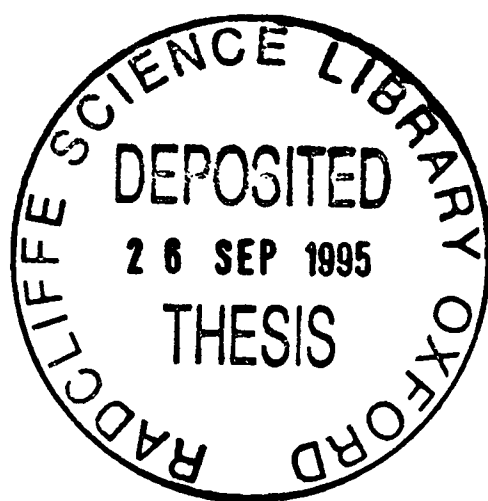


THE STUDY OF

HYPERPHAGIA IN DEMENTIA

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HYPERPHAGIA IN DEMENTIA - AN OBSERVATIONAL STUDY.

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ABSTRACT

About 750 000 people suffer from dementia in the United Kingdom. This number is rising as the proportion of those over 65 years old increases. Excessive eating (hyperphagia) occurs at some stage in about 25% of people suffering from dementia. This can lead to consumption of unsuitable substances and a significant gain in weight, which may make care at home impossible. Until now, reports of hyperphagia have been purely anecdotal. The aims of this thesis were to develop objective methods for the definition and measurement of hyperphagia and to use these as a basis for examining the phenomenon of hyperphagia in detail.

Two standardised and reliable methods for quantifying hyperphagia were developed and compared. Results showed that people with hyperphagia ate, on average, more than three times the quantity of food eaten by matched controls during test meals. The hyperphagic group were compared, in a series of experiments, with two control groups - subjects with dementia who were not hyperphagic and normal elderly. The food choice of the hyperphagic group differed significantly from normal elderly: they chose less protein and low-energy foods and ate more sweet food. The changes in food choice seem to be a more severe form of the changes which occur during the dementing process. Examining the microstructure of eating showed that the mechanisms controlling both the onset and cessation of feeding are abnormal. Satiety was examined by giving subjects and controls two preload drinks of different energy content and examining the effect on subsequent food intake. Compensation for the preload was found to be weaker in normal elderly controls and both dementia groups when compared with young controls.

Although people with hyperphagia show significantly more patterns of stereotyped behaviour than matched demented controls the prolonged period of eating does not seem to be due to a stereotypy but to a delay in the satiation mechanism. Hyperphagia typically occurs in the middle stages of the dementing illness and lasts for a mean of about three years. These studies demonstrated that subjects with dementia who are hyperphagic have a major disturbance in the mechanisms controlling satiation, hunger, food choice and satiety.

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SECTION 1 INTRODUCTION

This thesis describes a series of studies into the phenomenon of excessive eating ('hyperphagia') in people with dementia. This phenomenon is both important clinically and interesting theoretically. In this introduction I will:

- (a) give a brief overview of dementia and its causes;
- (b) review methods of studying behavioural problems in dementia;
- (c) review what is currently known of eating problems in dementia with particular emphasis on hyperphagia;
- (d) discuss hyperphagia within other clinical settings;
- (e) review theories of the control of eating and
- (f) discuss possible causes of hyperphagia in dementia.

Chapter 1 DEMENTIA AND ITS CAUSES

DEFINITION

‘Dementia’ is a clinical syndrome which is characterised by global deterioration of intellect, occurring in clear consciousness (Folstein *et al.*, 1975).

In the *International Classification of Disease [ICD-10]* (World Health Organisation, 1992), dementia is defined as ‘a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Consciousness is not clouded.’ The ‘decline in both memory and thinking is sufficient to impair activities of daily living’.

In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV]* (American Psychiatric Association, 1994) the essential feature of dementia is the development of multiple cognitive deficits which include memory impairment and at least one of the following cognitive disturbances - aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning. The criteria are very similar to those of ICD-10, i.e. the loss of short and long-term memory, and at least one of the following: impairment in abstract thinking, impaired judgement and disturbance

of higher cortical function or personality change. These changes usually interfere with daily living and they are not due to delirium or any apparent organic or mental disorder.

The two most common causes of dementia are Alzheimer's disease (AD) and vascular dementia (which includes multi-infarct dementia). Both ICD-10 and DSM-IV characterise Alzheimer's disease by a gradual onset and progressive deterioration with no evidence of other systemic or brain disease. Vascular dementia typically shows an abrupt onset followed by a step-wise and fluctuating deterioration with evidence of focal neurological signs and symptoms as well as evidence of cerebrovascular disease. Insight and judgement may be relatively well-preserved. Deterioration of intellectual, emotional and motivational behaviour in dementia can be assessed using the *Cambridge Examination for Mental Disorder in the Elderly* [CAMDEX] (Roth *et al.*, 1986). Criteria specifically for diagnosing AD are found in the *Criteria of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association in the USA* - [NINCDS-ADRDA Criteria] (McKhann *et al.*, 1984). The Hachinski Scale (Hachinski *et al.*, 1975) is often used to diagnose vascular dementia (see Chapter 8).

PREVALENCE

Dementia mainly affects the elderly although it occasionally develops in those under 65. Estimates of prevalence vary; this is probably mainly because of variation in the methods used to detect dementia (Copeland, 1994). However, when the same methods of detection are used, there is evidence that prevalence varies geographically.

Copeland *et al.*, (1987) used the computerised diagnostic algorithm AGE CAT in conjunction with standard diagnostic interviews and found nearly twice the proportion of people with dementia in New York as in London (8.4% and 4.3% respectively).

Jorm *et al.*, (1987) concluded that, over the age of 60, prevalence roughly doubles for every five years of life. The overall rate of dementia in people aged over 65 has variously been estimated at between 4% and 7%, and in people over 75 at 10%. In Russia and Japan, vascular dementia may be the most prevalent form of dementia (Copeland, 1994) but elsewhere, including Britain, AD is the most common cause. A major problem is that clinical assessment is not a robust way of distinguishing the cause of dementia and, although post-mortem diagnoses are more accurate, the group of people who receive post-mortem examination is probably not representative of the population as a whole. Post-mortem results show that vascular dementia can occur either separately or in combination with Alzheimer's disease and that there is a greater incidence of Alzheimer's disease in women but more vascular dementia in men. Growing evidence demonstrates that many cases of dementia may be wholly or partly associated with Lewy Body disease. There are many other less common causes of dementia, some treatable and some irreversible. There is much controversy over the question of whether dementia in general, and Alzheimer's disease in particular, is part of a complex continuum of age-related decline, or a disease (or series of diseases) quite separate from normal ageing (Huppert & Brayne, 1994).

In both AD and vascular dementia there is a progressive loss of cognitive function. Usually the first symptom which is noticed is impairment of short-term memory. In

later stages there is a progressive loss of long-term memory, agnosia, apraxia and ataxia. These changes are often accompanied by changes in behaviour.

MAIN CAUSES OF DEMENTIA

Alzheimer's Disease

Alzheimer's disease is defined using a combination of clinical and pathological criteria. The clinical features are global deterioration of mental functioning (i.e. the defining features of dementia described above) and the pathological part of the definition describes the histological changes. Both the clinical and pathological criteria are necessary for a definitive diagnosis of AD to be made. The pathological changes are neuronal loss, large numbers of neuritic plaques, neocortical neurofibrillary tangles and amyloid deposits. Neurofibrillary tangles are found in small numbers in normal ageing brains but in AD the quantity of paired helical filaments in the tangles, and also the number of plaques, has been correlated with the degree of the dementia. There are other biochemical changes such as the general reduction of many neurotransmitters, notably acetylcholine (Sims *et al.*, 1980; Hardy *et al.*, 1985; McDonald & Nemeroff, 1991). None of these pathological and biochemical features are unique to AD; they are also found - generally to a lesser degree - in the normal elderly. The most commonly used pathological criteria therefore define thresholds for the concentration of pathological features and use the density of plaques and tangles in the definition. Khachaturian (1985) measured the mean number of plaques to make a diagnosis whereas Tierney *et al.* (1988) defined AD by the concentration of both plaques and tangles in the neocortex.

There is a wide variability between individuals but in general the more severe the dementia (both cognitive and pathological changes) the greater is the biochemical, and especially the cholinergic, deficit. Many of the changes in behaviour, in particular hyperphagia, may be the result of the decrease in specific neurotransmitters.

Vascular dementia [Multi-infarct dementia (MID) or Multiple cerebral infarction]

Patients with cerebrovascular disease who are demented usually have widely distributed areas of cerebral infarction on both sides of the cerebrum, especially in the frontal, occipital and basal regions. Usually a total volume of more than 100 ml of affected area has been regarded as resulting in dementia but, in some specific locations, much smaller areas of infarct can cause dementia (Mackenzie, 1994).

Mixed AD/vascular dementia

At post-mortem examination, many cases of dementia show signs of both vascular dementia and AD.

With increasingly sophisticated techniques, two new causes of dementia have been categorised, frontal lobe dementia and Lewy body disease.

Frontal lobe dementia

This dementia differs from AD in not having many plaques and tangles but there is great neuronal loss in the frontal lobes. This resembles Pick's disease but there are no 'Pick bodies', which are taken as a necessary defining characteristic of Pick's disease.

Lewy body disease

There has been increasing interest in dementia caused by a large number of Lewy bodies in the cortex; severity being correlated with cortical Lewy body density. Lewy bodies, traditionally used in defining Parkinson's disease, are abnormal intracellular inclusions, found either singly or in clusters, and they have a dense laminated core with a radiating fibrillary corona. They react to immuno-staining with the antibody to ubiquitin (Esiri, 1991). There seems to be at least two forms of the disease: diffuse cortical Lewy-body disease, which gives a clinical picture similar to AD, and senile dementia of the Lewy-body type, which resembles vascular dementia clinically but there is no vascular pathology. There appears to be a spectrum of Lewy body disorders with diffuse cortical Lewy body disease at one extreme and idiopathic Parkinson's disease, where Lewy bodies are mainly in the brain stem, at the opposite end of the continuum.

Dementia in Parkinson's disease

About 20% (estimates vary from 14% to 40%) of people with Parkinson's disease develop dementia during the course of the illness. It is most common in older patients.

Some of the rarer dementias

There are a number of rare causes of dementia, including:

Creutzfeldt-Jacob disease - This is one of the spongiform encephalopathies which is transmitted by an agent similar to the scrapie 'prion'.

Pick's disease - This is mainly characterised by atrophy of the frontal and temporal lobes and defined pathologically by 'Pick bodies'. These are rounded, argyrophilic structures in the cytoplasm of neurones consisting of a variable collection of straight and paired helical filaments.

Huntington's disease - This is a neurodegenerative disease characterised by movement disorder and dementia. It is inherited, usually, as an autosomal dominant trait.

Secondary to other brain lesions - Dementia can be a side-effect of trauma after head injury, for example subdural haematoma or *dementia pugilistica* developed by boxers. Brain tumours may be associated with dementia.

Toxins - Many toxic substances such as heavy metals, alcohol and drugs can be responsible for dementia. In kidney patients dementia has also been induced by long-term dialysis (possibly through toxic effects of aluminium).

Secondary to transmissible diseases - AIDS victims may develop dementia and, in the past, dementia following syphilis was widespread (general paresis).

Treatable dementias - Reversible causes of dementia can result from metabolic disorders such as hypothyroidism and vitamin B₁₂ deficiency. Dementia caused by normal pressure hydrocephalus can often be improved with a shunt. 'Pseudo-dementia' is a term used when the symptoms of dementia are due to depressive illness.

Chapter 2 BEHAVIOURAL PROBLEMS IN DEMENTIA

Although cognitive impairment is a diagnostic feature of dementia it is often the behavioural problems which cause difficulties, both for the people themselves and their carers, and lead to their admission into institutional care (Margo *et al.* 1980). In this chapter I will first give examples of some of the behavioural problems; then I will discuss the various methods which have been used to study the behaviour of people with dementia; finally I will give a brief review of methods which have been used for studying eating behaviour in humans and consider their value in studying eating behaviour in people with dementia.

The prevalence and natural history of these changes has been investigated in depth in a longitudinal study of behavioural changes in dementia carried out by Tony Hope and colleagues at the University Department of Psychiatry at Oxford. A cohort of 104 people with dementia have been followed at four-monthly intervals. My own interest in overeating in dementia originates from having been a research assistant in this study. By means of a comprehensive, semi-structured interview with carers, the time sequence and progression of these changes has been studied throughout the course of the illness. The data from this study are currently being analysed. The loss of short-term memory in the initial stages is often accompanied by anxiety and depression (Burns *et al.*, 1990a). As the illness progresses, the main behavioural changes which affect everyday life, of both the people with dementia and their carers, are various types of aggressive behaviour (Reisburg *et al.*, 1987; Ryden, 1988;

Swearer *et al.*, 1988; Ware *et al.*, 1990; Beck *et al.*, 1991), loss of diurnal rhythm (Sanford, 1975; Cohen-Mansfield *et al.*, 1990), eating changes (Morris *et al.*, 1989) and the various forms of wandering (Hope & Fairburn, 1990). Other changes which cause difficulties are incontinence, screaming and shouting, coprophagia (Ghaziuddin & McDonald, 1985), hoarding and hiding objects. These exhausting and disruptive types of behaviour eventually give way to increasing immobility, apathy, and eventually, if the disease runs its full course, to the loss of vital reflexes such as those concerned with swallowing.

It is often behaviour changes, particularly wandering, aggressive behaviour, incontinence and loss of diurnal rhythm, which lead to the carer being unable to cope at home, single-handed, and the person with dementia being taken into institutional care (Margo *et al.*, 1980).

‘EXCESS’ BEHAVIOUR

Many of the behaviour changes, in the middle stages of the disease, involve ‘excess’ behaviour. Excess behaviour may be an exaggerated form of previous characteristics, for example an active person may become hyperactive, an irritable person may become prone to violent and uncharacteristic outbursts of aggressive behaviour (Patel & Hope, 1992a; Hope & Patel, 1993) or the change may be a new, uncharacteristic trait such as marked overeating, excessive walking (Hope & Fairburn, 1990; Hope *et al.*, 1994), repeated questioning, stereotypy (repetitive patterns of behaviour) and sometimes inappropriate sexual behaviour. This is in contrast to the reduced behaviour, characteristic of the terminal stages, when the person becomes immobile,

eats very little, does not show any emotion and is unable to speak.

There is evidence both from human and animal research that some of these types of behaviour are associated with reduced levels of neurotransmitters, especially monoamines such as 5-HT (5-hydroxytryptamine or serotonin) and noradrenaline. For example, a disturbance in 5-HT and its metabolites has been found consistently in people showing depression (Goodwin & Post, 1983; Coccaro *et al.*, 1989; Cowen & Anderson, 1991; Price *et al.*, 1991). Cowen (1993) suggests that depressive illness is caused by decreased 5-HT release rather than altered sensitivity of postsynaptic receptors. Disturbed 5-HT function is also linked with sleep disorders, anxiety, suicidal behaviour, a history of aggressive and impulsive behaviour (van Praag, 1991), Gilles de la Tourette syndrome (Cohen *et al.*, 1979), obsessive compulsive disorder (Fineberg & Montgomery, 1990) and, sometimes, in increased motor activity (Donnelly *et al.*, 1989). Deficiency of 5-HT is also found in eating disorders such as bulimia nervosa, as well as during food-craving conditions such as pre-menstrual syndrome (Rogers *et al.*, 1992), carbohydrate-craving obesity (Wurtman, 1988a) and seasonal affective disorder (Wirz-Justice & Richter, 1979; Kräuchi & Wirz-Justice, 1988; Wurtman & Wurtman, 1989). The relationships between measures of neurotransmitter function and abnormalities of eating will be discussed in greater detail below.

Neurochemical studies of AD show a general reduction in a variety of neurotransmitters although there is a wide variation in the extent of this lowering between individuals. There is a progressive loss of cholinergic activities, both in the

cortex and the sub-cortical areas, in normal ageing but a more marked deficit in AD. The decrease in choline acetyltransferase is correlated with the degree of dementia, decreased acetylcholinesterase degradation and fewer receptors, particularly the nicotinic receptors (Perry *et al.*, 1994). Noradrenaline, 5-HT, dopamine, GABA and somatostatin have been reported to be reduced in AD (Hardy *et al.*, 1985; Cross, 1990; Nazerali & Reynolds, 1992; Kopelman, 1993). It is interesting to speculate that reduced levels of monoamine transmitters may underlie some of the behavioural abnormalities such as the aggressive behaviour seen in AD. There is evidence that low levels of monoamine neurotransmitters may account for wandering behaviour in dementia (Hope *et al.*, 1991b) and low noradrenaline and 5-HT may be responsible for increase in major depression in primary dementia (Zubenko *et al.*, 1990).

METHODS OF STUDYING BEHAVIOURAL PROBLEMS IN DEMENTIA

Most studies into behaviour changes in dementia lack precision, validity and reliability as they are descriptive and have involved only a small number of cases. Recently a range of instruments has been developed to rate behaviour more accurately. These have been divided into four groups (Hope & Patel, 1993):

a) Collecting information from the patient

There are semi-structured interviews, for use with patients, such as the Geriatric Mental State [GMS] (Copeland *et al.*, 1976) and the Sandoz Clinical Assessment - Geriatric [SCAG] (Shader *et al.*, 1974). The GMS is designed as a standardised psychiatric interview for use with the elderly. For the assessment of dementia an

interview with the carer has been added (although this is not concerned with behaviour). A nutrition and weight questionnaire (Geriatric Community Health Center Nutrition questionnaire) has been used with AD patients (Wolf-Klein *et al.*, 1992). The central problem with collecting behavioural information from the patient is the unreliability of the report, due to the patient's cognitive impairment.

b) Collecting information from carers

Several instruments have been developed to collect information from a principal carer, either at home or in a ward, using semi-structured or structured interviews or rating scales, for example CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly, with special reference to the early detection of dementia (Roth *et al.*, 1986); the Social Behaviour Assessment Schedule [SBAS] (Platt *et al.*, 1980); Informant Questionnaire to Measure Cognitive Decline in the elderly [IQCODE] (Jorm *et al.*, 1989); Rating Scale for Aggressive Behaviour in the Elderly [RAGE] (Patel & Hope, 1992b). The only semi-structured interview developed principally to study a broad spectrum of behaviour changes in dementia is the Present Behaviour Examination [PBE] (Hope and Fairburn, 1992).

The main problem with all these methods is the lack of reliability between assessment of similar behaviour by different carers.

c) Direct Observation

Direct observation needs careful development to define target behaviour and to ensure consistency in recording and coding. It is time-consuming but allows a more

objective analysis of behaviour than the two methods discussed above.

d) Indirect objective measures

Some types of behaviour can be measured using automatic recording devices. For example pedometers and electronic monitors have been used to assess hyperactivity (Rheaume *et al.*, 1987). Electroencephalographic recording of sleep and physiological markers such as plasma melatonin, human growth hormone release and body temperature have been used to assess diurnal rhythm (Prinz *et al.*, 1982; Prinz & Vitiello, 1993).

GENERAL METHODS OF STUDYING HUMAN EATING BEHAVIOUR

Many methods have been used to study eating behaviour in non-demented subjects (Rodin, 1990). Questionnaires, semi-structured interviews and 'food diaries' have been extensively used in, for example, studies on obese people and people with eating disorders (Garner & Garfinkel, 1979; Cooper & Fairburn, 1987; Cooper *et al.*, 1989; Fairburn & Cooper, 1993). Concurrent verbalisation during behavioural tasks was used in patients with eating disorders (Cooper & Fairburn, 1992). Visual analogue scales (VAS) have been used to assess parameters such as hunger, fullness and mood (Hill & Blundell, 1986; Rogers & Hill, 1989; Rogers *et al.*, 1991). Checklists of foods with different macronutrient content have been used to assess the effect of drugs on macronutrient preference (Blundell & Hill, 1987b). Checklists, VAS, forced-choice food preference tests and diary records were used together to assess the effect of preload meals on subsequent food intake (Hill *et al.*, 1987). Direct observation

was used, often backed up by sophisticated recording devices, to record chewing and swallowing (Bellisle & Le Magnen, 1980; 1981). Videofluoroscopic examination of swallowing in people with dementia has been used successfully (Feinberg *et al.*, 1992). A computer can be linked to a table with a built-in electronic balance to measure food intake during a meal (Kissileff *et al.*, 1980). Automatic snack-food dispensers, linked to a computer, record when food is taken and what foods are chosen in order to monitor 'free range' eating (Goodall *et al.*, 1992). Direct observation with videorecording has been used (Rogers & Blundell, 1979), which has the added advantage that the microstructure of eating behaviour can be analysed.

