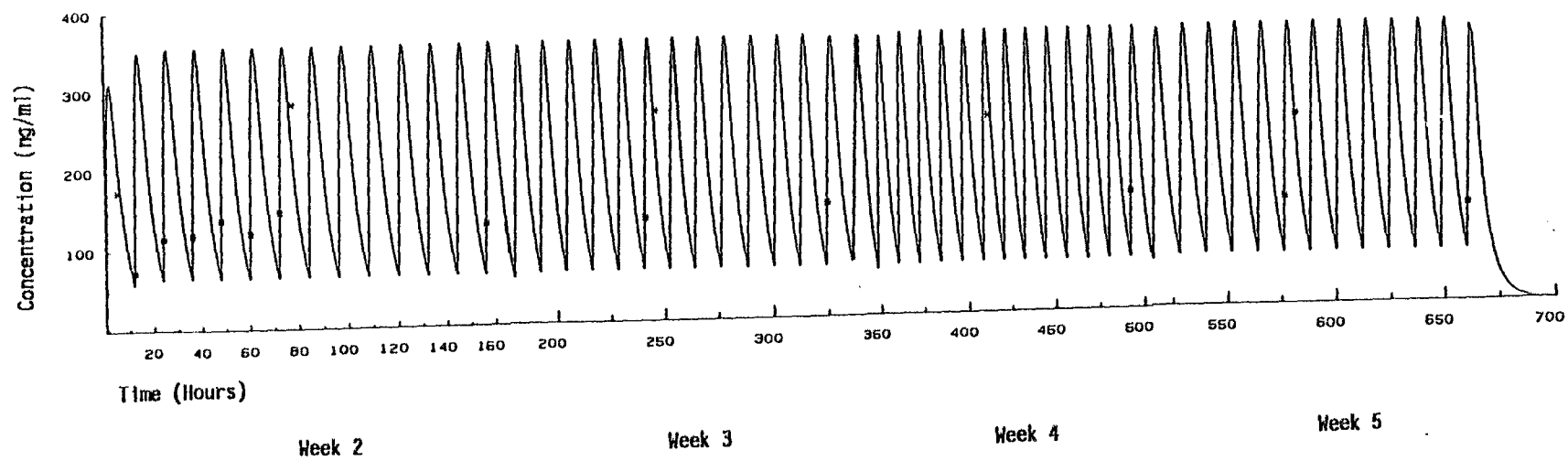


FIGURE A14.1

Simulated vs Observed Steady-state Profile [Subject 1 (SS)]