Limitations of these methods for use in dementia

It is not possible to explain complex procedures to people with moderate or severe dementia. This means that VAS, food dispensers and complex questionnaires cannot readily be used. Responses to simple questions are not reliable as short-term memory is very poor. A simple VAS drawn like a petrol gauge (see figure 12.4) was used unsuccessfully, as part of the work for this thesis, to try to assess hunger. Pictures of food, successfully used in assessing hunger in children with learning difficulties (Holland *et al.*, 1993), were also not successful when used on people with dementia in this study (for further details see Chapter 12).

Semi-structured interviews or questionnaires can be used with carers to collect indirect evidence. The PBE was used in the MRC study (described in Chapter 7) and both inter-rater and intra-rater reliability of the PBE are good (Hope & Fairburn, 1992). However, there remains the issue of validity. Carers' reports are not easy

to standardise: one carer's estimate of abnormal overeating might be regarded as normal by another person.

Direct observation is the most appropriate method for the detailed examination of eating behaviour. Direct observation allows standardised procedures to be set up and standardised rating scales to be used in their analyses. Using video-recordings allows these analyses to be checked for both inter- and intra-rater reliability. This, however, is very time-consuming as only one subject can be monitored at a time. Most of the experiments reported in this thesis involve using direct observations of eating behaviour.

Chapter 3 EATING ABNORMALITIES IN DEMENTIA

PREVALENCE

There are many reports of profound changes in eating behaviour during the course of dementia. Morris and Hope (1992) reviewed the main changes and categorised them as: decreased eating, increased eating, eating inedible objects and abnormal eating methods, change in food choice and changes in eating style.

These reports are mainly based on studies of Alzheimer's disease and vascular dementia (Fairburn & Hope, 1988a, 1988b; Morris *et al.*, 1989; Erb *et al.*, 1989) but there are also reports of overeating in Pick's disease (Hope & Allman, 1991), Huntington's disease (Janati, 1985), dementia of the frontal lobe type (Neary *et al.*, 1988), familial dementia of a non-specific nature (Kim *et al.*, 1981) and progressive subcortical gliosis, a rare form of presenile dementia (Neumann & Cohn, 1967).

Morris *et al.* (1989) and Hope *et al.* (1991a) studied the eating behaviour of a group of 33 subjects with dementia, living in the community, looking at changes which had occurred at some stage during the illness. Their results are summarised in table 3.1.

Table 3.1

EATING ABNORMALITIES IN DEMENTIA		
(Principally AD and vascular dementia)		
Results refer to the percentage of subjects (n=33) who showed abnormality at some stage during their illness.		
1 Alterations in eating behaviour:		
Increased eating		26%
Decreased eating		63%
Change in food choice		
change in sweet food choice		37%
liked more spicy food		15%
inappropriate foods		15%
Pica, non-food e.g. coprophagia		15%
Pica, inappropriate food		15%
2 Weight changes (loss or gain)		
Percentage who showed weight loss		70%
Percentage who showed weight gain		22%
		Hope <i>et al.</i> , (1991a)
		Morris <i>et al.</i> , (1989)

Other changes include physical difficulties in eating and changes in nutrition, for example biochemical indexes, nutrient intake and energy balance (Morris *et al.*, 1989).

In the Medical Research Council (MRC) longitudinal study of a cohort of 104 subjects (Hope & Fairburn, 1992), the main changes in eating at the first interview (point-of-entry data) were similar to the changes shown in table 3.1. Further details of the range and prevalence of these changes are discussed in Chapter 7.

Sinha and colleagues (1992) found that there was either an increase or decrease in eating in 29% of people with dementia. In a retrospective study, Trinkle and colleagues (1992) report eating changes as a prominent symptom of dementia in 15

out of 114 (13.2%) patients. This is a lower estimate than Morris and colleagues (1989), partly because no specific questionnaire was used to assess eating disorders and also 'oral behaviour' was not included. The longer-term MRC study, using the Present Behavioural Examination (PBE), shows that at least one of the abnormalities described by Trinkle and colleagues was present in 62 of 97 (64%) subjects at the point-of-entry interview and a further 21 (22%) developed an eating abnormality in the following 4 years (Morris *et al.*, 1993).

Excessive appetite has been reported in up to 20% of Alzheimer's disease patients (Teri *et al.*, 1989). Hope *et al.* (1991a) found that up to 25% of people with dementia showed signs of overeating at some stage during the course of the illness. Trinkle *et al.* (1992) report bingeing behaviour and altered food choice. Burns *et al.* (1990b) found that the proportion of people with dementia, who were said to be binge-eating, at any one time is around 10%, and this figure is the same for mild, moderate and severe dementia. They also found no association between binge-eating and prescribed neuroleptic drugs. There was a significant correlation between binge-eating and hyperorality.

In the MRC longitudinal study, at present being carried out in Oxford, carers reported that eating increased in 35% of the subjects at some stage in the dementing illness. This is remarkable as normally, with increasing age, activity and energy requirements decrease. Hyperphagia was reported to be severe, at some stage in the illness in 24 (23%) of the cohort of 104, i.e. carers reported that the person with dementia would eat an excessive quantity of any food available, frequently until it was finished,

especially when it was sweet food such as biscuits and cake. This sometimes seemed to be because of a marked preference for sweet foods (see Chapter 10) and sometimes because the foods which were most easily found, and recognised, were sweets or biscuits.

There is considerable variation in the estimates of the prevalence of eating disorders because different populations are examined, definitions and criteria vary and different methods of assessment are used. Some studies find little difference in food intake between controls and people with dementia (Stähelin *et al.*, 1983; Renvall *et al.*, 1989; Winograd *et al.*, 1991) and others find significant deficiencies in the diet of people with dementia (Litchford & Wakefield, 1987).

Hyperphagia has not been investigated in detail by direct observation. The only work using direct observation was a case study (Hope & Allman, 1991) which suggested that the massive food consumption, of a man with Pick's disease, could be significantly reduced with fluvoxamine.

HYPOPHAGIA IN DEMENTIA

Decreased eating in people with dementia is a major problem for carers and nursing staff (Watson, 1993). Sandman *et al.* (1987) found energy and/or protein malnutrition in 50% of institutionalised patients with AD or vascular dementia and a mean reference weight of 82% of ideal body weight in spite of adequate dietary intake for energy. In their review, Morley and Silver (1988) conclude that a decrease in eating, with or without loss of weight, is the most common eating change in

dementia.

There are likely to be many causes of undereating including lack of self-care, forgetting to eat, metabolic disturbances and a direct result of brain pathology. In the early stages of dementia, if people are living alone, social isolation may remove the incentive to prepare and enjoy meals. Perishable foods may pose a health risk if not eaten in time. Malnutrition can be an additional problem if physical and cognitive difficulties prevent efficient shopping and meal preparation (Nes *et al.*, 1988), for example people with dementia may only buy a few easily prepared items, such as biscuits or bread and butter, and live almost exclusively on them (Rubenstein, 1990). A change in food choice is common, sweet foods usually being preferred (Mungas *et al.*, 1990). Well-preserved social behaviour may even prevent a spouse from realising how little food is being eaten, as a consequence of apraxia (Blass, 1980). With increasing inactivity the basal metabolic rate decreases so that requirements are reduced, but it is easy for a vicious circle of undereating, nutritional deficiencies and apathy, to be set up.

In the terminal stages of dementia, Sourander and Sjögren (1970) reported an extreme and rapid decrease in body weight, apparently unrelated to either inadequate feeding or to cancer. In most people suffering from dementia, if the deterioration runs its full course, the final stages are usually characterised by hypophagia as the person becomes immobile and apathetic. People often take active measures to avoid feeding e.g. turning the head away, spitting out food in the mouth and keeping the mouth firmly closed when being fed. In the final stages the swallowing reflex is lost

(Volicer *et al.*, 1989).

Watson (1994a; 1994b) analysed these changes and found a cumulative pattern as more feeding difficulties occurred. The early signs indicate a refusal to eat, for example by turning the head away or refusing to open the mouth. A later, more severe, sign is spitting out food and finally the patient refuses, or is unable, to swallow. These progressively more severe aspects of feeding difficulties revealed a cumulative and unidimensional pattern when he analysed them by means of Guttman scale analysis.

Causes of hypophagia

It is likely that there are many factors contributing to undereating. There are biological causes, for example lesions of the lateral hypothalamus cause hypophagia (Anand & Brobeck, 1951) and in AD there is extensive damage in this area. There are less sensitive taste cells in the elderly, and in people with AD the olfactory sensory pathway shows early damage with significantly greater cell loss and more neurofibrillary tangles than in the normal elderly (Esiri & Wilcock, 1984). In addition poor eyesight makes it difficult to recognise or identify objects as food. As the sense organs atrophy, the sense of smell and taste may diminish (Schiffman & Warwick, 1988) and the hedonic qualities of food probably decrease. Some endocrine and neurotransmitter changes, for example decrease of noradrenaline and neuropeptide Y would lead to hypophagia and weight loss (Morley & Silver, 1988; Silver, 1990). Blundell (1988) suggests that anorexia in the elderly may not be due to a single mechanism malfunctioning but to the neurotransmitter system in general

becoming disregulated. Circulating levels of cholecystokinin (CCK) are raised in the elderly, resulting in early satiety (Glick, 1992).

Psychological causes could account for undereating. Late onset anorexia nervosa might account for some hypophagia (Morley & Silver, 1988). Depression is widespread in dementia; occurring in 63% of dementia patients according to one study (Burns *et al.*, 1990a) and may be responsible for a reduced appetite. In analysing data from the MRC study, a significant association was found between ratings for anhedonia and eating less, although, in some cases, eating less preceded anhedonia (McShane, personal communication).

In the early stages of dementia, if people are living on their own, poor nutrition and undereating may be the result of self-neglect or people may eat inappropriately, inadequately or may forget to eat (Morris & Hope, 1992). Many people with dementia either have poor teeth or, if they need dentures, they are often not tolerated, are mislaid or broken. In later stages, behaviour changes such as increased restlessness, agitation or resistiveness may prevent people from sitting long enough to eat. In addition there are numerous physical conditions (such as concurrent illness) which are associated with older subjects in general (Bowman *et al.*, 1992; Berry, 1992). Eventually, in the final stages of dementia, coordination becomes too poor for self-feeding and finally the person gags or chokes frequently as the swallowing reflex is lost.

HYPERPHAGIA IN DEMENTIA

Hyperphagia is an excessive ingestion of food beyond that needed for basic energy requirement. Although, as discussed above, hyperphagia is not as common as hypophagia it is, nevertheless, a significant behavioural problem in dementia.

It is of clinical importance for several reasons. The increase in weight, which often accompanies hyperphagia, can lead to loss of mobility which may make caring at home impossible (Fairburn & Hope, 1988a). The disappearance of food from larders and fridges can be very inconvenient for carers but it can also be dangerous when, for example, people try to take food, which is being cooked, out of saucepans on the stove. There is a great health risk to people with dementia who scavenge. Carers report people eating the contents of waste bins, food from pets' dishes, soap, shampoo or faeces. Pot or garden plants have been eaten and one person I examined ate a live frog which a child was showing him. In the home, carers have to lock away food and keep constant watch. In a ward or nursing home aggressive episodes often result when people take food from other residents.

In the next chapter I will review the occurrence of hyperphagia in clinical settings other than dementia. I will then discuss theories of the control of eating and, in the final chapter of the introductory section, I will consider the possible causes of hyperphagia in dementia.

Chapter 4 HYPERPHAGIA IN CLINICAL SETTINGS OTHER THAN DEMENTIA

Dementia is not the only clinical setting in which increased eating occurs. Overeating can either be sporadic, as in the binge-eating of bulimia nervosa, or sustained hyperphagia. In this chapter I will review a number of clinical conditions which may be associated with hyperphagia.

BULIMIA NERVOSA

Although not recognised as a separate disorder until the end of the 1970s, bulimia nervosa is the most common eating disorder currently encountered in psychiatric practice (Fairburn, 1993). The DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for bulimia nervosa are:

- A - recurrent episodes of binge eating, characterised by eating definitely more food, in a discrete period of time, than most people in similar circumstances and feeling a lack of control over eating behaviour during the eating binges;
- B - recurrent inappropriate compensatory behaviour is taken to prevent weight gain e.g. self-induced vomiting, misuse of laxatives, diuretics, enemas or other medications, fasting or excessive exercise;

C - the binge-eating and inappropriate compensatory behaviours both occur, on average, at least twice a week for three months.

Periods of overeating or binge-eating are common, for example Healy and colleagues (1985) found that 30% of Irish college students admitted to binge-eating but only a quarter of these reported that they lost control during the binge. Binging is normally resisted by avoiding situations where food is available but when sufferers succumb, they eat on their own and surreptitiously. The greater the self-control, the greater is the fear of losing control. Bulimics may also show an excess of other behaviour such as dependence on chemicals or alcohol (Mitchell *et al.*, 1985). Bulimics often suffer from a low mood, which is worse on binge days, but it may be alleviated as they eat. Food is usually, but not always, eaten quickly and the foods chosen are highly palatable, often described as junk foods, and rich in fat (van der Ster Wallin *et al.*, 1994). Fairburn (1993) states that the distinctive feature is that energy-rich foods are eaten, and they are low in protein rather than being high in carbohydrate, with an average consumption of 3000 kcal (over 12 000 kJ) per episode.

Experiments involving patients with bulimia nervosa suggest that there is an absence of sensory-specific satiety, that is, they do not eat more when a variety of foods is offered than they eat at a single-course meal (Hetherington & Rolls, 1989). The binge continues until one of the following occurs, the food runs out, there is acute discomfort, an interruption occurs or the sufferer falls asleep. Binging is usually followed by self-induced vomiting or laxative abuse.

Typically bulimia affects young women and it is rare in males or older females. Like other eating disorders, bulimia is most frequent in cultures where there is the greatest pressure to be slim (Garner & Garfinkel, 1980). Herman and Mack (1975) found that people who did not deliberately limit their food intake (unrestrained eaters) ate less after a preload milkshake and less still after two. On the other hand, people who constantly restricted their food intake (habitual restrainers), ate more after a preload. This overconsumption or rebound eating could be due to cognitive or physiological factors. If the low, self-imposed, upper boundary is breached, eating may continue in what Herman and Polivy (1984) call the 'What-the-hell effect!'. This counter-regulation after a high energy preload, was confirmed experimentally in people with bulimia by Hetherington and Rolls (1989).

Bulimia nervosa in the elderly

Although bulimia nervosa is typically a disorder of young women, Hsu and Zimmer (1988) believe that eating disorders are becoming more common in the elderly. They report four cases of bulimia (or a mixture of anorexia and bulimia) involving post-menopausal women over the age of 50. Other cases are reported in a review by Cosford and Arnold (1992). Some patients did have a past history of eating disorders or dieting whereas in others there seemed to have been no prior eating difficulties.

Comparison of bulimia nervosa with hyperphagia in dementia

Superficially hyperphagia in dementia shows some similarities to bulimia nervosa, but there are fundamental differences.

a) Similarities with bulimia nervosa (BN)

In both these eating disorders high-energy foods are chosen; binge meals usually have a high percentage of fat and carbohydrate and contain a low proportion of protein foods (see Chapter 10). In BN and hyperphagia very large amounts of food can be eaten at a single sitting, sometimes a meal is only brought to an end by uncomfortable abdominal distension.

b) Differences from bulimia nervosa

In people with dementia who are hyperphagic, there is no concern about weight or shape, attempts to restrict food intake or to exercise self-control. In dementia there is no evidence that subjects try to overcome the fattening effect of food by self-induced vomiting or by using laxatives or diuretics. Although some people who are hyperphagic are excessively active, there is no evidence that the motive in exercising is to prevent weight gain. The majority of people with hyperphagia do not eat quickly and they do not restrict food intake between bouts. Unlike bulimia there is no marked difference in prevalence between the sexes and no history of eating disturbances, dieting, obesity or previous belief that they had a tendency to gain weight. Onset is much later, BN typically presents in the 20s.

In summary the hyperphagia observed in dementia is not associated with the extreme concern about shape and weight which are central to the diagnosis of bulimia nervosa.

PRADER-WILLI SYNDROME (PWS)

This syndrome results from a deletion on chromosome 15 (the 15q11-13 region in the majority of patients), probably causing anatomical abnormality of the hypothalamus, although to date no gross anatomical or microscopic defect has been found in autopsy material (Holland *et al.*, 1993). The features of the syndrome are hypotonia, mental retardation, short stature, obesity, hypogenitalism and hyperphagia. Typically there is neonatal hypotonia and feeding difficulties followed, in early childhood, by both excessive appetite and obesity. Gross obesity starts at 9-15 months and is associated with compulsive eating habits, eating excessively and stealing food. There are characteristic physical changes and usually mild or moderate mental retardation. Obesity is reported in 100% of the patients in all of the large clinical reviews (Zipf & Berntson, 1987).

Twenty-three out of 29 males and 29 out of 32 females were reported to steal food (Clarke *et al.*, 1989). Appetite appears to be insatiable and children will eat all the food that is available, searching for food when it is not. Food intake patterns were compared with weight-matched obese children with no signs of PWS (Holland *et al.*, 1993). Both groups were given chicken-salad sandwich squares which were continuously replaced as they ate. The control subjects usually stopped eating after about 15 minutes, while all but one of the PWS children continued for much longer, eating up to 100 chicken sandwiches in 60 minutes. Most subjects did eventually slow or stop eating but this apparent satiation may have been the result of mechanical factors such as stomach distension. This experiment confirmed a previous study by Zipf and Berntson (1987) which demonstrated the delay in the onset of satiety.

In some studies, obese humans, including PWS subjects (Kyriakides *et al.*, 1980), show appetite suppressant effects of the opioid antagonist naloxone, which are not found in normal weight controls. One explanation is that, as with genetically obese and hyperphagic mice and rats, there are high levels of beta endorphin in the pituitary. Zipf and Berntson were not able to confirm this. Improvement in weight control and behaviour were seen after treatment with fluoxetine, a 5-HT reuptake inhibitor, suggesting that the excessive appetite might be the result of low 5-HT (Dech & Budow, 1991). PWS appears therefore to represent an example of genetic obesity due to failure of satiety.

HYPOTHALAMIC TUMOURS

Hypothalamic tumours and lesions are known to result in hyperphagia associated with marked obesity (Reeves & Plum, 1969; Celesia *et al.*, 1981; Bray, 1984). Tumour in the ventromedial and posterior nuclei resulted in the patient eating continuously with a resultant weight gain (Beal *et al.*, 1981).

KLEINE-LEVIN SYNDROME (also known as Bulimia hypersomnia)

This syndrome is typically seen in male adolescents, who have attacks of somnolence which last days or even weeks. When they are awake, they are usually irritable and restless with a ravenous appetite. They are compulsively polyphagic, eating everything within sight, in particular consuming large amounts of high-carbohydrate sweets if available. The cause is not known but Kleine-Levin syndrome sometimes appears after flu-like symptoms (Lishman, 1987) or traumatic brain damage. It seems

to be the result of lesions of the prefrontal area, the hypothalamus or both (Thompson *et al.*, 1985; Magalini *et al.*, 1990). In one family, autosomal inheritance has been reported. Low levels of dopamine are reported in the periods of hypersomnolence (Chesson *et al.*, 1991).

SANFILIPPO SYNDROME (or Mucopolysaccharidosis III)

Sanfilippo syndrome is a genetically heterogeneous, autosomal recessive disorder which results in an enzyme deficiency. By the age of three, it is characterised by sleep disturbance and by the age of eleven there is explosive aggression, pacing and lack of satiety. Most of the children are hyperactive with poor impulse control (Nidiffer & Kelly, 1983). Children overeat in a way that suggests that they do not satiate normally. Unless their food intake is controlled they become obese (Dennis, personal communication).

FRAGILE X SYNDROME

Fragile X syndrome is an X-linked recessive trait which usually affects boys severely although girls may be more mildly affected. Typically it results in overactivity and boys cannot go for more than 2 hours without food; it is as if they need constant 'refuelling'. They appear to be unselective in their choice of food and eat small amounts at frequent intervals. They seem to need something in their mouth and when food is available they rapidly cram it in. Some of the boys overeat but they do not become obese (Dennis, personal communication), although there is a subphenotype characterised by extreme obesity with a full round face (de Vries *et al.*, 1993).

KLÜVER-BUCY SYNDROME

Klüver and Bucy (1938) described a striking syndrome occurring in monkeys after bilateral temporal lobectomy including the amygdala, uncus, hippocampus and most of the temporal neocortex. People with this syndrome exhibit several marked symptoms including hyperphagia (Pilleri, 1966).

SYMPTOMS OF THE KLÜVER-BUCY SYNDROME

- 1 Visual agnosia
- 2 Hyperorality
- 3 Hypermetamorphosis (as used by Wernicke)
- 4 Loss or diminution of emotions
- 5 Hypersexuality
- 6 Profound changes in dietary habits ("bulimia")

This syndrome is considered in the setting of dementia in Chapter 6.

PARKINSON'S DISEASE

Marked increase in appetite has been seen in people with Parkinson's disease before they start treatment. This may imply a possible role of dopamine in appetite control (Rosenberg *et al.*, 1977).

HEAD INJURY AND BRAIN DAMAGE

There are instances of head injury causing hyperphagia, for example a case is reported by Morris and Hope (1990). Overeating can probably occur as a result of aqueductal stenosis which increases intracranial pressure, expanding the third ventricle and compressing the ventromedial hypothalamus (Krahn & Mitchell, 1984). Egodystonic overeating or compulsive overeating due to a neurological deficit has been reported (Rau & Green, 1975). Some of these cases have abnormal EEGs and

respond to anticonvulsive treatment. Herpes simplex encephalitis has also led to overeating and pica (Hierons *et al.*, 1978; Greenwood *et al.*, 1983). Overeating was found in adults with moderate to severe learning difficulties. Those who were depressed ate excessive quantities, mostly carbohydrate and sweet foods and autistic adults searched for food and ate frequent snacks (O'Brien & Whitehouse, 1990).

Chapter 5 THE CONTROL OF EATING

Humans take in energy in the form of carbohydrates, lipids and proteins. These macronutrients can be regarded as interchangeable sources of metabolic energy. As the food supply is heterogeneous in composition, and uneven in its availability, efficient nutritional homeostasis is necessary. Food intake is controlled by a complex interaction of internal and external signals.

Humans usually maintain a relatively stable set-point for body-weight (Le Magnen, 1983). However, there is a strong defence against undernutrition but only a weak defence against overconsumption, therefore the regulatory system is not symmetrical.

Rhythms of food intake in humans

Babies, fed on demand, initially receive 10-11 meals a day but this gradually decreases to the adult pattern of eating three to four discrete meals, separated by periods of 3-4 hours, during which little or no food is eaten. As a circadian rhythm develops, meals are usually only eaten during the daytime. The daily pattern of meals and snacks often follows a similar, culturally-determined pattern in timing, approximate size and macronutrient content. Humans, having evolved to be omnivorous, show an eating pattern intermediate between intermittent gorging, typical of carnivores, and the herbivores' comparatively continuous feeding pattern.

Annual feeding cycles flatten out when humans have ample food all the year round

and live in artificially heated environments. Long-term increases in food intake compensate for periods of growth and activity. Intake increases during gestation to store food in preparation for lactation and remains high while lactation continues.

INTERNAL CONTROL OF EATING

There are two levels of explanation for the internal control of eating. The first is in terms of mechanisms such as hunger and satiety. The experiments in this thesis are aimed at examining the mechanisms underlying hyperphagia in dementia at this level. The second level of explanation is in terms of the specific physiological and psychological processes which underlie the general mechanisms.

A full understanding requires the integration of both of these levels. In the current state of knowledge such integration is only partly possible. In this chapter I will give an overview of the first level of explanation and review the psychological and physiological processes with reference to the relationships between the two levels of explanation. In Chapter 6, I will speculate on the physiological mechanisms which may underlie hyperphagia in dementia.

Some definitions of factors controlling eating behaviour

Elements controlling food intake have been variously defined and include a combination of physiological and psychological or emotional factors. Blundell has used a 'systems' approach in trying to understand the biopsychological control of eating (Blundell, 1991b; Blundell & Halford, 1994). The key features of this approach are a regulated variable and a receptor sensitive to the variable. This is

bound to be complex for the energy relations of the whole body and depends on signals related to food intake and total energy storage. Listed below are some of the elements involved as defined by Rogers (1990b), Blundell (1991b), Read (1992) and others.

Hunger is the urge to begin eating or the somatic sensations of needing food and is the process which stimulates the onset of eating. It is the psychological expression of physiological change following food deprivation.

Appetite is measured by the amount of food consumed and is the process which directs and guides eating once feeding has begun. It is the product of a complex interaction of internal (physiological) and external (environmental factors). Internal and external stimuli to eat have an additive or synergistic effect. Appetite includes the enjoyment of eating (hedonic qualities), the desire to eat (caloric appetite) and possibly the selective desire to eat certain foods (nutrient specific appetite).

Satiation is the process that brings a period of eating to a halt. The satiating efficiency of a food is its capacity to suppress hunger and inhibit the onset of a further period of eating.

Satiety is the inhibition of hunger and eating that arises as a consequence of food consumption or the feeling of satisfaction as a result of food intake. After the end of one meal there is a period of satiety before hunger stimulates the onset of the next meal.

Palatability is the ingestive response to the hedonic qualities of the food such as its taste, smell or texture. Palatability is partly innate (Steiner, 1979) and partly conditioned as a result of the post-ingestive nutritional effect of a food.

Aversion is the intense dislike of certain foods. This also is partly innate and partly the result of conditioning.

Neophobia, the avoidance of unfamiliar food, is probably innate in humans and has been clearly demonstrated in rats. The initial low consumption of novel foods (one trial and long delay) minimises the danger of eating toxic substances. Any unpleasant sensations which follow prevents its future consumption.

PSYCHOLOGICAL FACTORS CONTROLLING EATING

Hunger and satiety can be powerful sensations which have many physiological causes but, in humans who have a reliable and plentiful food supply, food intake is often influenced as much by psychological factors and social conditioning as by physiological control. Food selection and the order in which foods are eaten may be culturally determined and may not reflect the individual's needs or desires at that moment. Innate hunger and satiety signals can be overridden by deliberate decisions, as in the case of dieting to lose weight.

Appetite and aversion are mainly under psychological control. Appetite may have a physiological basis, as when salty food is craved if the body is salt-deficient, or it may be the result of innate or acquired preferences. Food preference is highly

dependent on affective attitude towards the food for example influenced by religious or regional beliefs.

Palatability may override physiological regulation mechanisms and often overconsumption is encouraged by the habit of eating regular meals, even when they are not necessarily required. Increasing the palatability of familiar foods by adding sweetness or fats increases meal size and frequency. Conversely reducing palatability by adding bitter flavouring reduces meal size and frequency.

Variety effect or sensory specific satiety is observed if a variety of foods is available, i.e. foods with different tastes, textures or appearances stimulate greater intake than a single food (Rolls *et al.*, 1981; Hill & Blundell, 1986). Experiments in humans have demonstrated that when one food is eaten to satiety its relative pleasantness decreases when compared with foods which have not been eaten. As this satiety is dependent on senses rather than macronutrient content it has been called 'sensory-specific satiety'.

When satiated by one food, the presentation of a different, palatable food results in further consumption until gastro-intestinal feedback results in total satiation. This mechanism may have had an evolutionary advantage of ensuring that a wide range of nutrients was consumed but, when food is plentiful, it can lead to overeating and obesity (Rolls *et al.*, 1981).

Emotional factors such as moods and emotions can affect food intake, for example

fear and depression decrease gastric secretion and slow the motility of the stomach. Stress can increase or decrease eating depending on whether the person is lean or obese and also on the type of stress experienced (Levine & Billington, 1991).

PHYSIOLOGICAL CONTROL OF EATING

Hunger, satiation and satiety can be regarded as being under physiological control from internal positive and negative feedback mechanisms. Feedback control has been summarised by Blundell (1991a) in the form of a complex pattern of factors and feedback mechanisms. I will first outline the physiological mechanisms in terms of the control of the initiation, continuation and cessation of eating; then examine the control of food choice and finally summarise the main control mechanisms within the central nervous system.

THE INITIATION, CONTINUATION AND CESSATION OF EATING

1. Initiation of the meal

Initiation of the meal depends on hunger and the palatability of food.

a) Hunger

Lack of food generates the sensation of hunger. Several specific theories have been proposed:

- (i) stimulation of mechano-receptors in the stomach wall by contractions of the empty stomach;
- (ii) reduced availability of glucose detected by glucoreceptors in the GI tract, liver and diencephalon (the glucostatic hypothesis of hunger, Mayer, 1953);

- (iii) low environmental temperatures trigger thermoreceptors in the diencephalon (thermostatic hypothesis, Brobeck, 1948; extended by Glick, 1982);
- (iv) reduction in fat stores, in the long-term triggers food intake (lipostatic hypothesis, Mayer, 1955).

b) Palatability and appetite

Sensory information, is transmitted to the brain, generally resulting in positive feedback for eating (see Chapter 13). The sight and smell of food generate signals to prepare the gastro-intestinal (GI) tract for the ingestion of food, even before it enters the mouth, and can cause insulin release (Louis-Sylvestre & Le Magnen 1980; Le Magnen, 1983). The release is influenced by the perceived palatability of the food. The resulting hypoglycaemia may be one of the trigger signals for eating. Other signals may be plasma levels of fatty acids and amino acids or liver glycogen levels.

2. Continuing eating

Once the meal has started, eating is probably controlled principally by the CNS, through a balance between positive feedback resulting from orosensory stimuli, such as the taste, smell and texture of food in the mouth and negative feedback from sense cells in the GI tract as food accumulates in the gut (Rogers, 1993).

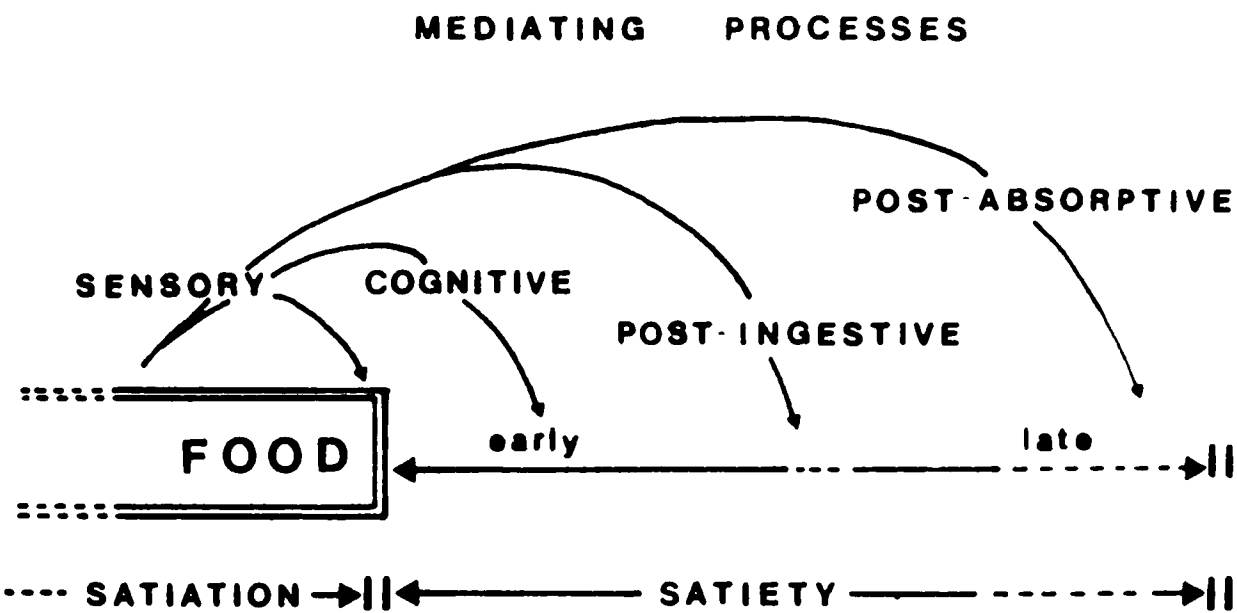
3. Termination of a meal (satiation)

Satiation is brought about by complex interactions where internal changes lead to a decline in the general motivation to eat (figure 5.1).

There are many mechanisms which contribute to the termination of a meal:

a) **Preabsorptive feelings of satiation**, are induced by gastric fullness, GI hormones such as cholecystokinin (CCK), sensory stimuli from the smell and taste of food and from chemoreceptors in the GI tract relayed to the hypothalamus.

Figure 5.1 Components of the satiety cascade (Blundell, 1991b).



(i) **Stomach** - At low volumes food intake is controlled by nutrient-sensitive cells which sense the energy (caloric) content and density of the stomach contents. They are probably exposed progressively as the stomach distends. At the upper limits of the stomach's capacity, mechano-receptors in the wall of the GI tract, sensitive to stretching, limit intake via the vagus nerve.

The ending of a meal is unlikely to be due to restoration of depleted body nutrients because meals end long before absorption has finished. The end of the meal must therefore involve predicting when sufficient food has been ingested, estimated from

both oro-pharyngeal and gastric signals (Deutsch, 1987).

(ii) Intestine - Intestinal receptors can regulate stomach emptying (Rayner, 1992).

Fats decrease the gastric emptying rate and reduce post-prandial glycaemia. Protein and fat stimulate the release of CCK as food enters the duodenum, inhibiting feeding (Blundell & Halford, 1994).

Gastro-intestinal satiation depends on volume or energy density although there is evidence that macronutrient composition affects post-prandial satiety. Stimulation of GI glucoreceptors, osmoreceptors and receptors for tonicity, amino acids, acid and alkali inhibit food intake (negative feedback).

b) Postabsorptive satiety signals, preventing the immediate return of hunger, include the increased concentration of plasma glucose, hormones which regulate carbohydrate and fat metabolism (e.g. insulin and glucagon) and raised body temperature. Liver glucoreceptors and glucose-sensitive neurones of the hypothalamus monitor plasma glucose and reduce food intake when stimulated (Booth, 1972; Oomura, 1988). Appetite may be controlled by the rate of oxidation of glucose and free fatty acids in the liver (Friedman *et al.*, 1986). GI information and post-absorptive signals are interpreted by the brain, in the light of previous experience, effecting the onset of satiety.

In humans, meal intervals are often determined by social factors rather than by hunger but, in 'free-running' conditions, it is the post-meal intervals which are

correlated with the energy value of the previous meal, the size of the next meal is not affected (Le Magnen, 1983). A meal seems to be a store in anticipation of future expenditure.

THE CONTROL OF FOOD CHOICE

Positive feedback during eating depends on the palatability of the food. Humans are preprogrammed genetically to prefer sweet tastes (Steiner, 1979), even if they are non-caloric, as sweetness is usually associated with safe carbohydrate sources of energy. Sour and bitter tastes are usually rejected (Birch, 1987), even when they are non-toxic. This is adaptive as most bitter substances are harmful.

a) Macronutrient choice

Ingestion of the three macronutrients, protein, fat and carbohydrate, are controlled by different mechanisms. In broad terms protein intake is under quite tight control, whereas there is little physiological control of fat intake (Hill & Blundell, 1986; Blundell & Halford, 1994). Fat is highly palatable and energy dense, causing CCK release which affects satiety, but fat's satiating effect during a meal appears to be weak (Rogers, 1990a). There are probably good evolutionary reasons why these levels of physiological control are so different as fat, which has a weak satiating effect, would not be abundant in the hunter-gatherer diet and the short-term benefits of the energy-dense food would outweigh the long-term health risks of obesity.

When humans are given a free choice of food after a high or low protein intake there is an approximate compensation for protein over a 24-hour period. Like other

nutrient-specific appetites, the detection of amino acid content must be due to sensory cues, which are associated with the rapid post-ingestive effects which followed their intake on a previous occasion. When hungry, at the start of the meal there is a relative preference for protein over carbohydrate, whereas, at the end of the meal, carbohydrate is preferred (Hill & Blundell, 1986; Blundell *et al.*, 1987).

b) Micronutrient choice (vitamins and minerals).

Vitamin or mineral micronutrient deficiency can under special circumstances result in a specific appetite, proportional to the deprivation (Rozin, 1976). As micronutrients (apart from common salt) cannot be detected by taste or smell, discrimination must be the result of the conditioning by the sensory cues. These cues are assumed to be associated with foods containing the micronutrient which previously led to recovery from symptoms induced by depletion.

CONTROL BY THE CENTRAL NERVOUS SYSTEM

The central nervous system (CNS) plays an important role in the control of food intake. Since the abnormalities of food intake seen in dementia are likely to be principally due to the damage to the CNS, I will review these changes in some detail. The products of digestion probably act as post-absorptive or metabolic satiety signals through binding to brain chemoreceptors.

Since the early work of Hetherington & Ranson (1940) the hypothalamus has been regarded as an important centre for the control of feeding. For many years the 'dual-centre' hypothesis held sway (Anand & Brobeck, 1951). This was based on evidence

that bilateral lesions to the lateral hypothalamus (LH) resulted in reduced eating and weight loss whereas lesions to the ventro-medial hypothalamus (VMH) resulted in overeating and obesity (Waldbillig *et al.*, 1981). Conversely, stimulation of the LH led to increased eating and stimulation of the VMH decreased eating.

The dual centre hypothesis in its simple form therefore proposed that the LH controlled the onset and continuation of eating and the VMH controlled satiety. However, this hypothesis is probably too simple. Further studies (Rolls, 1981) showed that the reduced eating which had been observed following lesions to the LH were at least partly due to damage to the nearby nigrostriatal bundle, preventing correct orientation to sensory stimuli, needed to coordinate feeding and drinking. The hypothalamus however seems to be an important 'crossroads' in the complex neurocircuits controlling eating behaviour (Sclafani & Kirchgeßner, 1986).

Furthermore there is evidence that the different neurotransmitter systems within the same hypothalamic area have different effects. For example noradrenaline (NA) and 5-HT probably act antagonistically in the PVN, NA facilitates feeding and 5-HT inhibits it (Blundell, 1977; Hoebel *et al.*, 1989).

The control of the satiety centre's activity probably involves glucose-sensitive neurones, called glucostats (Mayer, 1953). When blood sugar is low the activity of the satiety centre 'glucostats' decreases and therefore they do not inhibit the feeding centre and the result is hunger. High glucose levels cause glucostats to inhibit the feeding centre (Campfield *et al.*, 1985).

Lesions to the temporal lobe or amygdala result in Klüver-Bucy syndrome (see Chapter 4) with increased orality and the ingestion of noxious substances or novel foods. The limbic system is concerned with appetite regulation and amygdala lesions cause moderate hyperphagia. The overeating observed following lesions to the amygdala is different from that following lesions to the VMH (Rolls, 1986). Amygdaloid lesions, at least in rats, leads to them becoming omniphagic, eating tainted, novel or adulterated foods. The amygdala is apparently needed in order to learn what constitutes food. VMH damage leads to hyperphagia and obesity, usually until a new, higher set-point for body weight is established.

NEUROTRANSMITTERS AND THE CONTROL OF FOOD INTAKE

The neural control of food intake can be considered not only in terms of anatomical sites but also in terms of the neurotransmitters involved. The transmitter systems which are particularly involved are noradrenaline, 5-HT, dopamine, neuropeptide Y and galanin (Leibowitz, 1990).

Catecholamines

Stimulation of CNS catecholamines (noradrenaline and dopamine), for example by amphetamines, decreases protein consumption, increases the latency before eating starts, increases local eating rate (i.e. rate within an eating bout) and decreases subjective feelings of hunger (Rogers & Blundell, 1979). The eating rate overall is unaltered but the duration of the meal decreases (McGuirk *et al.*, 1991). If catecholamines are depleted, the latency before eating starts is reduced but meals are longer.

Noradrenaline (norepinephrine), possibly mediated by receptors of the PVN, is probably responsible for the preference, shown by rats, for food rich in carbohydrate during the first meal of the active period (Leibowitz, 1985). This mechanism helps to restore depleted glucose levels. Noradrenaline does not seem to change fat intake but may suppress protein intake.

Dopamine appears to inhibit intake of fat and protein but carbohydrate intake is unaffected.

5-Hydroxytryptamine - (5-HT or serotonin)

Blundell (1984) summarised the research data and suggested that 5-HT (a) plays an inhibitory role in feeding and is selectively involved in satiation (Blundell, 1977); (b) contributes to circadian rhythm of satiety control; (c) may modulate other systems regulating body weight; (d) interacts reciprocally with dopamine in the control of ingestive behaviour; (e) regulates the intake of protein and (f) controls the relative proportions of protein and carbohydrate, selectively suppressing carbohydrate intake.