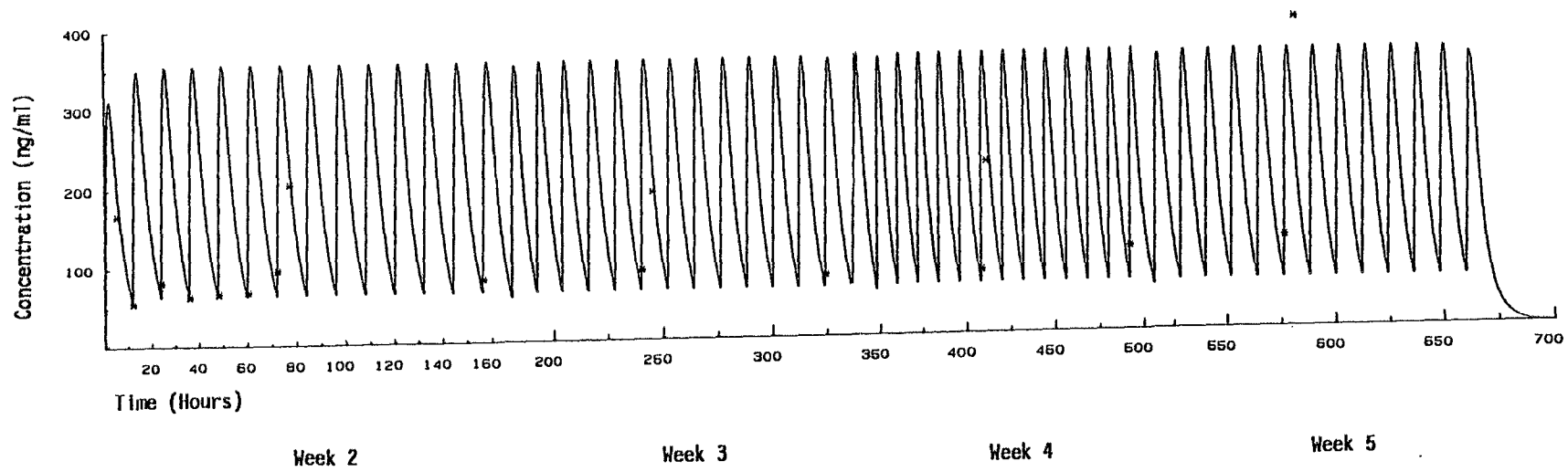


FIGURE A14.2

Simulated vs Observed Steady-state Profile [Subject 2 (CA)]

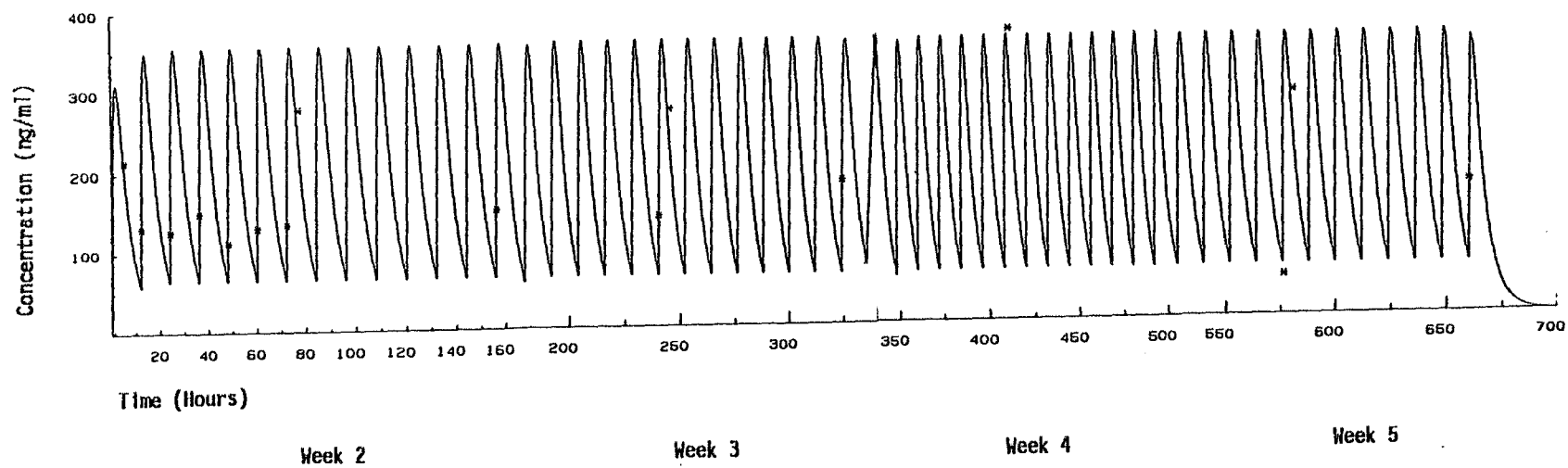


FIGURE A14.3

Simulated vs Observed Steady-state Profile [Subject 3 (LE)]

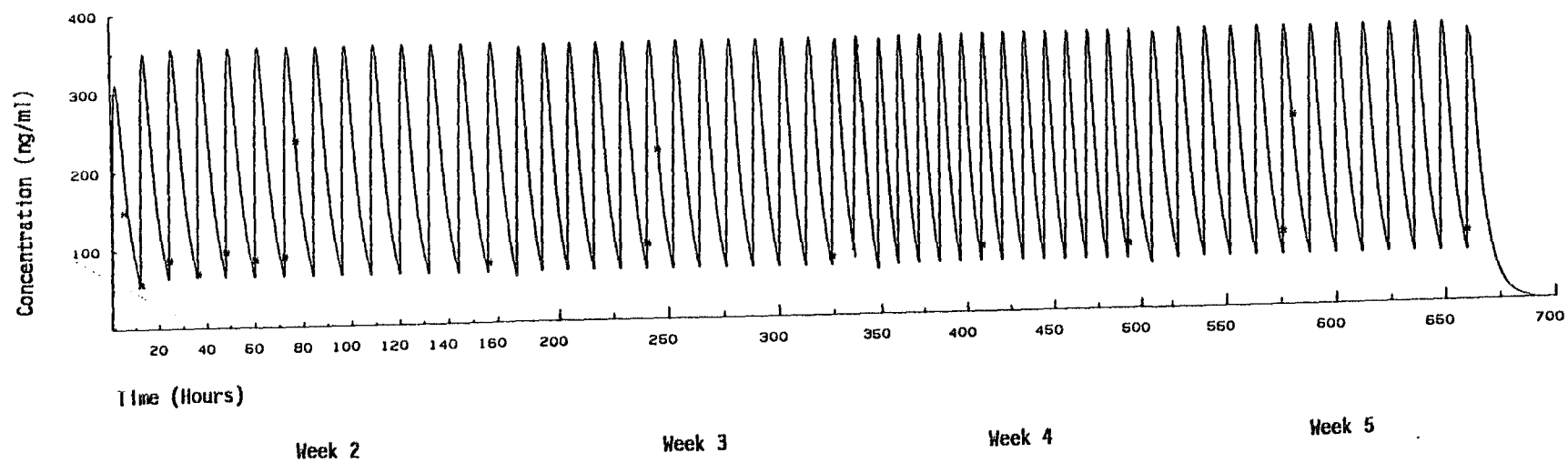


FIGURE A14.4

Simulated vs Observed Steady-state Profile [Subject 4 (EA)]

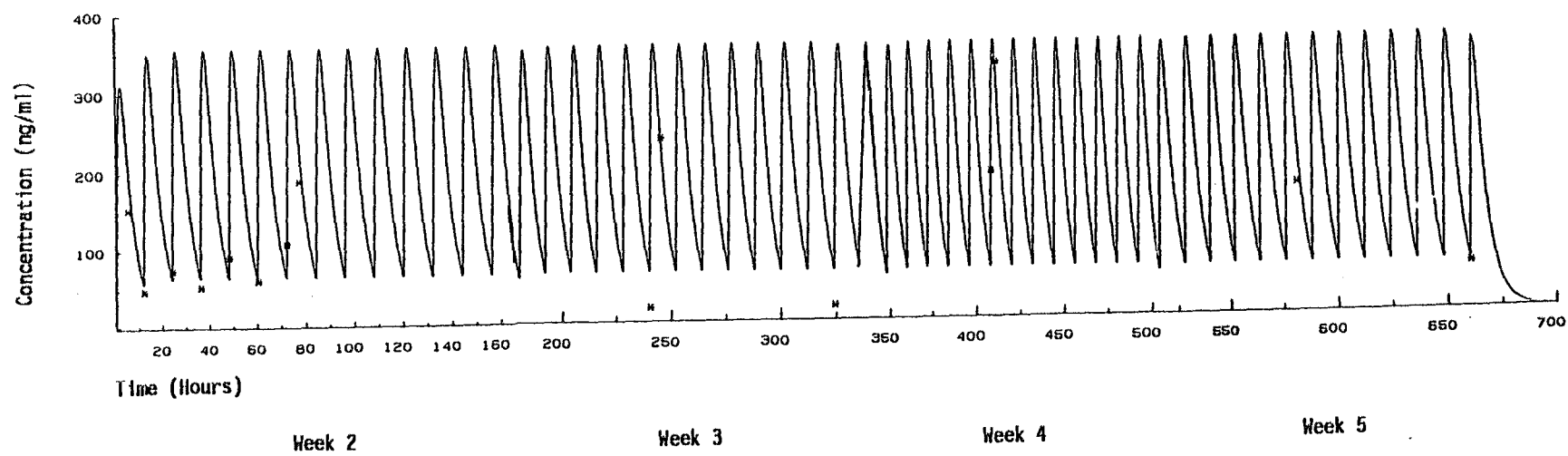


FIGURE A14.5

Simulated vs Observed Steady-state Profile [Subject 5 (VH)]