The synthesis of 5-HT is regulated by the supply of its precursor tryptophan across the blood-brain barrier. Transport is in turn dependent on the ratio of plasma tryptophan to large neutral amino acids (Wurtman, 1978; 1983). Although brain synthesis depends on tryptophan from the diet there is a strong defence to protect the brain from tryptophan deficiency and 5-HT synthesis may not be affected under normal conditions (Teff *et al.*, 1989). Blundell and Hill (1987a; 1987b) found that tryptophan affected carbohydrate intake and tryptophan depletion experiments

decreased protein intake in normal men (Young *et al.*, 1988).

5-HT reacts with at least four main families of receptor, each with many subtypes, and each has a different regulatory effect on behaviour (Cowen, 1991). From drug studies it seems that the action of 5-HT, when mediated by 5-HT_{1B}, 5-HT_{1C} and 5-HT₂ receptors, decreases eating, reduces carbohydrate intake and brings forward the onset of satiation. Stimulation of the 5-HT_{1A} autoreceptors increases feeding by inhibiting the release of 5-HT (Leibowitz, 1990). A peak of 5-HT production at the beginning of the active cycle (night in rats and daytime in humans) preferentially reduces carbohydrate intake because the onset of satiety curtails the carbohydrate-rich first meal of the active cycle. 5-HT seems therefore to act antagonistically to noradrenaline, inhibiting NA induced feeding. This mechanism may be responsible for switching to a preference for protein at the next meal.

Other neurotransmitters

Neuropeptide Y (NPY) is a potent, centrally acting appetite stimulating agent which is thought to regulate eating behaviour and body weight (Leibowitz, 1989). Like noradrenaline it stimulates carbohydrate consumption especially at the beginning of the active period or after food deprivation. In rats NPY increases the rate and duration of eating and there is some evidence that increased levels of NPY induce binge behaviour in people with bulimia (Leibowitz, 1989).

In the short term, **galanin** stimulates carbohydrate intake and gluconeogenesis at the beginning of the active period. In the long-term it stimulates fat intake (Leibowitz,

1989).

Opioids in the brain are thought to be involved in registering the hedonic qualities of food and learning, associated with recovery from hunger or illness. At least in infants (rat and human), feeding is calming, raising the pain threshold and reducing distress (Blass, 1991). The preference for high-fat and sweet foods in adults when stressed may stimulate the production of opioids.

CONTROL BY THE ENDOCRINE SYSTEM

Several hormones are involved in the control of feeding. Insulin is released in response to the sight of food and is possibly a satiety hormone. Stimulation of chemosensors in the duodenum also may be responsible, via a vagal reflex, for the peak of insulin release between the pre- and post-absorptive phases. This peak may be the final step in satiation. Corticosterone and insulin act synergistically with central neurotransmitters and peak at the start of the active cycle.

Cholecystokinin (CCK) is secreted when nutrients, in particular the products of protein and fat digestion, enter the duodenum. CCK reduces the appetite and decreases food intake. It inhibits gastric emptying so hastening satiety as the stomach fills (Liddle *et al.*, 1985; McHugh & Moran, 1986).

Enterostatin seems to regulate the craving for fat. Somatostatin, known to be reduced in dementia, inhibits food intake in rats and baboons and inhibits most GI hormones (Lotter *et al.*, 1981). Gastrin slows stomach emptying but does not affect voluntary

food intake whereas bombesin causes eating to stop sooner but does not affect gastric emptying. Adrenalin, increases during feeding and may act as a satiety signal. Calcitonin and glucagon depress feeding. Satiety, vasopressin, adipocytic satiety factor, secretin and gastric inhibitory polypeptide are also thought to play roles in the control of eating.

SUMMARY

The size and composition of the meal is determined by a complex network of neural, humoral and environmental factors (Blundell, 1991a). A number of mechanisms are involved, no one mechanism is indispensable but together they provide maximum adaptive value. By this complex, interconnected mesh of positive and negative feedback mechanisms, food intake is regulated to compensate for changing nutritional requirements so that macronutrient supply and body-weight are kept remarkably stable in normal individuals.

Chapter 6 POSSIBLE CAUSES OF HYPERPHAGIA IN DEMENTIA

Eating changes in dementia are of scientific interest, because they raise both the issue of what the abnormalities are, in the control of eating, and what the mechanisms are. The causes may be biological or psychological in origin, or a mixture of both, and the changes may be a 'marker' of a particular pathology (Fairburn & Hope, 1988a; 1988b). Many mechanisms may contribute to hyperphagia in dementia and brain damage, due to dementia, is likely to be a major cause. In this chapter I will briefly review evidence that some of the mechanisms controlling feeding, reviewed in the previous chapter, are damaged in Alzheimer's disease.

BRAIN DAMAGE

The various CNS systems which control eating were discussed in the last chapter. There is evidence that in Alzheimer's disease (the most common cause of dementia) several of these systems are damaged.

a) Hypothalamic damage

The polarisation of the eating disorders found in dementia into hyperphagia or hypophagia, may indicate which areas of the hypothalamus happen to be most severely affected. Loss of cell function in the ventro-medial hypothalamus, with a consequent loss of serotonergic cells, may lead to hyperphagia whereas damage to the lateral hypothalamus may result in hypophagia. There is no specific evidence on this

point but hypothalamic damage is well-described in Alzheimer's disease (Ishii, 1966), furthermore the amygdala is severely affected in AD (Hirano & Zimmerman, 1962; Herzog & Kemper, 1980).

b) Temporal lobe damage

In AD the temporal lobes are one of the cortical areas most severely affected with neurofibrillary tangles and plaques. The Klüver-Bucy syndrome, which includes hyperphagia as one of its features, is associated with temporal lobe damage. Sourander and Sjögren (1970), looked for the six symptoms (listed in Chapter 4) of the Klüver-Bucy syndrome in neuro-psychiatric patients; particularly in patients with Alzheimer's disease and related disorders. Apart from hypersexuality all the symptoms were frequent in the 60 cases of Alzheimer's disease who were examined. Forty-seven of the 60 patients showed hyper- and heterophagia and the changes in dietary habits consisted of a strong inclination to eat voraciously - not only food but all sorts of objects such as gauze bandages, flowers and matchboxes. They found that morphologically, the temporal lobes of all their patients showing a pronounced Klüver-Bucy syndrome, were severely affected. There are other reports of symptoms of the Klüver-Bucy syndrome in AD (Jelgersma, 1964; Pilleri, 1966) but Fairburn and Hope (1988b) found little evidence of features of Klüver-Bucy syndrome, other than overeating, in people with dementia who were hyperphagic. The apparent discrepancy may be in the very different cohorts of patients. Sourander and Sjögren studied patients with long-standing dementia, who were living in a long-stay hospital ward. Fairburn and Hope's subjects, although suffering from moderate and severe dementia, were still mostly living in the community.

NEUROTRANSMITTER CHANGES

Many of the changes in eating behaviour are likely to be due to impairment of the various neurotransmitter systems of the brain, as progressively more cells are lost or damaged during the course of dementia. Many neurotransmitters, including catecholamines, acetylcholine and 5-HT, and their associated enzymes and receptors are reported to be reduced in dementia (for example see Hardy *et al.*, 1985; Palmer *et al.*, 1988, McDonald *et al.*, 1991).

a) Acetylcholine

Acetylcholine (known to be involved in memory function) together with choline acetyltransferase and acetylcholinesterase, are greatly reduced in AD (Hardy *et al.*, 1985). Some of the changes in meal pattern have been attributed to lack of short-term memory in AD, which is widely believed to be the result of neuronal loss in the acetylcholine system of the brain. However, as has been argued (Fairburn and Hope, 1988b), memory loss is unlikely to account for the marked hyperphagia which is the subject of this thesis.

b) Noradrenaline

Noradrenaline (and probably neuropeptide Y) is significantly reduced in AD, possibly leading to anorexia (Morley & Silver, 1988). Noradrenaline loss in dementia is particularly severe in the hypothalamus (Hardy *et al.*, 1985) and there is some evidence that depletion of noradrenaline in the lateral hypothalamus, resulting from damage to the ventral noradrenergic bundle, causes hyperphagia and weight gain (Hoebel *et al.* 1989) as well as dysregulation of the normal circadian rhythm of

carbohydrate and protein intake (Leibowitz, 1988; 1990).

c) 5-HT (serotonin)

A diminished serotonergic system leads to changes in choice of foods and control of intake (see Chapter 5). After depletion of 5-HT, using a selective neurotoxin, long-lasting and stable hyperphagia was shown by rats fed a high-fat diet. This led to increased adiposity (Waldbillig *et al.*, 1981). In dementia, 5-HT and its metabolite 5-HIAA are reduced in many parts of the brain including the hypothalamus and cortex, especially in the frontal areas (Hardy *et al.*, 1985; Nazerali, 1992). This reduction may relate to several behavioural changes, including overeating. Carbohydrate foods are postulated to increase the availability of the 5-HT precursor, tryptophan, for transport across the blood-brain barrier. Fenfluramine was used to stimulate the brain 5-HT system, in 12 subjects with probable AD (Cooper & Mungas, 1992). The results suggested that sweet-food craving might be due to chronic understimulation of the 5-HT receptors, which have consequently been up-regulated to compensate for the damage to the 5-HT system.

d) Somatostatin

Somatostatin is a neurotransmitter which is known to suppress feeding. A reduction in somatostatin is consistently found in AD and has been correlated with the severity of the disease (Hardy, *et al.*, 1985).

PSYCHOLOGICAL CAUSES

In people who are not demented, overeating can be the result of psychological causes; this raises the question of whether such causes could make a significant contribution to hyperphagia in dementia. I will consider the possible contribution of bulimia nervosa and of anxiety.

a) Binge eating

Binge eating is seen in the psychiatric illness bulimia nervosa (see Chapter 4). Although bulimia nervosa is normally diagnosed in young women, there have been reports of it developing in older people (Hsu & Zimmer, 1988). Could hyperphagia in dementia be a form of bulimia nervosa? This will be discussed further in Chapter 11, where I will argue that the beliefs and characteristics of bulimia nervosa - the extreme concern over shape and weight - are absent in dementia and that the resemblance between bulimia nervosa and hyperphagia in dementia is superficial.

b) Agitation, stress and depression

Stress can cause hyperphagia in animal models (Stricker, 1978). In normal people, stress may cause overeating especially in the elderly (Meyer & Pudal, 1972) and may lead to hyperphagia in 11% of people (Meyer *et al.*, 1980). Depression and boredom (inactive stress) can also increase appetite. Boredom was reported to increase appetite in 27.5% of people. In Levine and Billington's review (1991) even higher percentages of people are reported to eat more when stressed; 46% of those eating more had a preference for sweet food.

Cognitive impairment can be very stressful as the environment may seem unfamiliar, carers cannot be recognised and people do not know where they belong or what is happening to them. Agitation increases in the middle stage of dementia raising energy requirements (Rheame *et al.*, 1987) but, in spite of the greater intake, people with dementia may still stay thin. Many people, particularly in the earlier stages of dementia, show various symptoms of stress and depression. In dementia, overeating, especially if it involves eating sweet, highly palatable foods, may have a calming effect, perhaps mediated by endogenous opioids or increased 5-HT production following a high carbohydrate, low-protein diet. Although stress may account for some increase in eating, it seems unlikely to account for the marked hyperphagia described in this thesis.

OTHER POSSIBLE CAUSES

The results of some of the experiments reported in this thesis suggest that the mechanisms controlling satiation and satiety are damaged. Since the CNS is a major site for these control mechanisms, the most likely cause of such dysfunction is brain damage and brain damage is extensive in Alzheimer's disease, presumably being the main cause of the cognitive impairment. However, it is possible that in AD there is also damage to some of the mechanisms controlling eating which are outside the CNS. This would be an interesting area for further study. In Chapter 5, some of these mechanisms were discussed, such as feedback mechanisms involving GI tract receptors and hormones such as CCK. Nothing is known of the effects of dementia on these mechanisms but there is evidence that complex homeostatic mechanisms are likely to become less responsive with age. If dementia is an extreme form of ageing,

hyperphagia may occur in people whose homeostatic control of eating is dysfunctional, in particular the mechanisms controlling satiation and satiety. These hypotheses are examined in Chapters 9, 11 and 12 of this thesis.

There are several other factors which have not been discussed previously in this introduction and which might contribute to hyperphagia. These are discussed briefly below.

a) Malabsorption

There is some evidence to suggest that malabsorption of food may be found in AD (Abalan, 1984). This could, in theory, result in compensatory hyperphagia. However, Singh *et al.* (1988) did not find malabsorption in AD. They demonstrated that although AD patients on average weighed 21% less than non-demented controls in hospitals and 14% less than vascular dementia patients, the weight loss, found in AD, was not caused by malabsorption or by any obvious deficit in food intake.

There is also some evidence that tryptophan malabsorption occurs in dementia (Lehman, 1979; Lehman *et al.*, 1981). The brain is usually well-protected against tryptophan deficiency but if there is malabsorption, combined with low-protein meals, this could affect 5-HT synthesis.

Whether or not malabsorption occurs in some people with hyperphagia it seems unlikely that this is the main mechanism for hyperphagia because those who are hyperphagic normally put on weight, to more than their premorbid level (Hope *et al.*,

1989; Morris *et al.*, 1989). The hyperphagia, therefore, does not appear to be a response to malabsorption.

b) Sensory deficits

(i) Sense of smell and taste (Cephalic senses) - Many senses are blunted in old age and this is often more extreme in dementia (Esiri & Wilcock, 1984). The sense of smell is often impaired at an early stage in dementia. In normal people the stimuli from taste and smell contribute to the feeling of satisfaction (satiation) on eating. People who lose their sense of smell or taste may need to monitor their food intake consciously to avoid overeating but people with dementia are unlikely to be aware that they are eating too much.

A marked preference for sweet foods in dementia might be because, with a deficient sense of smell, food is only sensed by the tongue receptors (these mainly detect sweet, salt, sour and bitter tastes). Increased consumption of sweet foods might encourage overeating as sweetness is known to stimulate food intake (Rogers & Blundell, 1989a; 1989b). Sweet foods are usually rich in carbohydrate, and are often high in fat, which might also contribute to overeating as carbohydrate and fat are less satiating than protein (Blundell *et al.*, 1987). Eating, especially sweet foods, may be a source of pleasant sensory stimulation in conditions of deprivation. A decreased ability to taste or smell could explain the indiscriminate intake of noxious substances frequently observed in dementia.

(ii) **Gastro-intestinal sense cells** - Although in humans many other factors are involved, satiety can be regarded as being a conditioned reflex (Stunkard, 1975; Booth, 1977). Even if there is no memory of how much food has been eaten previously, internal cues of incipient satiety might still be expected to determine future intake if such reflexes are still intact. If receptors in the GI tract are affected by dementia, damage to the cells, which monitor such things as gastric distension, energy density and metabolite concentration of the food in the GI tract, could explain increase in food intake, change in macronutrient choice, inability to compensate for previous food intake and lack of discrimination.

c) Drugs

Some drugs cause weight gain. These include neuroleptics, tricyclic antidepressants and lithium carbonate (Silverstone, 1985). These are commonly prescribed in dementia. Tricyclic antidepressants have the side effect of creating a craving for sweet foods. Stein *et al.* (1985) found that tricyclics caused increased appetite in 38% of elderly patients, a craving for sweet foods in 34%, and 48% showed one or both changes. The question of whether drugs are associated with hyperphagia is examined in Chapters 8 and 15. The conclusion is that they are not. In any case, the reported effect of drugs on food intake is much less than would account for much of the hyperphagia seen in dementia.

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d) Cognitive deficiencies

(i) Loss of memory - It is evident that sufferers from dementia forget that they have eaten. Carers often account for the consumption of repeated meals, and hyperphagia, by forgetfulness (Fairburn & Hope, 1988b). However, this is not an adequate explanation of the hyperphagia seen in dementia, for two reasons. First, even if people have forgotten that they have just eaten, the mechanisms controlling food intake (e.g. mechanisms controlling hunger and satiety) should prevent further food consumption, and secondly, many people with dementia, who are unable to remember that they have just eaten, do not continue to eat.

(ii) Misinterpreting body signals - There is a possibility that people with dementia have a problem interpreting body signals and identifying the sensations leading to satiety (Norberg & Athlin, 1989). This happens in some other eating disorders where sensations such as pain, discomfort or emotional tension are interpreted as hunger (Bruch, 1974). Although this is unlikely to be the cause of excessive intake of food during test meals, it could account for frequent requests for food or for constant snacking.

(iii) Loss of social inhibition - Mild cases of hyperphagia may be due to loss of social inhibition. People with dementia are usually no longer concerned with fear of putting on weight or of other people's disapproval of overeating or 'greediness'. This might account for people finishing off boxes of chocolates or packets of biscuits but it is unlikely to account for the marked cases of hyperphagia.

(iv) Loss of self-restraint in former dieters - Many people consciously limit their food intake to avoid putting on weight. If people who previously restricted their food intake lose their self-restraint, as the dementia progresses, they may persistently overeat. This would apply particularly to former chronic dieters who, forgetting or losing their former self-control as dementia progresses, increase their food intake with an accompanying gain in weight. Hope and colleagues considered this explanation. In the people they studied, with hyperphagia, none had been 'dieters' prior to the onset of dementia (Hope *et al.*, 1989; Morris *et al.*, 1989). This has been confirmed by this present research.

e) Secondary to change in activity

A high proportion of people with dementia become more active for many different reasons (Hope & Fairburn, 1990), consequently some of the increase in food intake could be compensating for hyperactivity. Rheaume and colleagues (1987) gave three overactive patients and three controls, whose activity was normal, a standardised diet. From pedometer readings it was calculated that energy expenditure of walking, for the group who paced excessively, required an estimated extra 1600 kcals (6700 kJ) a day to keep their weight constant. However, most people with hyperphagia are not hyperactive, and some who are hyperactive still put on weight. Although there is a sub-group in whom hyperphagia might be a compensatory response to energy output through hyperactivity, this does not account for the majority of people who are hyperphagic.

f) Hypermetabolic state

Wolf-Klein *et al.* (1992) suggest that there may be a hypermetabolic state in AD. They reported that 92% of patients with AD lost weight in the course of a year whereas 57% of normal controls had gained weight. There was also a frequent and highly significant craving for sweet food in the Alzheimer group, who had often been described as 'cookie monsters' although they had lost weight. The reported loss of weight may be the result of lack of access to food, and reliance on carers to select and provide food, but the authors also suggested that the increased carbohydrate intake may be linked to altered cellular glucose metabolism (Blass & Zemcov, 1984; Sims *et al.*, 1987). Although hyperphagia might be a method of compensating for increase in metabolic rate or for increased activity, Prentice *et al.* (1989) found no evidence of hypermetabolism or hyperactivity to account for the acute weight loss in elderly mental patients, including those with dementia. Their average daily intake was 6.3 MJ a day and their expenditure was only 6.1 MJ a day. As with the explanation that hyperphagia might be secondary to overactivity, hypermetabolism as an explanation would expect a link between hyperphagia and loss of weight, whereas many of those with hyperphagia gain weight.

g) Loss of circadian rhythm

Circadian rhythms often become disrupted in dementia, resulting in a loss of the normal pattern of sleep and wakefulness (Prinz *et al.*, 1982; Prinz & Vitiello, 1993; Bliwise, 1993; MRC study, unpublished data). Disturbance of the circadian rhythm could disrupt the normal adult pattern of three or four main, daytime meals, each followed by several hours of satiety. When people ask or search for food between

meals or at night, it could be the result of losing the normal rhythm and might give the impression of the constant hunger, which is frequently reported by carers. However, this explanation would not account for the excessive size of meals eaten by people who are hyperphagic.

h) Stereotypy

There are many examples of stereotyped behaviour in people with dementia. It could be argued that overeating is a form of stereotyped behaviour in which eating is the pattern of behaviour which is repeated. This possibility is examined in detail in Chapter 14.

CONCLUSION

Many mechanisms, both physiological and psychological might contribute to the hyperphagia observed in dementia. However, the marked hyperphagia, often accompanied by weight gain, would seem most likely to be due to brain damage, which is the central cause of dementia itself. This brain damage can be fruitfully considered both in terms of anatomical site and the neurotransmitter affected.

SECTION 2 EXPERIMENTAL SECTION

THE AIMS OF THE STUDY

Hyperphagia in dementia is a clinically significant behaviour problem in Alzheimer's disease. It is also a remarkable phenomenon as it appears to be one of the most marked examples, in humans, of damage to mechanisms which control food intake. Animal studies, and work with healthy human volunteers, have provided considerable information both on the mechanisms which control the intake of food and some experimental paradigms. Up to now the phenomenon of hyperphagia in dementia has only been the subject of anecdotal reports. The central purpose of the research reported here is to examine the phenomenon in detail, using experimental methods.