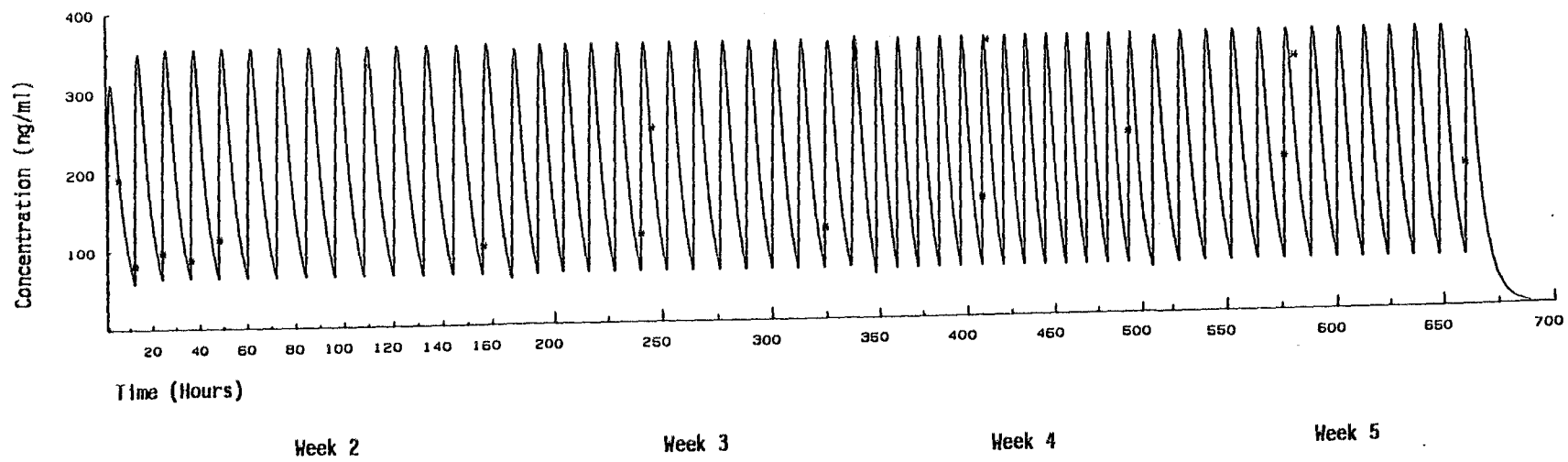


FIGURE A14.6

Simulated vs Observed Steady-state Profile [Subject 6 (L1)]