The specific aims of the study are:

1. to characterise in detail the nature of this overeating;
2. to develop standardised methods for defining and measuring overeating;
3. to investigate some possible mechanisms to account for the overeating;
4. to investigate the natural history of hyperphagia in dementia.

Chapter 7 THE RANGE AND PREVALENCE OF ABNORMAL EATING IN DEMENTIA

Although many studies have noted changes in eating behaviour and the problems these can pose for carers, little is known about how common eating problems are, or about their natural history. The most detailed information about these issues has been collected during the course of the long-term study into behaviour changes in dementia funded by the Medical Research Council (MRC study), which was mentioned briefly in Chapter 3.

I worked on this study as a research assistant for the first 4½ years. In this chapter I will present data, from the MRC study, on abnormal eating in general, and hyperphagia in particular. Together with one other research assistant I have carried out the analyses presented. However, in contrast with work presented elsewhere in the experimental section, I did not initiate and design the study itself. This was done by my supervisor, Tony Hope, and Chris Fairburn.

MEDICAL RESEARCH COUNCIL (MRC) LONGITUDINAL STUDY

In 1988-89 a cohort of 104 elderly people with dementia were recruited through general practitioners or hospital-based old age psychiatry teams.

The entry criteria were:

1. Diagnosis of dementia (using DSM-III criteria) confirmed by history and examination.

2. Living at home, with a carer capable of giving a clear account of the day-to-day behaviour.

Exclusion criteria were:

1. Evidence (from history, examination and investigations) of a cause for dementia other than AD or vascular dementia.
2. History of alcohol intake greater than 30 units a week, for more than two years, at any stage in the past.
3. The carer did not appear to be able to give an accurate account of the day-to-day behaviour of the subject.

Potential subjects were assessed using the CAMDEX interview (Roth *et al.*, 1986), described on page 72, and were given a full dementia screen. The mean Mini-Mental State Examination (Folstein *et al.*, 1975) score, at the point of entry, was 14.9 (S.D. 7.1; range 0-28; median 15). The Mini-Mental State Examination involves asking the subject a number of questions which test memory, orientation in time and place and other intellectual abilities. The maximum score is 30. Most normal people score 30. A score of less than 25 strongly suggests brain damage.

The clinical diagnosis of AD and/or vascular dementia was supported with data from a CT scan in the majority of cases. There were 55 men and 49 women in the cohort with a mean age of 77.6 (S.D. 6.97, range 60-95) at the time of entry into the study. Since recruitment, each subject and carer have been followed up at four-monthly intervals using the following instruments:

1. The Present Behaviour Examination (PBE)

This is a semi-structured interview with the carer (Hope & Fairburn, 1992). It covers the period of the previous four weeks. Ratings are made of a wide range of abnormal types of behaviour. There are 121 main questions and a further 66 'nested' questions i.e. questions which are only relevant if a specific main question is answered positively.

2. Cognitive tests on the subjects themselves

- a) **MRC memory tests** - The Medical Research Council's Alzheimer's Disease Workshop, 1987, produced a series of questions to test different aspects of memory and cognitive function. The test incorporates questions from the Mini-Mental State Examination (MMSE), CAMDEX and Geriatric Mental State (Copeland *et al.*, 1976).
- b) **The Rivermead Behavioural Memory Test** - This battery of tests, originally devised for people recovering from stroke or head injury, consists of more practically based memory tests.
- c) **The National Adult Reading Test (NART)** - This is designed to estimate premorbid IQ, based on the subject's ability to pronounce correctly words with unusual spellings, e.g. ache and simile (Nelson & O'Connell, 1978). This was given once a year.

3. Past Behaviour History Interview (PBHI)

This interview, based on the PBE, was used once only with each carer, soon after the first PBE. It covered a similar range of questions about behaviour to the PBE but referred to any change in behaviour which had occurred from the time the first symptoms of dementia were noticed until the time of the interview.

4. Cambridge Mental Disorders of the Elderly Examination (CAMDEX) Interview

CAMDEX was used once, at the initial screening interview, together with a physical examination, to obtain the best clinical diagnosis. The interview includes an extensive cognitive assessment of the subject (CAMCOG) and an interview with the carer to obtain the history of the onset of dementia, past medical history (such as head injury, drink- or drug-related problems and other information which might indicate the probable cause of the dementia), an assessment of current behaviour and relevant family history.

The PBE, MRC and Rivermead tests were repeated at four-monthly intervals, in some cases for more than six years, to track the course of any behaviour changes. Six people withdrew during the course of the study and thirteen are still alive and in the study. Of those who have died, 55 have come to post-mortem. This has provided histological diagnoses and also biochemical analyses are being carried out to correlate brain pathology with behaviour.

One section of the PBE is concerned with abnormal eating behaviour, including hypophagia and hyperphagia, changes in food choice and changes in drinking behaviour.

CHANGES IN EATING BEHAVIOUR

1. Point-of-entry data (Eating behaviour noted by carer in last four weeks)

The information from the first PBE gave the prevalence, in this particular cohort of 104 subjects, of different types of eating behaviour during a period of four weeks immediately preceding the interview.

Table 7.1 gives the percentage of the total sample who rated positively (i.e. the behaviour was observed by the carer at least once in the preceding month) at each subject's point of entry into the study. This therefore gives point prevalence for a sample consisting mainly of people in the early to middle stages of dementia.

As a source of epidemiological data this sample is not ideal as it was not a random sample from the population. Subjects were recruited from people with dementia, known to the medical services and living at home with a carer. It is not clear, however, what systematic biases are likely. Possibly carers are more likely to have consulted a doctor if there have been behavioural problems, therefore the eating disorders might be over-represented in this group. By the time the medical services are consulted, dementia is usually apparent, so this sample does not include the very early stages or the very late stages when carers can no longer cope at home.

Table 7.1 Eating changes reported at point-of-entry PBE (n = 104)

INCREASED EATING AND EVIDENCE OF WANTING MORE FOOD	
Eating more than premorbidly	13%
Eating at least 50% more than premorbidly	3%
Eating more sweet food if given the chance	24%
Eating more non-sweet food if given the chance	15%
Asking for more food	7%
Carer restricts food as response to overeating	10%
Eating food between meals (apart from a routine snack)	11%
EVIDENCE OF EATING LESS FOOD	
Eating less than premorbidly	40%
CHANGE IN FOOD CHOICE	
Food choice changed from premorbidly	33%
More sweet or carbohydrate foods chosen	13%
Less savoury food chosen	5%
More savoury or strongly flavoured food preferred	7%
Loss of discrimination or will eat anything	5%
OTHER CHANGES IN EATING BEHAVIOUR	
Putting food in inappropriate places	16%
Pica - eating inedible substances	3%
- eating inappropriate substances	3%
Oral behaviour	1%

2. Longitudinal data

Longitudinal data were collected to find at what stage in dementia the behaviour changes started, how long they persisted and their outcome. There were two sources of this information. The first source of information came from the serial PBEs which gave a one-month sample every four months from the point of entry onwards until the person died. The number of interviews varied (see table 7.2) from those who received a single PBE (7%) to those who have been followed-up for more than five years (19%).

Table 7.2 Numbers of PBEs per subject

Number of PBEs	Number of subjects (n =104)
1	7
2	8
3	6
4	5
5	5
6	4
7	5
8	12
9	4
10	7
11	7
12	5
13	3
14	5
15	3
16	0
17	6
18	5
19	5
20	1
21	1

The second source of information was from the PBHI which gave information about behaviour changes since the onset of the disease. The data given below are based on these two sources of information.

PREVALENCE OF EATING CHANGES OVER THE COURSE OF DEMENTIA

To give the best estimate of prevalence over the entire dementing process these figures exclude the 13 people who are still alive and the six people who withdrew during the course of the study as there is no information of changes in the late stages of dementia.

Prevalence of eating more

Analysis of the PBHI and all the PBEs shows that, of the 85 subjects followed through the whole course of dementia until death, 28 (33%) ate more at some stage in their illness (see table 7.3). Of the 28 rated as eating more, 7 (8%) were said to eat at least 150% of their premorbid intake. If sweet food was accessible, at least 20 (24%) would continue to eat until it was finished and 9 (11%) were reported to continue eating any non-sweet food available until there was no more left.

Carers of 22 (26%) subjects took active steps to limit food intake by hiding sweets and biscuits and restricting food at mealtimes.

Table 7.3 Prevalence, over entire course of dementia, of eating more food

Summary of items	Total (n=85)	%
Eating more than premorbidly	28	33%
Eating between meals (apart from a routine snack)	23	27%
Eating more non-sweet food when given the chance	23	27%
Eating more sweet food when given the chance	46	54%

Prevalence of wanting more food

Although some subjects were not able to express themselves verbally and some were immobile, 28 (33%) had shown they wanted more food either by searching or asking for more food (see table 7.4).

Table 7.4 Prevalence, over entire course of dementia, of wanting more food

Summary of items	Total	%
Evidence that would eat more if not restricted	22	26
Evidence of wanting more food by asking or searching	28	33

Prevalence of change in food choice

A preference for sweet foods was shown by 47 (55%) although 21 (25%) had always enjoyed sweet foods. Another 4 were prevented from eating sugary foods because of diabetes. Thirteen (15%) subjects became less discriminating and would eat anything including foods they used to dislike (see table 7.5).

Table 7.5 Prevalence, over entire course of dementia, of change in food choice

Food choice changed from premorbidly	67%
Changes included:-	
More sweet or carbohydrate foods chosen	31%
More savoury or strongly flavoured food preferred	5%
Loss of discrimination or will eat anything	15%
Other change in choice	2%
4 had sweet food limited for health reasons (diabetes)	

Prevalence of eating less

At some stage during the course of dementia, 64 (75%) people were reported to have eaten less than they did premorbidly, with 41 (48%) of them eating two-thirds or less than prior to memory problems. Some people showed fluctuating appetite with 17 eating more than premorbidly at one stage and less at another. In 15 of these 17 (88%) overeating was followed by undereating, in the later stages of dementia.

Other eating changes

Thirteen people ate inappropriate foods, either eating inappropriately large amounts of foods such as mint sauce, horseradish sauce, marmalade or cream, or eating unsuitable foods such as pet food, potato peelings, raw meat or uncooked rice. It is unclear whether this behaviour is the result of hunger, confusion or mis-identification. Nineteen (22%) people put things which were not food into their mouth and chewed

or swallowed them. They frequently tried to eat anything small which came to hand such as paper tissues, table mats, soap or plants. ‘Oral behaviour’ such as feeling things with the mouth (as seen in the Klüver-Bucy syndrome), was reported in 13 (15%).

Carers of 39 (46%) subjects found food which had been put in odd places such as in wardrobes, pockets or the down the sides of chairs. The reasons for this varied, sometimes it was because the food was not wanted, it was stored for future consumption or sometimes it seemed to be the result of confusion (see table 7.6).

Table 7.6 Prevalence, over the entire course of dementia, of changes in eating behaviour

Summary of items	Mild *	Severe **	Total %
Putting food in inappropriate places	24	15	46%
Pica - inedible objects in mouth	14	5	22%
Pica - inappropriate food	12	1	15%
Oral behaviour	13	0	15%

* mild = has occurred on up to half the days for at least one month
 ** severe = has occurred on half of the days or more for at least one month

As coordination and cognition decreased, eating gradually became more difficult, food was spilt and people gulped food or spat it out. Problems with teeth, or lack of teeth, made chewing difficult for 20 (24%) subjects and 25 (29%) had difficulty swallowing food and usually needed a soft diet or puréed food. Some 48 subjects (56%) have inappropriately used their hands when eating, 54 (64%) had difficulty using cutlery and 5 (6%) used unusual utensils for eating, for example using a carving knife or cutting a cake using keys. Eventually many people are only given a spoon, and, in

the final stages of the illness, 27 (32) people needed to be fed.

CONCLUSION

The results of the longitudinal study described in this chapter show that eating changes are frequently seen in dementia and there is a wide range of such changes.

Chapter 8 RECRUITMENT AND INCLUSION/EXCLUSION CRITERIA FOR EXPERIMENTAL SUBJECTS AND THEIR CONTROLS.

In the remainder of the experimental section of this thesis I will report the results of a series of experiments to investigate in detail the phenomenon of hyperphagia in dementia.

Many of these experiments involved three groups of subjects:

- 1) Subjects with both dementia and hyperphagia (the experimental group).
- 2) Subjects with dementia who were not hyperphagic (the demented, non-hyperphagic controls) - matched for age, sex, type and degree of dementia with experimental subjects.
- 3) Normal (non-demented) elderly subjects, age and sex-matched with the experimental group (normal controls).

However, as will become obvious (see Chapter 9), the definition of a 'hyperphagic' subject is by no means clear. In this chapter, I will describe the methods for the recruitment of subjects, and the criteria for inclusion.

RECRUITMENT AND DIAGNOSES OF SUBJECTS

Subjects for these studies were recruited from a variety of sources: five local psychogeriatric wards; a number of local nursing homes; community psychiatric nurses and two local research studies of people with dementia. The criteria for referral of potential subjects were: that the person had been diagnosed as suffering from dementia; that the main carer reported evidence of the person overeating or of wanting more food.

Consent

All stages of the study were approved by the Psychiatric Sector Research Ethics Committee. As most potential subjects were not capable of giving informed consent, the subject's next-of-kin, or other main carer as appropriate, was contacted. The project was explained and consent, both for the experimental procedure and for videotaping, was obtained verbally. This was followed up by a letter explaining the conditions under which videoing would be carried out and also stating the methods taken to ensure confidentiality.

Verbal and written explanations for each stage of the study were given to the next-of-kin. They were asked to read a résumé of the procedure and, if they were in agreement with the study being carried out, to fill in and sign standard written consent forms.

Diagnosis

The CAMDEX (Roth *et al.*, 1986) was administered to both the carers and subjects (see previous chapter). Additional information was obtained from the subject's medical and psychiatric notes when available; the GP's notes; data from the OPTIMA and MRC studies, when relevant and, in some subjects, there were results of a brain scan (CT or SPET). The OPTIMA study is an independent study of dementia in Oxford in which subjects receive a detailed diagnostic work-up.

From all this information the best diagnosis was made for the cause of dementia using the NINCDS-ADRDA criteria (McKhan *et al.*, 1984) for Alzheimer's Disease and making use of the Hachinski Ischaemic Score (Hachinski *et al.*, 1975), which is the most widely used scale for helping to diagnose vascular dementia. Of the 18 subjects identified as hyperphagic and included in the study, 16 were diagnosed as pure AD and two were diagnosed as having dementia of mixed origin. In the absence of post-mortem examination, these diagnoses remain uncertain.

Additional information

The carers were also asked questions from the eating sections of the Present Behavioural Examination (PBE) and Past Behavioural History Examination (PBHI) augmented by questions on current walking behaviour, stereotyped and obsessional behaviour. On the day of the test-meal, the subject's weight and medication were recorded, as well as food intake for the whole day, both before and after the test-meal.

INCLUSION AND EXCLUSION CRITERIA

A. Reported hyperphagic demented group

Of the people with dementia who were reported to overeat, only subjects who fulfilled the following criteria were eligible for entry into the study.

1. Inclusion criteria

- a) Diagnosis of dementia.
- b) Probable cause of dementia: Alzheimer's Disease, vascular dementia or both.
- c) Carers reported in answer to PBE questions (see Appendix I) that subjects showed signs of overeating. The specific criterion was that at least one of the following obtained:
 - (i) They were currently eating more than before the onset of dementia (i.e. question 70 was rated 4).
 - (ii) They frequently showed signs of wanting more food, either by searching or asking for more (i.e. either of PBE questions 74 or 75 were rated 3 or more).
 - (iii) They ate distinctly more than normal when extra food was available (i.e. either of questions 76 or 77 was rated 2 or more).

2. Exclusion criteria

- a) Dementia had a cause other than AD or vascular dementia e.g. Pick's disease or dementia due to Parkinson's disease.
- b) A diagnosis of diabetes mellitus.

- c) A premorbid history of heavy alcohol intake i.e. regularly exceeding 30 units a week for a period of more than two years.
- d) A serious head injury which might have contributed to the dementia.

B. Demented, non-hyperphagic controls

Controls were recruited using the same sources as for the hyperphagic group.

1. Inclusion criteria

- a) Diagnosis of dementia.
- b) Probable cause of dementia: Alzheimer's Disease, vascular dementia or both.
- c) The carer reported that the subject did not show signs of hyperphagia i.e. the carer's answers to PBE questions confirmed that there were no signs of an excessively large appetite or of an abnormally large food consumption.
- d) Capable of feeding themselves.
- e) Neither severely emaciated nor very obese i.e. body mass index (BMI) between 15 and 35 (see table 8.1).

2. Exclusion criteria

As for experimental group.

3. Matching to experimental group

Each control was individually matched with a member of the hyperphagic group.

Controls were matched for:-

- a) age - within 3.5 years of the subject's age;

- b) sex;
- c) same type of dementia - both control and subject had the same clinical diagnosis of either AD, vascular dementia or probable mixed cause of AD and vascular dementia;
- d) same degree of dementia - with a Mini-Mental State Examination (MMSE) score no more than 4 points above or below the subject at the time of recruitment.

C. Normal elderly controls

Normal controls were recruited mainly from amongst carers of subjects in the MRC study or this study. They were screened for eating abnormalities, using a modified version of the PBHI (see Appendix III), and also checked for symptoms of dementia using the MMSE.

1. Inclusion criteria

- a) Normal appetite and eating habits.
- b) Body mass index (BMI) between 15 and 35 (see table 8.1).

2. Exclusion criteria

- a) Signs of dementia (MMSE ≤ 24).
- b) Currently dieting to lose weight.

Matching to experimental group

Each control was individually matched with a member of the hyperphagic group.

Controls were matched for:-

- a) age - within 3.5 years;
- b) sex.

ENTRY INTO THE STUDY

a) Reasons for non-inclusion of subjects into experimental group

During the initial screening of people who were described as overeaters, the main reason for non-inclusion was evidence of diabetes mellitus. After passing the initial screening, two possible subjects died before the first meal, and for one woman, illness (influenza) stopped the overeating behaviour before the first meal was arranged. She did not recover her excessive appetite during the following 12 months.

b) Reasons for exclusion of hyperphagic subjects after initial meal(s)

Thirty-four people, reported to be hyperphagic, were assessed by being given one or more meals. Two were subsequently found to have a diagnosis of dementia other than AD or vascular dementia, two were apparently mis-reported as hyperphagic, three had strong evidence of hyperphagia in the past but were no longer hyperphagic, and one refused to cooperate. Twenty-six subjects reported to be hyperphagic were entered into the experimental cohort (the **reported hyperphagic group**). Seven of this group were not followed through beyond the first meals, because although there was good reported evidence of hyperphagic behaviour, they appeared to be restraining under experimental conditions. One person was followed up for a year as she had

some features of hyperphagia but she never exceeded the threshold to enter the experimental group (see next chapter).

For the series of experiments a pool of 18 of the people reported to be hyperphagic were included in the ‘**observed hyperphagic group**’. This group of subjects therefore were both reported to be hyperphagic and were observed to be hyperphagic under experimental conditions, i.e. they exceeded a stringent threshold (see Chapter 9) during at least one of the initial test meals. Two control groups were screened and entered into the study, they consisted of 14 non-hyperphagic demented people and 14 normal elderly people. Each of the 14 people in the two control groups were matched with one person from the experimental group for the characteristics specified above.

COMPARISON OF THE EXPERIMENTAL AND CONTROL GROUPS

Age

All the controls were matched individually within the prescribed age range. The mean age of the three groups were:

Observed hyperphagic demented group - 75.3 years (S.D. 8.0; range 54-91; n=18).

Non-hyperphagic demented controls - 77.6 years (S.D. 6.3; range 67-89; n=14).

Normal elderly controls - 76.2 years (S.D. 8.4; range 55-87; n=14).

Sex

In each of the three groups there were 5 men, with 13 women in the experimental (observed) hyperphagic group and 9 women in each of the two control groups.

Degree of dementia

The mean MMSE, at the point of entry, was 3.7 (S.D. 5.3; range 0-20) for the hyperphagic group and 4.6 (S.D. 5.5; range 0-17) for the non-hyperphagic demented controls. The CAMCOG scores (the cognitive section of the CAMDEX interview) were 15.7 (S.D. 15.7; range 0-67) and 15.4 (S.D. 16.2; range 0-45) respectively. No-one in the normal elderly group showed signs of dementia; their mean MMSE score was 28.1 (S.D. 1.1; range 26-30).

Body mass index (BMI)

Had there been a significant difference in obesity or emaciation between the three groups, it might have reflected very different levels of normal food intake between the groups and might have affected the amount eaten in test meals. Obesity is measured by the body mass index, or Quetelet index (see table 8.1) -

$$\text{BMI} = \text{weight (kg)} / \text{height (m}^2\text{)}.$$

In elderly people BMI is often difficult to assess as it is sometimes difficult to measure height if people cannot stand up straight, especially with demented patients who do not understand instructions. Also it is difficult to weigh severely demented people.

Observed hyperphagic group

Mean BMI was 25.2 (S.D. 4.1; range 19.0 - 31.1; n=17).

Non-hyperphagic demented controls

Mean BMI was 23.9 (S.D. 3.85; range 16.6 - 29.5; n=14).

Normal elderly controls

Mean BMI was 25.3 (S.D. 3.7; range 19.9 - 33.5; n=14)

Table 8.1 Body mass index

Group	Grade	BMI (range)	Description
Normal			
Grade	0	19-24.9	normal range
Overweight and obesity			
Grade	I	25-29.9	overweight (trivial risk)
	II	30-39.9	obesity (significant risk)
	III	40+	severe or morbid obesity
Underweight and emaciation			
Grade	I	15-18.9	underweight
	II	under 15	emaciation

The three groups were similar in their BMI, and the differences between the groups were not significant (independent t-test). More of the observed hyperphagic group had gained weight at some stage during the course of dementia (13/17) than the non-hyperphagic demented group (3/14). This difference was significant (chi square: after Yate’s correction: 7.2, $p = 0.007$).

Medication

The carer was asked for a list of current medications to check for drugs such as major tranquillisers which might increase appetite and food intake. At the point-of-entry

meal, 9/18 (50%) of the hyperphagic group and 3/14 (21%) of the non-hyperphagic demented controls were taking such medication. The difference between the two hyperphagic groups was not significant (chi-square after Yates' correction: 1.7, $p = 0.20$). None of the 14 normal control group was taking medication which might increase appetite.

Past eating behaviour

One possible explanation for overeating in dementia is that people who previously had dieted to lose weight or who had always been careful to avoid putting on weight had now lost their former self-control. Questions in the PBHI asked carers if the person with dementia had ever dieted or shown concern about body weight before the illness started. None of the 18 people in the hyperphagic group had ever dieted or shown concern over their weight. Premorbidly, four of the non-hyperphagic demented control group had dieted to lose weight. In the normal elderly control group, no-one was currently on a diet to lose weight although three had restricted their food, to prevent weight gain, in the previous 5 years.

Present eating and drinking behaviour

There is an apparent paradox in that some people in the hyperphagic group were currently reported to eat less than premorbidly in spite of being described as overeating. One reason for this was that carers were limiting access to food (12/18 of the hyperphagic group, whereas none of the 14 non-hyperphagic controls was limited), and also as people get older their energy requirements are lower, partly because usually they are less active. None of the normal elderly group had eaten

more in the previous five years and six had eaten definitely less. Six of the hyperphagic group, but none of the non-hyperphagic controls, had a tendency to drink more (non-alcoholic drinks) than premorbidly. This difference was significant (Fisher's exact test: $p = 0.013$, 1-tail).

Changes in food choice were markedly different between the demented and non-demented groups. Of the eleven carers of people in the hyperphagic group, who knew enough about the subject's previous taste in food, nearly two-thirds (7/11) reported that they now preferred sweeter foods or ate anything indiscriminately. Five out of 13 in the demented control group reported such changes. This was not a significant difference (chi-square after Yates' correction: 0.67, $p = 0.41$). None of the normal elderly said they preferred sweeter food now. Indeed, any change was towards a 'healthier' diet more fish, pasta, fibre and less alcohol.

Questions were asked to see if the types of behaviour associated with overeating in dementia had similarities with Klüver-Bucy syndrome (see Chapter 4). Some of the other characteristics of the syndrome were found in a proportion of individuals in both the demented groups but were more frequent in the hyperphagic group (table 8.2). The frequency of each of these types of behaviour was not significantly different between the two groups.

Table 8.2 Features of Klüver-Bucy syndrome

Results of PBHI/PBE (Behaviour reported by carer of any changes in the past)	Hyperphagic, demented group	Demented, non- hyperphagic controls
Oral behaviour	1/16	0/14
Non-food pica	8/17	5/14
Eating inappropriate food	4/18	1/13
Hypermetamorphosis	7/16	4/14

Present walking behaviour

Excessive food intake could be the result of overactivity (Rheame *et al.*, 1987). Ten of the 18 in the hyperphagic group were reported to be hyperactive, which might contribute to their overeating (only 3/14 of the non-hyperphagic demented were described as overactive). This was not a significant difference (chi-square after Yates' correction: 2.5, $p = 0.11$). Although some of the non-hyperphagic demented controls had limited mobility, the normal elderly control group were all mobile and several were considerably more active than average, cycling or walking more than normal for their age group.

Addiction

It has been argued that it is possible to become addicted to food (Orford, 1985). There was some evidence of other addictive behaviour in the past, but the difference between hyperphagic and non-hyperphagic group was not significant at the $p = 0.05$ level. Anyone with a history of a heavy intake of alcohol was excluded from the study but in the hyperphagic group, two had regularly used tranquillisers or hypnotics premorbidly, and 7/16 (44%) were known to have been heavy smokers (20 or more a day). The non-hyperphagic demented control group had 3/13 (23%) who had been

heavy smokers but none had been regular users of other drugs.

SUMMARY

There were no significant differences between the two demented groups in changes in eating style or inappropriate placing of food. The main differences in behaviour concerned those directly involved in hyperphagic behaviour i.e. more of the hyperphagic group showed an increase in food and drink intake, more weight increase and more food-seeking behaviour. A wide variety of changes were reported showing that, as well as excessive quantities of food being eaten, inappropriate foods or normally inedible substances were eaten. Food was frequently requested or sought, even immediately after a meal, and food preferences changed. The carers reports usually confirmed a longstanding change in eating pattern, sometimes lasting for years. This corroborated findings of the MRC study (see Chapter 7). There is no evidence that people with hyperphagia were ex-dieters, that they were prescribed a significantly greater number of major tranquillisers or that they were significantly more active. The normal elderly showed no abnormal eating behaviour.

Chapter 9 THE DEFINITION AND MEASUREMENT OF 'HYPERPHAGIA'

Carers' reports suggest there is a subset of people with marked hyperphagia. Each person with dementia had a different carer and the carers were diverse in their experience of caring - ranging from relatives coping with dementia for the first time to experienced psychiatric nurses. The carers also varied in the amount of contact with the subject, from a caring neighbour, who visited periodically, to a husband or wife coping 24 hours a day. Some of these reports are likely to have low validity and do not allow precise quantification, necessary for experimental work. To confirm the validity of these reports experimentally the following questions needed to be answered.

1. Can hyperphagia be confirmed under standard and objective conditions?
2. Can a standardised setting be devised for defining hyperphagia? A definition is necessary for devising experiments to look at its nature and mechanism.
3. What is the extent of the hyperphagia; can hyperphagia be quantified?

As a result of pilot work, two standardised situations were examined in order to investigate these questions. Both involved the subjects in a situation where a virtually unlimited supply of food was available.

- A. A single food meal
- B. A mixed 'buffet' meal consisting of many food types.

The following relationships were examined.

- a) The relationship between carer's report and 'performance' in these standardised settings (i.e. to what extent is there agreement between the two in classifying hyperphagic subjects).
- b) Test-retest reliability of two identical meals.
- c) The difference between the single food meal and the mixed meal, both in comparing the amount eaten and the difference in the two methods for identifying a hyperphagic group.

THE CONCEPT OF HYPERPHAGIA

These questions assume that we know what we mean when we talk of a subject being hyperphagic or non-hyperphagic. The concept of hyperphagia can be defined as eating an abnormally large quantity of food, but what level of intake should be regarded as hyperphagic? This is not a clear-cut issue as a wide variety of abnormal eating patterns were reported, for example some people ate excessive quantities but only of a particular type of food, others would eat any food to excess but only when it was easily accessible and some ate relatively small amounts but at very frequent intervals. Over what period of time should hyperphagia be judged? In order to define hyperphagia, should behaviour be judged by a single meal or over a more sustained period of time? Some people overate at one time of day but ate normally for the rest of the day. Is hyperphagia a continuum or a distinct category? Although people who were reported as hyperphagic ate extraordinary amounts, which would be vanishingly rare in a non-demented population, there was no indication whether this represented one extreme of a continuum or whether hyperphagia is a distinct and

separate category of eating behaviour.

Defining hyperphagia is an 'iterative' process: we have to have some idea what we mean, in order to devise relevant experiments, but the experiments will help to clarify further what the concept of hyperphagia means and how it is defined. The definition of hyperphagia might at first sight appear straightforward, as carers clearly report extraordinary quantities of food being eaten when the opportunity arises, but carers' reports are highly variable and assessing what is abnormal is subjective.

If hyperphagia is defined in a standardised experimental setting there is a problem as some people restrain under these conditions. Carers' reports describe the typical behaviour but lack validity and precise, standardised measurements.

To investigate hyperphagia and to arrive at a definition it was necessary to:

1. define 'reported hyperphagics' on the basis of carer's reports;
2. observe eating behaviour directly in a standardised experimental setting.

It was then possible to look at the relationship between the two. To look at the differences between those with hyperphagia and those without, a clear objective operational definition was needed based on carer's reports. To do this, full accounts of the history of premorbid eating behaviour, the history of the onset and progress of the dementia, changes in eating and other relevant behaviour, were collected using semi-structured interviews (sections of the PBHI and PBE) as well as the CAMDEX interview (Roth *et al.*, 1986). This gave a detailed history of changes in eating

behaviour during the course of the illness and an indication of the degree of abnormality of the present behaviour.

DEFINITION OF HYPERPHAGIA

The original informal reports of hyperphagia were quantified from the interviews. From carers' reports potential subjects were defined as hyperphagic using the same criteria as the MRC study (see Chapter 7) i.e. if the carer, in answer to the PBE questionnaire, reported one or both of the following:

a) Increased food intake - eating considerably more than normal (extra snacks, larger meals or eating any food encountered) i.e. question 70 was rated 4 or either of questions 76 or 77 was rated 2 or more.

b) Increased hunger (if food was restricted) - repeatedly asking or searching for food i.e. if PBE questions 74 or 75 were rated 3 or more.

This definition of hyperphagia could define potential subjects to be included in a hyperphagic group but these criteria did not give a quantitative measure of hyperphagia. The following experiments describe how this method was developed.

EXPERIMENTAL INVESTIGATION OF HYPERPHAGIA - DEVELOPING A STANDARDISED SETTING.

AIM

The aim of the experiments, described in this chapter, was to define hyperphagia and develop a valid and reliable method of measuring it.

A. A SINGLE FOOD MEAL

INTRODUCTION

For experimental purposes, in order to look at the differences between those who were hyperphagic and those who were not, a clear objective definition was required. This was attempted by observing a meal, eaten under controlled conditions but in as natural a setting as possible. The amount eaten at such a meal could be used to establish a threshold to distinguish people who were hyperphagic from those who were not.

What should determine the type of food given at a test meal and should more than one food be given? Behaviour was assessed at a single meal, at a normal mealtime, in a familiar setting, with a familiar, generally well-liked and easily recognised food. A single food meal has the advantage that a uniform texture would allow the microstructure of eating (e.g. changes in loading rate, chewing rate and intra-meal pauses) to be monitored during the course of the meal (see Chapter 11). A suitable single food could be used to assess total intake and to eliminate the variation in microstructure of the meal, which might result from the variety of textures, tastes and palatability found in a mixed meal. The method of using a single food had proved

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to be highly reliable in a study of PWS children (Berntson *et al.*, 1993).

Very few studies of eating behaviour have involved demented subjects. One study used a liquid food, sucked by a straw, from a food dispenser (Meyer *et al.*, 1980). This was not suitable for severely demented people and it also had the disadvantage that subjects had to visit a laboratory, so both the food and the location were unusual. A case study used a biscuit meal to assess the efficacy of fluvoxamine in suppressing the appetite of a man with Pick's disease (Hope & Allman, 1991). This proved to be a reliable method of assessing total food intake. Biscuits were certainly reported to be a preferred food of many people with dementia, both hyperphagic and normal eaters. Previously, at least two carers specifically mentioned that they found giving digestive biscuits was a good way of defusing aggressive behaviour.

A single type of biscuit could prove suitable but there was the problem that excessive food intake might be driven by sweetness. Small, low-sugar digestive biscuits were therefore chosen. Small portions of food were desirable as people tend to finish any item of food that they select, therefore with smaller food units the endpoint could be more finely judged.

Pilot work, providing small, low-sugar digestive biscuits *ad libitum*, showed that a single-food meal of biscuits distinguished the subjects reported as hyperphagic from demented controls who ate normal quantities of food, although giving biscuits did exclude two people who had difficulty eating hard food.

METHOD

After experimenting in the pilot study, the most appropriate method seemed to be to place ten biscuits on a plain white plate with a similar empty plate directly in front of the subject. This was to enable subjects to feel free to help themselves to as many biscuits as they wanted but ten biscuits on a separate plate did not give an impression of an overwhelming quantity of food, which might inhibit normal eaters. When only two or three biscuits were left, the plate was replenished, as unobtrusively as possible. Topping up the plate did not give the impression that the meal was over because if only a small amount of food is left on a plate it could act as an external satiety signal (Booth, 1992). Similarly, the glass of water was replenished when it was considered necessary.

In order to standardise the procedure it was important have set responses at key points. Safety precautions were also necessary to avoid dangers such as choking or over-distension of the stomach.

The following general rules were followed for all experimental meals.

Before the meal

Variables were controlled as far as possible, for example each test meal was given at the time when subjects usually had their midday meal, standardised instructions were given and the same environment was used for each retest. To try to make test-retest reliability as good as possible, carers were asked to provide a similar breakfast at a similar time before each meal.

The environment was kept as familiar as possible. At home, subjects sat in their usual place for the meal. In nursing homes and wards this was not practical as subjects would normally eat with other people. This was not desirable as the presence of other people at a meal is known to influence the amount eaten (Meyer *et al.*, 1980) and also it acts as a distraction.

Before the meal, I asked people to eat as much as they felt like eating, to regard this (whether biscuits or mixed meal) as their midday meal, to eat until they felt comfortably full and to begin as soon as they liked. I started the video-camera when the subject was seated at the table and timing was started as the food was put in front of the subject.

Start of the meal

Once food was put on the table no further instructions were given unless they asked questions. However, some people, mainly in the non-hyperphagic demented control group did not start to eat so, if necessary, after two minutes, a standardised prompt was given. If, after a further prompt, eating still did not start food was placed on the plate in front of the subject and they were encouraged to start by further prompting.

During the meal

In the pilot study, some of the hyperphagic people also seemed to be hyperdipsic; one person drank two litres of water during the course of a meal when water was available *ad libitum*. In the main study, subjects with dementia had their glass of water topped up sufficiently often to prevent their mouth getting too dry but not

enough to distend the stomach excessively. Surprisingly, some people ate tens of biscuits without drinking at all. This could have been because they did not connect discomfort of a dry mouth and sensations of thirst with the fact that they had not had a drink.

Normal controls were given the choice of being left on their own to ease any embarrassment they might feel by being watched. If they were left on their own, I returned at approximately 5-minute intervals to check all was well and to replenish food if necessary. People with dementia could not be left but were observed as unobtrusively as possible the whole time to check for choking and to prevent spillage or inappropriate mixing of water and food. To minimise distraction, eye contact was avoided and I did not engage in conversation unless the subject started it, in which case responses were kept to a minimum.

Three of the women, who were more cognitively intact, were very concerned that they were eating and I was not. This was apparently inhibiting them from eating so, to prevent their obvious discomfort, I assured them that I too had something to eat and held a biscuit in my hand and occasionally took a bite.

Pause in meal

It was sometimes difficult to judge when a meal had ended, for example if eating ceased and the subject appeared to have lost interest (i.e. was not talking, obviously selecting food or holding food). After a pause of 2 minutes following the last mouthful a neutral prompt was given "Would you like some more to eat or have you

had enough?". This question turned out to have two shortcomings; it was complex and also the answer was unreliable if the subject showed echolalia. If the answer was "Had enough", the sentence could be inverted to check for echolalia i.e. "Have you had enough to eat or would you like some more?".

Even an apparently meaningful refusal of more food in the relatively unimpaired, was not always a reliable indication that they had finished as some people, after assuring me they had had enough, immediately took and ate more food. Subjects who were relatively cognitively intact may have restrained from eating and not eaten more than would be thought appropriate. If I packed up in a leisurely way and without obviously watching, some subjects continued to eat 'leftovers' as they helped to pack away, presumably this seemed more socially acceptable.

Stopping the meal

The meal was stopped if the person eating reached a maximum intake of 12 000 kJ (nearly 3000 kcals) or if they appeared to be uncomfortably full, for example if they started hiccupping or appeared distressed.

End of meal

The meal was counted as over when five minutes had elapsed from the last mouthful or, if the subject was still actively chewing food or appeared to be interested in food, a longer period was allowed to elapse before clearing food away. Hyperphagic subjects who were overactive, sometimes walked away. They were asked to sit, if they started to get up while still eating, and encouraged to return to the table if they

insisted on walking away. If they walked away without food in their hand or mouth, they were asked if they had had enough and then allowed to go or return for more without further prompting. If they did not return for more within five minutes, the meal was rated as ending, either from the time when they stood up or after their last chew, whichever was the sooner.

SUBJECT GROUPS

There were three subject groups:

- a) **Reported hyperphagic group** - Twenty-six people with dementia met the above criteria for 'reported hyperphagia'.
- b) **Demented, non-hyperphagic control group** - Fourteen people were matched to 14 of the 26 hyperphagic group for degree and type of dementia, age and sex but with no history of hyperphagic behaviour (see Chapter 8).
- c) **Normal elderly control group** - Fourteen normal elderly were matched to 14 of the hyperphagic group for age and sex (see Chapter 8).

RESULTS

The mean and S.D. of the age and MMSE of the three groups are given in tables 9.1 and 9.2

Table 9.1 Age at point of entry

SUBJECT GROUP	MEAN (years)
All reported hyperphagics	77.9 (S.D. 8.6; range 54-92; n=26)
Non-hyperphagic demented controls	77.6 (S.D. 6.3, range 67-89; n=14)
Normal elderly controls	76.2 (S.D. 8.4, range 55-87; n=14)

Table 9.2 MMSE at point of entry

SUBJECT GROUP	MEAN MMSE
All reported hyperphagics	4.41 (S.D. 6.0; range 0-20; n=26)
Non-hyperphagic demented controls	4.64 (S.D. 5.5; range 0-17; n=14)
Normal elderly controls	28.14 (S.D. 1.1; range 26-30; n=14)

ENERGY VALUE AND MEAL TIME

The total energy intake results are summarised in figure 9.1 and table 9.3.

a) All reported hyperphagics

When all the people who were reported to be hyperphagic by their carers were included the mean intake was 3160 kJ. The variation in food intake was large, ranging from 1 to 55 biscuits. The time taken to eat the meal ranged from two minutes to two people who ate steadily until they were stopped at the end of 2 hours.