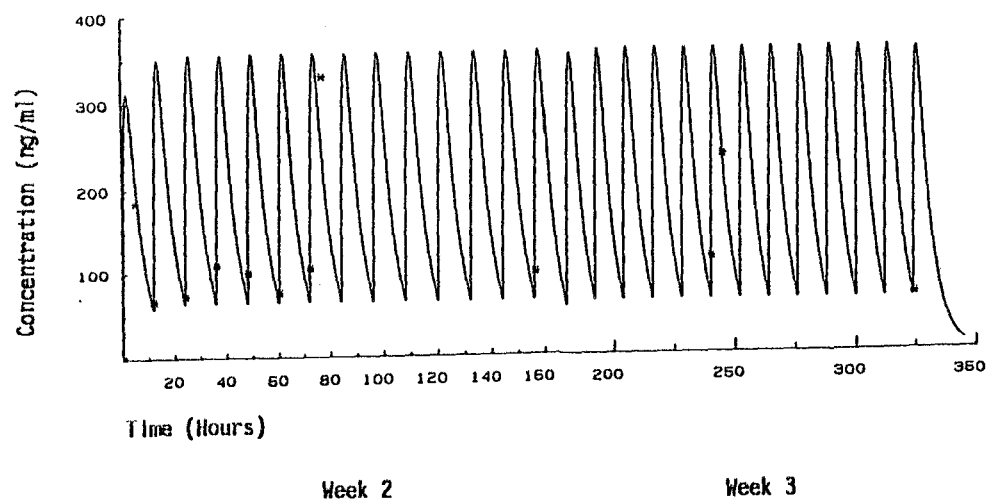


FIGURE A14.7

Simulated vs Observed Steady-state Profile [Subject 7 (EG)]

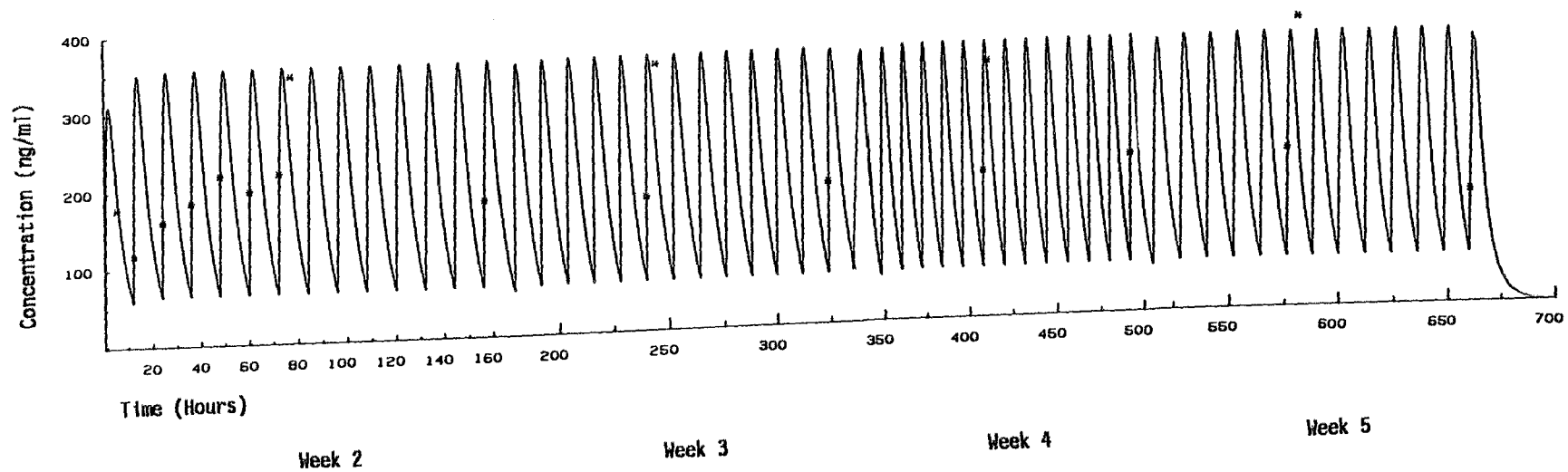


FIGURE A14.8

Simulated vs Observed Steady-state Profile [Subject 8 (CV)]

TABLE A15.1 Fraction PPA.HCl Dissolved (Product LE)