Figure 9.1

Digestive biscuit meal

(All reported hyperphagic subjects)

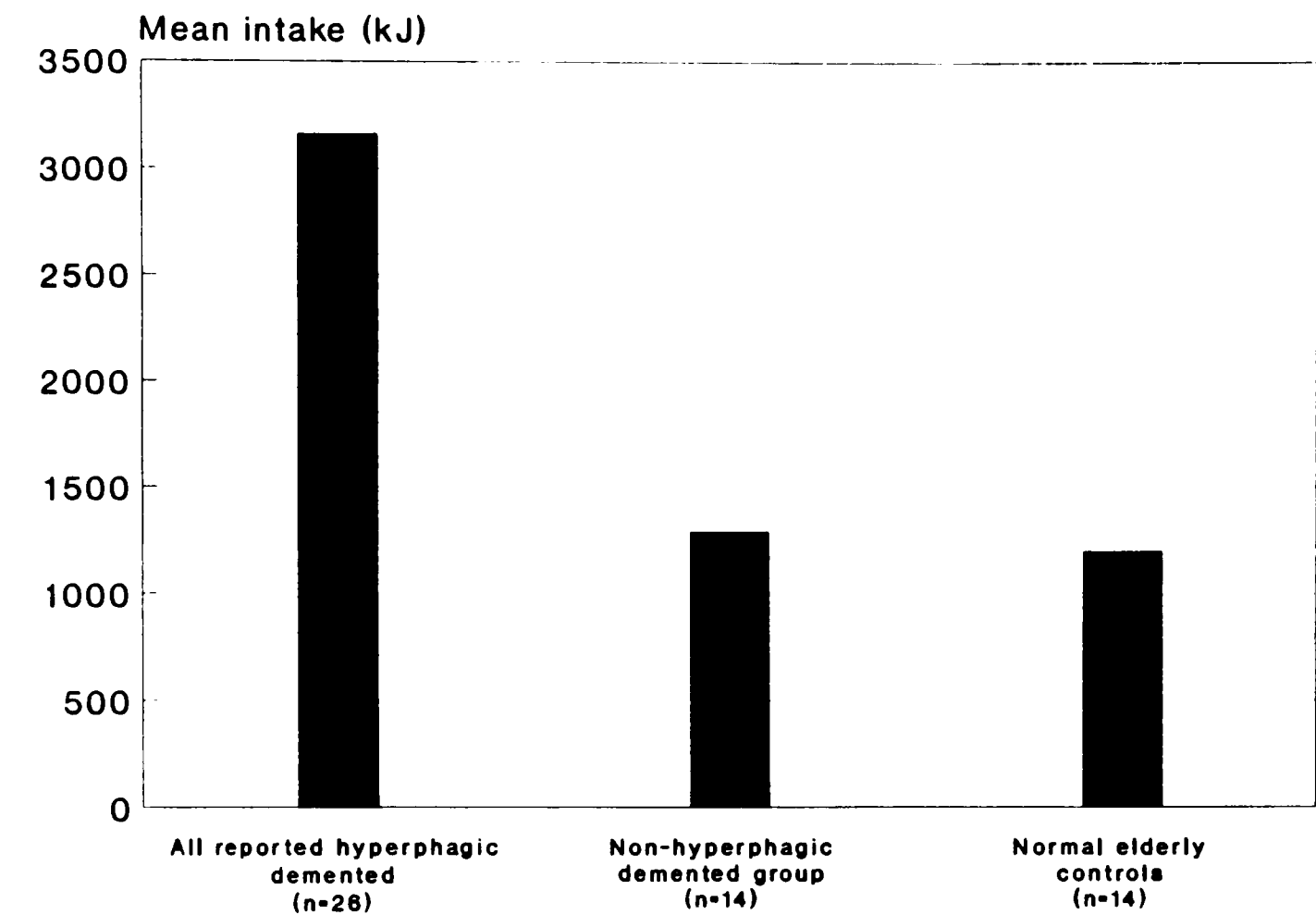


Table 9.3

Energy value of digestive biscuit meal 1 (kJ)

SUBJECT GROUP	MEAN (kJ)
All reported hyperphagics	3160 (S.D. 2928; range 192-9540; n=26)
Non-hyperphagic demented controls	1292 (S.D. 1063; range 126-3648; n=14)
Normal elderly	1204 (S.D. 540; range 525-2112; n=14)

b) Demented non-hyperphagic control group

People with dementia who were reported by their carers not to be hyperphagic, were very variable both in the amount eaten and in the time taken. They ate a mean of 1292 kJ, about 7 biscuits (S.D. 1063, range 126-3648) with a mean meal-time of 34 minutes (range 5 minutes to over 2 hours). However, the person who was still eating after two hours only consumed 2577 kJ during that time. This group ate significantly less than the hyperphagic group (t-test: $t = 3.58$, $df = 30$, $p = 0.001$) but there was no significant difference between their intake and that of the normal elderly.

c) Normal elderly controls

The normal elderly ate a mean of 1204 kJ (S.D. 540, range 525-2112) with a mean meal-time of 11 minutes (S.D. 6 minutes, range 5-24 minutes).

STOPPING THE MEAL

Three people in the hyperphagic group were stopped because they became uncomfortably full and two were stopped after two hours. One of the demented controls ate very slowly and was stopped because she was still eating after two hours. No-one was stopped because they had reached the maximum permitted intake of 12 000 kJ, which had been previously decided.

DRINKING

Although with some people in the hyperphagic group it was necessary to limit water intake, many people with dementia did not drink at all. Some of the people in the hyperphagic group ate 30 or more of the dry biscuits without drinking any water,

even when it was offered. Typically, people in the normal control group sipped water periodically through the meal.

COMPENSATION AFTER THE MEAL

The carers and the normal controls were asked about the intake of food during the rest of the day and to assess whether it was more, less or the same as usual, to see if there was compensation after the biscuit meal. About half of the normal elderly and the demented controls (57% and 40% respectively) ate more than normal during the rest of the day. This was presumably because they had not eaten as much of the single-food meal as they usually would have done during an ordinary midday meal. The normal elderly, who ate more afterwards, seemed to be compensating, as all had less than 2000 kJ (which was less than the mean intake at the more conventional, buffet-style mixed meal), whereas the only person who ate less afterwards, had eaten more than 2000 kJ in the test meal. The six non-hyperphagic demented controls, who ate more afterwards, also seemed to be compensating; they had all eaten less than 1000 kJ during the biscuit meal. One of the two, who ate less than usual afterwards, had eaten 3650 kJ. In the hyperphagic demented group, even after excessive quantities of biscuit, only one ate less during the rest of the day, the rest ate normally or more than usual. The evidence suggests that non-hyperphagic people may compensate for unusually small or large meals but hyperphagic people did not. This is investigated further in Chapter 12.

DISCUSSION - Experimental definition of hyperphagia using a single-food meal

In order to see if there was a relationship between 'reported hyperphagia' and observed behaviour, a threshold of what could be considered normal and what abnormal needed to be established. If hyperphagia is a continuum this is bound to be an arbitrary threshold. Even if hyperphagia is a category there is a complication that food intake is highly dependent on such variables as activity, gender and body size.

For the purpose of making an experimental definition, an arbitrary 'cut-off' was used to define 'hyperphagia'. To designate a level which was clearly abnormal for that age-group the figure chosen was the mean of the food intake of the 14 normal elderly controls plus 3 standard errors. Therefore, the percentage of normal people likely to exceed this threshold is 0.13%. The mean intake of the normal group was 1204 kJ and the standard error was 540, so 2824 kJ was taken as the threshold. This figure represents about a third of the normal daily food intake calculated for a slightly younger group of 97, free-living, 70-71 year-olds (Fraser & Durnin, 1993). In this study men had a mean intake of 8256 kJ and 7306 kJ for the women.

The proposed definition for 'observed hyperphagia' is therefore an intake of more than 2824 kJ at a digestive biscuit meal. Figure 9.2 and table 9.4 include the 18 people finally included in the experimental 'observed' hyperphagic group (see page 121 for criteria), whereas figure 9.1 and table 9.3 include all the people, reported to be hyperphagic, who were entered into the study initially.

Digestive biscuit meal
(Including observed hyperphagic group)

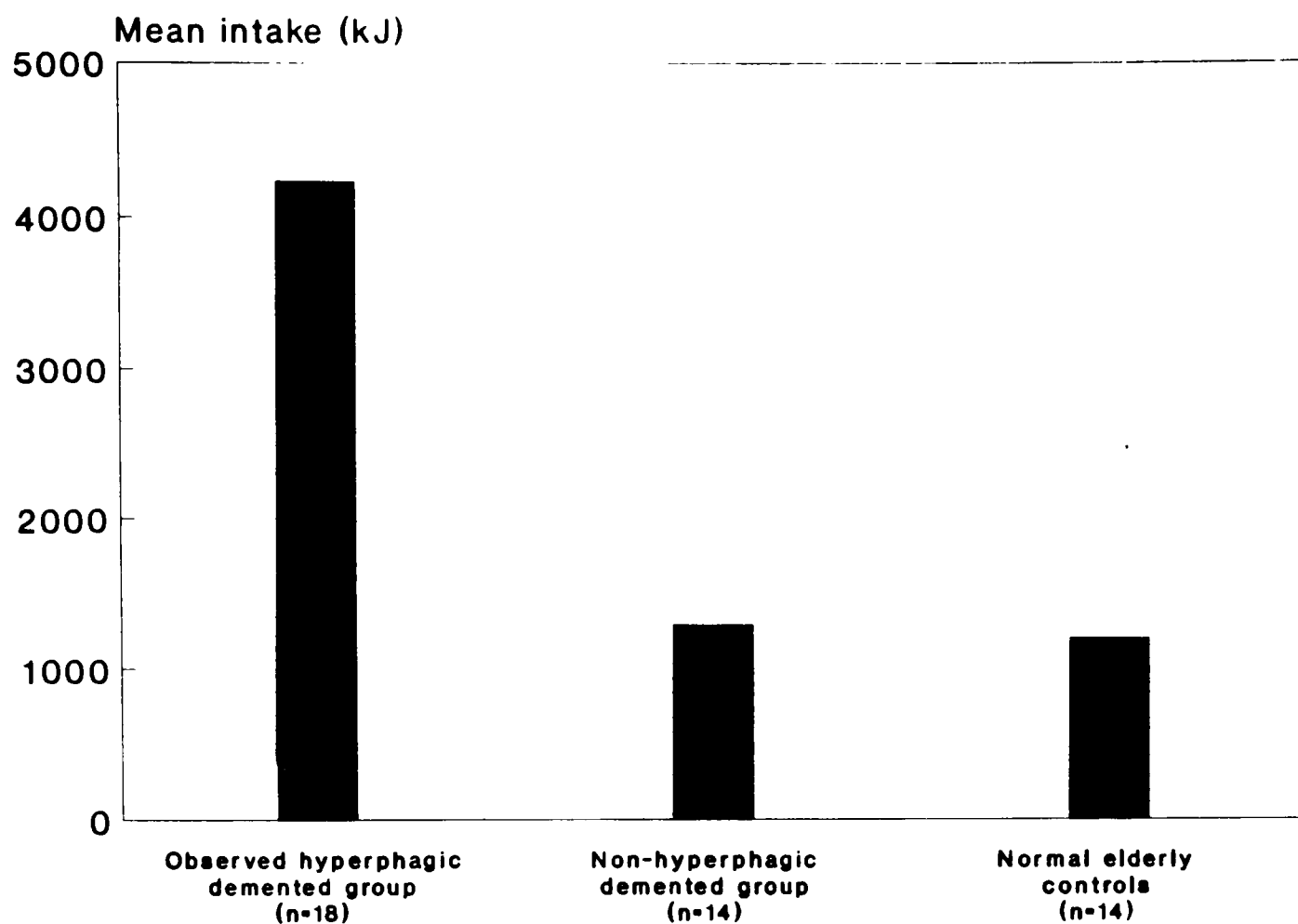


Table 9.4 Energy value of digestive biscuit meal 1 (kJ)

SUBJECT GROUP	MEAN (kJ)
Hyperphagic group	4239 (S.D. 2921; range 192-9540; n=18)
Reported hyperphagics not overeating when observed	733 (S.D. 416; range 192-1330; n=8)

THE RELATIONSHIPS BETWEEN ‘REPORTED HYPERPHAGIA’ AND ‘OBSERVED HYPERPHAGIA’

a) All reported hyperphagics

- (i) **Positive confirmation of hyperphagia** - Ten of the 26 reported hyperphagics exceeded the threshold of 2824 kJ on the first digestive biscuit meal.
- (ii) **Negative results** - Of the 26 people with dementia who were reported to be hyperphagic and who were willing to eat the digestive biscuit meal, 16 did not exceed this (stringent) threshold. Lowering the threshold would not have a marked effect. If the threshold was lowered to the mean of the normal elderly + 2 S.E. two more people would have exceeded the threshold and a further reduction to mean + 1 S.E. would have included two more (see figure 9.3).

Figure 9.4 shows that there is a continuum of eating in the group reported to be hyperphagic and therefore an arbitrary threshold needs to be defined. Although only ten of the reported hyperphagic people exceeded the threshold in the digestive biscuit meal, it was necessary to keep the threshold high because subsequent work needed a group of people whose eating was clearly abnormal.

b) Reported hyperphagics not classified as observed hyperphagics

The discrepancy between the reported and observed hyperphagic people was not simply a question of threshold as figure 9.4 demonstrates. Many of those reported

Figure 9.3 Digestive biscuit meal intake (kJ)

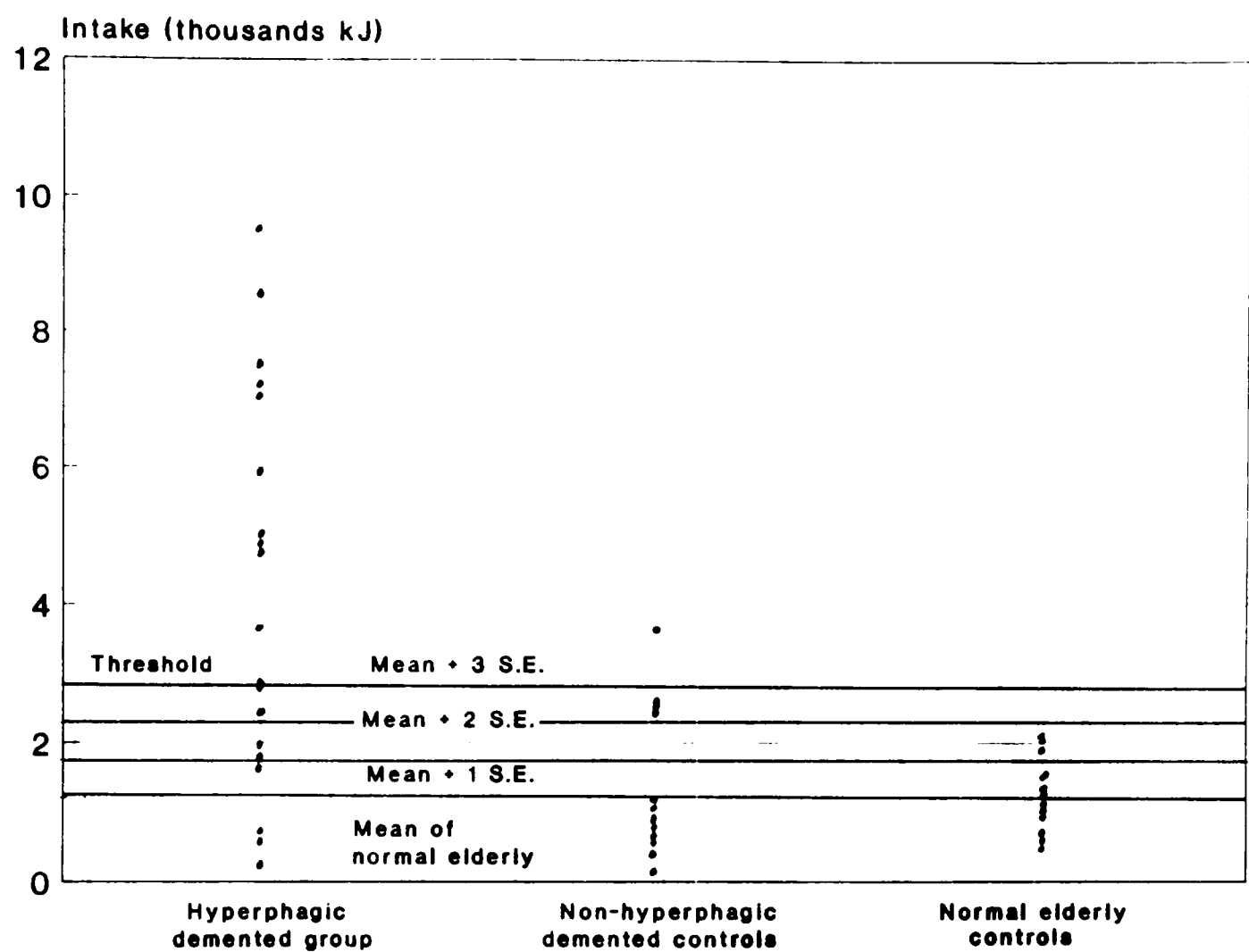
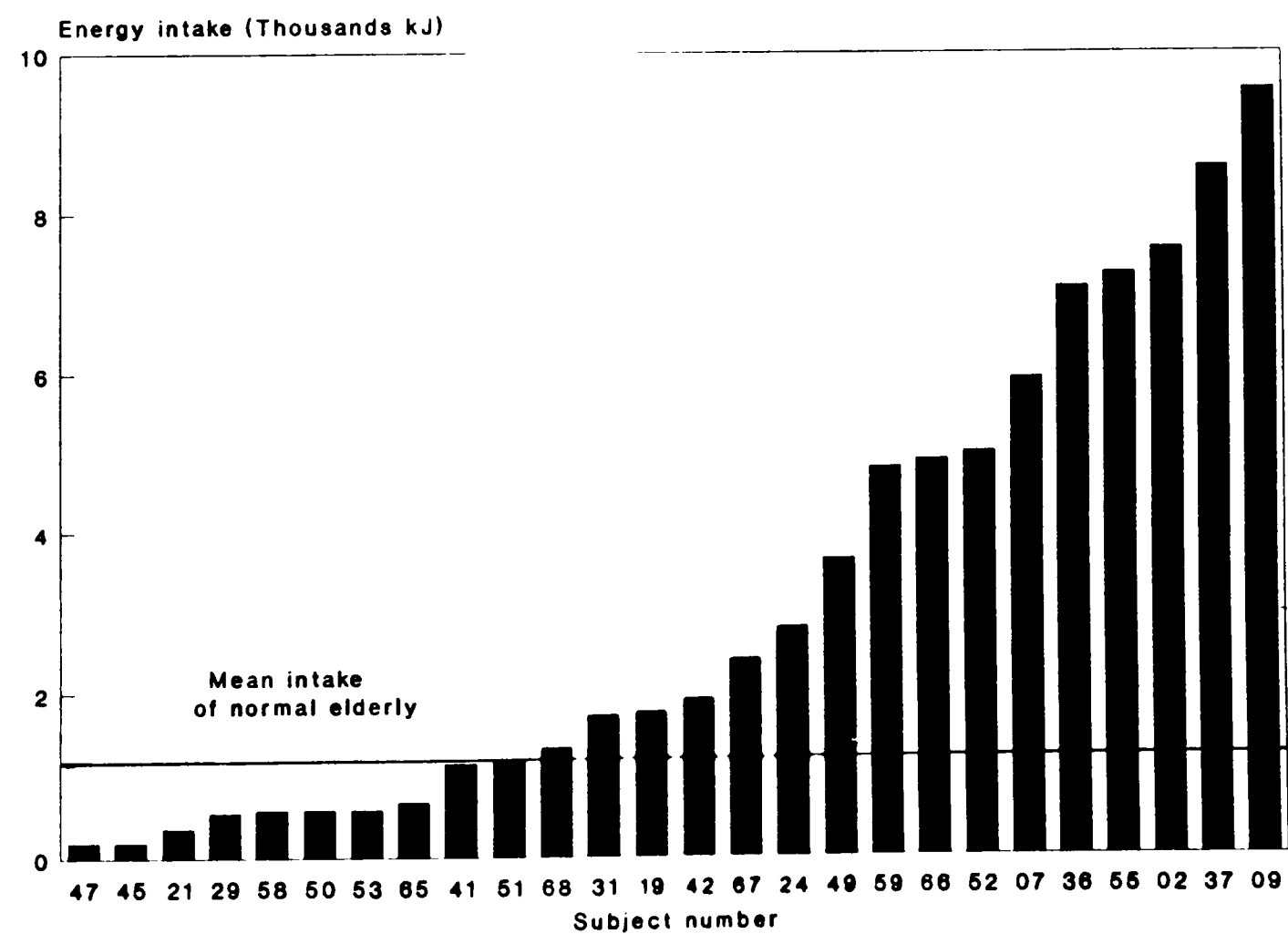


Figure 9.4 BISCUIT MEAL - all reported hyperphagics



to be hyperphagic ate less, or only a little more, than normal elderly controls when presented with the standard 'biscuit meal'.

There seemed to be a variety of reasons for this:

- (i) Some subjects appeared not to understand the request to treat the biscuit meal as the midday meal and also, not being aware of the time of day, they regarded it as a mid-morning snack. They may therefore have eaten only a few biscuits because this seemed socially appropriate.
- (ii) Some subjects may have found the single food (digestive biscuits) unattractive or unpalatable and this limited the amount they ate under experimental conditions.
- (iii) In the case of one subject, the carer reported that the subject overate only on chocolates. It is not surprising that this subject did not eat a large amount at the standardised biscuit meal. Whether overeating only on chocolates should count as hyperphagia is unclear.
- (iv) Some subjects may have been sufficiently socially aware to be self-conscious of overeating when being observed.
- (v) Food intake prior to the standard meal might have an effect. Although people were given a standard breakfast one person was known to have helped herself to a substantial snack during the course of the morning and shortly before the experimental meal.
- (vi) One subject refused to eat biscuits because of the state of her teeth.
- (vii) One subject was too restless to settle to eat.
- (viii) One subject refused to eat, saying he wanted a normal meal.