Time (Hrs)	Fraction PPA.HCl Dissolved Replicate Capsule Numbers						Mean	± SD
	1	2	3	4	5	6		
0.017	0.000	0.000	0.000	0.000	0.000	0.000	0.000	± 0.000
0.033	0.000	0.000	0.000	0.000	0.000	0.000	0.000	± 0.000
0.067	0.002	0.039	0.066	0.032	0.064	0.107	0.052	± 0.033
0.100	0.052	0.117	0.140	0.093	0.183	0.111	0.116	± 0.040
0.133	0.090	0.163	0.206	0.147	0.237	0.134	0.163	± 0.048
0.167	0.112	0.215	0.244	0.201	0.282	0.173	0.204	± 0.054
0.208	0.163	0.266	0.278	0.249	0.317	0.201	0.246	± 0.051
0.250	0.195	0.307	0.307	0.288	0.352	0.224	0.279	± 0.053
0.333	0.238	0.354	0.368	0.339	0.410	0.262	0.328	± 0.060
0.417	0.287	0.386	0.391	0.385	0.463	0.342	0.376	± 0.053
0.500	0.312	0.424	0.422	0.436	0.493	0.334	0.403	± 0.062
0.750	0.386	0.492	0.472	0.517	0.563	0.404	0.472	± 0.061
1.000	0.448	0.555	0.529	0.576	0.617	0.463	0.531	± 0.059
1.500	0.529	0.630	0.600	0.652	0.680	0.546	0.606	± 0.054
2.000	0.592	0.693	0.676	0.715	0.738	0.633	0.674	± 0.049
3.000	0.684	0.781	0.753	0.828	0.829	0.703	0.763	± 0.056
4.000	0.747	0.850	0.816	0.888	0.868	0.776	0.824	± 0.050
5.000	0.788	0.916	0.858	0.934	0.915	0.829	0.873	± 0.53
6.000	0.844	0.947	0.879	0.959	0.957	0.855	0.907	± 0.049
7.000	0.876	0.949	0.897	0.983	0.947	0.888	0.923	± 0.039
8.000	0.894	0.961	0.935	0.994	0.971	0.901	0.943	± 0.036
9.000	0.901	0.985	0.937	1.006	0.982	0.912	0.954	± 0.039
10.00	0.913	0.996	0.960	1.018	1.006	0.924	0.970	± 0.040

TABLE A15.2 Fraction PPA.HCl Dissolved (Product RD)

Time (Hrs)	Fraction PPA.HCl Dissolved Replicate Capsule Numbers						Mean	± SD
	1	2	3	4	5	6		
0.017	0.000	0.000	0.000	0.000	0.000	0.000	0.000	± 0.000
0.033	0.000	0.000	0.000	0.000	0.000	0.000	0.000	± 0.000
0.067	0.000	0.000	0.000	0.000	0.000	0.000	0.000	± 0.000
0.100	0.013	0.019	0.007	0.000	0.035	0.000	0.012	± 0.012
0.133	0.055	0.064	0.019	0.000	0.058	0.034	0.038	± 0.023
0.167	0.060	0.078	0.030	0.024	0.074	0.085	0.058	± 0.024
0.208	0.087	0.087	0.031	0.036	0.073	0.098	0.068	± 0.026
0.250	0.098	0.102	0.043	0.047	0.085	0.111	0.081	± 0.027
0.333	0.110	0.111	0.071	0.0601	0.109	0.1222	0.097	± 0.023
0.417	0.143	0.127	0.106	0.073	0.121	0.133	0.117	± 0.023
0.500	0.1722	0.148	0.111	0.085	0.121	0.147	0.131	± 0.031
0.750	0.192	0.181	0.141	0.110	0.161	0.184	0.162	± 0.029
1.000	0.228*	0.2078	0.185	0.136	0.184	0.221	0.194	± 0.030
1.500	0.297	0.267	0.239	0.194	0.186	0.258	0.240	± 0.040
2.000	0.369	0.342	0.309	0.255	0.323	0.369	0.328	± 0.039
3.000	0.493	0.449	0.416	0.369	0.418	0.473	0.436	± 0.041
4.000	0.589	0.538	0.505	0.448	0.498	0.548	0.521	± 0.044
5.000	0.642	0.592	0.570	0.523	0.535	0.613	0.579	± 0.042
6.000	0.697	0.646	0.620	0.585	0.608	0.665	0.637	± 0.037
7.000	0.752	0.697	0.661	0.632	0.665	0.718	0.687	± 0.040
8.000	0.784	0.737	0.723	0.669	0.705	0.798	0.736	± 0.044
9.000	0.828	0.790	0.768	0.714	0.742	0.803	0.774	± 0.038
10.00	0.858	0.833	0.795	0.742	0.781	0.827	0.806	± 0.038

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