(ix) One subject lacked sufficient coordination to feed himself efficiently.

All these are reasons why a genuinely hyperphagic subject might fail to eat enough to be classified as hyperphagic at the test meal. It is likely that there are also subjects who are reported to be hyperphagic but who are not genuinely hyperphagic i.e. subjects who are correctly classified by the test meal as not hyperphagic. Some carers may misreport behaviour and overestimate the amount eaten. In some cases the subjects may once have been hyperphagic, causing the carer to restrict food, but have ceased to be so.

c) Objective hyperphagics, not classified as reported hyperphagics.

One person, in the group which was reported to show no signs of hyperphagia, consumed 3648 kJ, at the standardised biscuit meal and would therefore be classified as an objective hyperphagic using the proposed criterion. This subject was a very active man, with severe dementia and in a hospital ward where he would not have easy access to food. Had he wanted extra food he would have been unable to ask for it or find it. Thus signs of hyperphagia might have been hidden. This subject is likely to have been genuinely hyperphagic and is an example of misclassification from reporting.

TEST-RETEST RELIABILITY

AIM

To examine whether food intake during the biscuit meal can be repeated reliably.

METHOD

To establish the reliability of the digestive biscuit meal, the meal was repeated with a sample from each experimental and control group. Ten people from the reported hyperphagic group and five from each of the demented non-hyperphagic control group and the normal elderly control group were given an identical repeat biscuit meal at least two weeks after the first meal. The time interval was to avoid memory of the previous meal affecting intake. Reliability was defined as the degree of agreement in the amount consumed on two separate occasions. Because the measure (energy consumed at each meal) is a continuous variable (and not categorical) the measure of reliability used was the Pearson correlation coefficient. When using this measure it is also important to check that the mean consumption for each subject group on the two test occasions does not differ significantly. This is because high correlation can occur with poor reliability (if, for example, all subjects ate half the amount at the second meal - but the rank ordering remained the same).

RESULTS

The test-retest reliability was high (correlation 0.956, $p < 0.0005$) when all the three groups were combined (see figure 9.5 and table 9.5). The difference between the mean consumption at the two test-meals for each of the individual groups was not significant (see table 9.6). Individuals were plotted on a scatter graph (figure 9.6)

Figure 9.5 Digestive biscuit meal - reliability

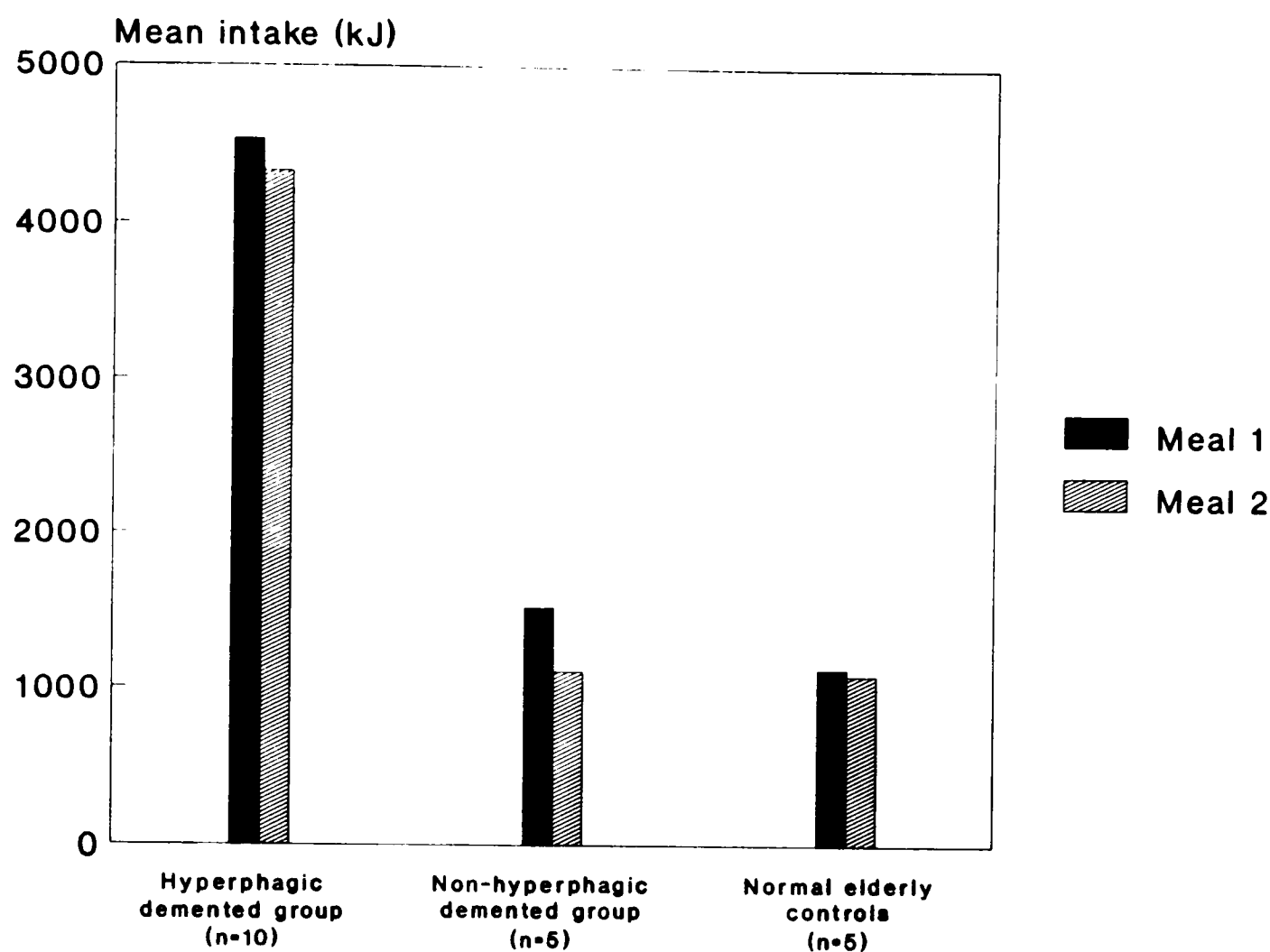


Table 9.5 Total energy intake of digestive meals 1 and 2

Comparison of 2 digestive biscuit meals by group - Mean (kJ)		
Hyperphagic group (n=10)		
Digestive meal 1	4534	(S.D. 3196, range 192-9540)
Digestive meal 2	4336	(S.D. 2700, range 576-8575)
Non-hyperphagic demented controls (n=5)		
Digestive meal 1	1522	(S.D. 900, range 633-2536)
Digestive meal 2	1110	(S.D. 597, range 350-1953)
Normal elderly controls (n=5)		
Digestive meal 1	1128	(S.D. 504, range 700-1920)
Digestive meal 2	1086	(S.D. 662, range 525 -2107)

Figure 9.6 CORRELATION OF DIGESTIVE BISCUIT MEALS
Meal 1 and meal 2

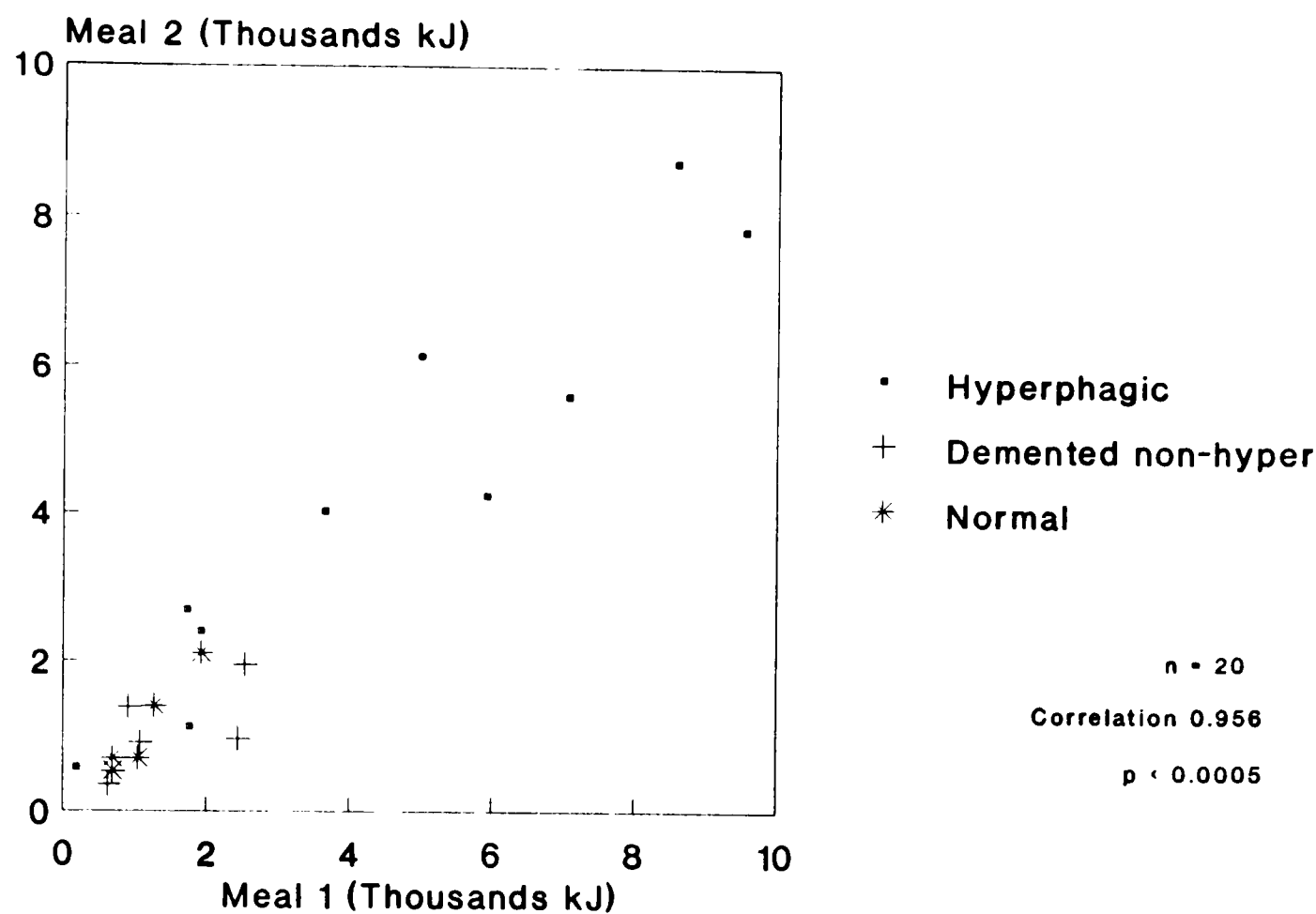


Table 9.6 Intra-subject reliability - digestive meals 1 and 2.
Correlation and paired t-test

GROUP	Correlation	t-value
Hyperphagic group (n=10)	0.947 (p < 0.0005)	0.58 (p = 0.575)
Non-hyperphagic demented controls (n=5)	0.611 (p = 0.27)	1.29 (p = 0.267)
Normal elderly controls (n=5)	0.963 (p = 0.008)	0.42 (p = 0.699)
All groups (n=20)	0.956 (p < 0.0005)	1.15(p = 0.266)

which showed the high intra-subject reliability. There was good correlation between the intake at the two meals within the hyperphagic group and the normal group (0.947 and 0.963 respectively). Generally the variation between individuals was relatively narrow and each person ate a very similar amount at the two meals. The non-hyperphagic group was the most variable (correlation 0.611), both in the amount eaten by different individuals and between how much each individual ate on the two occasions i.e. the reliability for this group was poor. The amount they ate seemed to depend on their mood, their concentration and their level of activity that day.

DISCUSSION - test-retest reliability of single-food test meal

The purpose of this experiment was to examine whether the hyperphagia reported by carers could be reliably confirmed and measured objectively using a standardised meal. A simple meal of non-sweet digestive biscuits was chosen because it is simple and because a single substance meal is best for studying the microstructure of eating.

Two key questions have been examined. The first is whether this measure, the energy intake at this standardised meal, is reliable. That is, do subjects consume the same amount when given the meal on two separate occasions. The second question is, what is the relationship between 'reported hyperphagia' and the amount eaten at this standardised meal?

The results show first, that there was a high degree of reliability (measured by the Pearson correlation coefficient) in the amount eaten at the two mealtimes, both when the three groups of subjects were examined together and when individuals were

compared. This suggests that, if an objective measure of hyperphagia can be made using standardised meals then a single meal is sufficient, at least for most purposes.

Reliability was also looked at from the point-of-view of using the standardised meal to classify subjects as hyperphagic or non-hyperphagic. Using the criterion proposed for defining 'objective hyperphagia', all 20 subjects, who were tested and retested, were classified in the same way on the basis of each of the meals and no subjects were classified differently. Thus, the standardised biscuit meal appears to provide a reliable basis both for classifying and measuring hyperphagia.

However, the question remains concerning its validity. One issue is what threshold, in terms of energy consumption, should be used to separate hyperphagics from non-hyperphagics. The second question is, that whatever threshold is chosen, is the 'correct' classification made.

The results showed that there were some subjects, reported to be hyperphagic, who consumed extraordinarily large amounts under the standardised situation. This showed both that the standardised meal was able to identify, and quantify, a group of 'extreme' hyperphagics. It also showed that there are some subjects with dementia in whom the normal mechanisms controlling eating are clearly grossly abnormal.

The results also suggest that hyperphagia is not a categorical concept but rather that there is a continuum in the amount consumed. Taking the demented group as a whole, or the hyperphagic group alone, there was a wide range in the amount eaten,

and there was no 'region of rarity' (i.e. level of food intake in which few subjects fell) to suggest that there are two clear-cut **categories**: those who are hyperphagic and those who are not (see figure 9.3). This conclusion cannot be considered definitive however. First, the numbers of subjects involved is too small to be certain that any 'region of rarity' would be manifest. Secondly, even if hyperphagia were a categorical concept, a 'region of rarity' might be 'filled' with subjects just becoming or just ceasing to be hyperphagic. In addition, thirdly, truly hyperphagic subjects might consume less than their natural amount at the standard meal for the reasons given above.

On *a priori* grounds, one might expect hyperphagia to be a continuum. This is because Alzheimer's disease, at any rate, is a slowly progressive disease in which brain damage gradually increases both in density within a brain region and the size of the areas affected also increases. Whatever the neural mechanisms underlying hyperphagia, it would be most unlikely that these would switch from being normal to absent. Much more likely is that the mechanisms gradually become damaged and, that as they do, the quantity of food intake gradually changes.

Whether or not hyperphagia is to be seen as a continuum, or as a category, if the standardised meal is to be used to identify a group of hyperphagic subjects for further study, a threshold of energy intake needs to be chosen to distinguish the group to be classified as **hyperphagic**, from the group to be classified as **non-hyperphagic**.

To some extent, this is an arbitrary decision and the decision will be affected by the

reason for wanting to define subject groups. It was decided to use a stringent criterion (i.e. a high threshold) because, for the purposes of the research reported in this thesis, those classified as **hyperphagic**, and studied in the later experiments, should be clearly abnormal. It was decided to adopt a threshold of three standard errors above the mean consumption of the normal elderly. The choice of three standard errors was to ensure that those who were classified as hyperphagic were eating an amount which would be very rare in the normal population. However, the classification of individuals was not greatly affected by changing this threshold to two standard errors. It might be asked why it was decided to base the threshold on the normal elderly and not on subjects with dementia. The reason for this was that the epidemiological data suggest that hyperphagia is quite common in dementia. Therefore, if one were to define the threshold based on the mean and standard error of people with dementia, the level might be unduly high. More profoundly, the point is that the **concept** hyperphagia should be a concept based on normal functioning. Thus, it should be possible logically that all people with dementia are hyperphagic. This would be ruled out, even as a logical possibility, if the threshold for hyperphagia were based on the deviation from the mean of a group of people with dementia.

The main weakness in the criterion adopted is the small number of normal elderly on which it was possible to base the mean and standard error. Ideally a larger sample of normal elderly would be studied but the constraints of time made this impossible within the present body of work.

Using the thresholds chosen, to categorise subjects as either 'observed' (or

‘objective’) hyperphagics or ‘objective non-hyperphagics’, only 38% of reported hyperphagics were classified as observed hyperphagics. In addition one subject (7%), who was reported as non-hyperphagic, was classified as an ‘observed hyperphagic’. There are many likely reasons for this discrepancy - and the likely but uncertain proportion of those falsely classified as observed non-hyperphagics. These reasons have been specified above. For many purposes, these potential misclassifications are not serious since the standardised meal is able to identify and quantify marked hyperphagia and this group of subjects is the key group for studying the abnormalities in the control of eating. It is also difficult to overcome some of the reasons why true hyperphagics may not ‘perform’ under the standardised meal condition. However, one reason, the possibility that digestive biscuits alone were unpalatable to many and were seen as a snack rather than a meal, was open to investigation.

In the next experiment I set out to devise a more varied, ‘buffet-style’, mixed meal which was still amenable to standardisation.

B. A MIXED MEAL

AIMS

1. To assess total energy consumption using a more natural meal, giving a choice of familiar foods, to overcome the possible limitations of the biscuit meal. These limitations were that there was a lack of variety and biscuits gave the appearance of a snack and not a 'proper' meal.
2. To compare results with the digestive biscuit meal to see how it affects the classification of people observed to be hyperphagic.

METHOD

Developing the method

The purpose was to devise a standardised situation, to assess total energy consumption during a mixed meal, giving a choice of familiar foods. The main advantage of a buffet-style, mixed meal was that it appeared to be a 'proper' meal and not just a snack. A large choice of different foods contributed to validity as each subject's liking for a single food might vary. The aim was to give a virtually unlimited supply of a variety of foods of different macronutrient content, satiating efficiency, taste, texture, appearance and energy value. Another advantage of this type of meal was that food preferences and macronutrient choice could be examined (see next chapter).

Eight food types were given. The criteria for choosing the foods were that foods should be:

- easily recognised, everyday foods so that palatability and energy values of the different foods would be familiar;
- easy to pick up without the use of cutlery;
- not easily spilt, mixed or smeared;
- easy to chew and swallow to avoid choking;
- of equivalent palatability (similar hedonic qualities) and liked by most people but not attractive enough to encourage overeating;
- easy to prepare and pleasant when eaten cold;
- easy to transport without spoiling or becoming a health risk.

The foods used were ham, cheese, bread with a little margarine, small sweet digestive biscuits, pork cocktail sausages, thick cheese and butter sandwiches, pear and cucumber. Apart from pear and cucumber, the foods were cut into portions of similar energy value, approximately 175 kJ (40 kcals). Each type of food was placed separately on a similar plain plate so that it could be seen and picked up easily.

Timing

To prevent changes in eating which might be due to ageing, increased dementia or change in hyperphagia status, the first mixed meal usually followed the digestive biscuit meal after an interval of a week. An interval was needed to ensure that any compensation after excessive food intake would have no effect on the next meal. The optimum gap was less than a month.

Meals were given to the same three groups of subjects as the digestive biscuit meal.

They were:-

- reported hyperphagic demented subjects (n=25);
- non-hyperphagic demented controls matched for age, sex, cognitive ability and diagnosis (n=14);
- normal elderly matched for age and sex (n=14).

Meal procedure

The plates were arranged in a semicircle, equidistant from the subject (figure 9.7).

The foods were arranged in blocks according to their macronutrient content (figure 9.8), this was designed to investigate macronutrient choice (see next chapter). For each consecutive subject or control, the order was rotated in a fixed sequence to avoid any position effect.

To reduce the independent variables affecting eating, the aim was to make each plate appear to have a similar quantity of food on it of comparable palatability. If necessary the plates were 'topped up' during the course of the meal so that a virtually unlimited quantity of any food could be eaten if desired. Replenishing was done unobtrusively when only two or three units remained on a plate. If necessary, foods were sorted out again if they had been mixed up during the course of the meal. Again a safe maximum intake of 12 000 kJ was observed. The plate needed to be plain, as patterned plates confuse people with poor eyesight or cognition and they often try to pick up the pattern.

Figure 9.7 Arrangement of food on the table

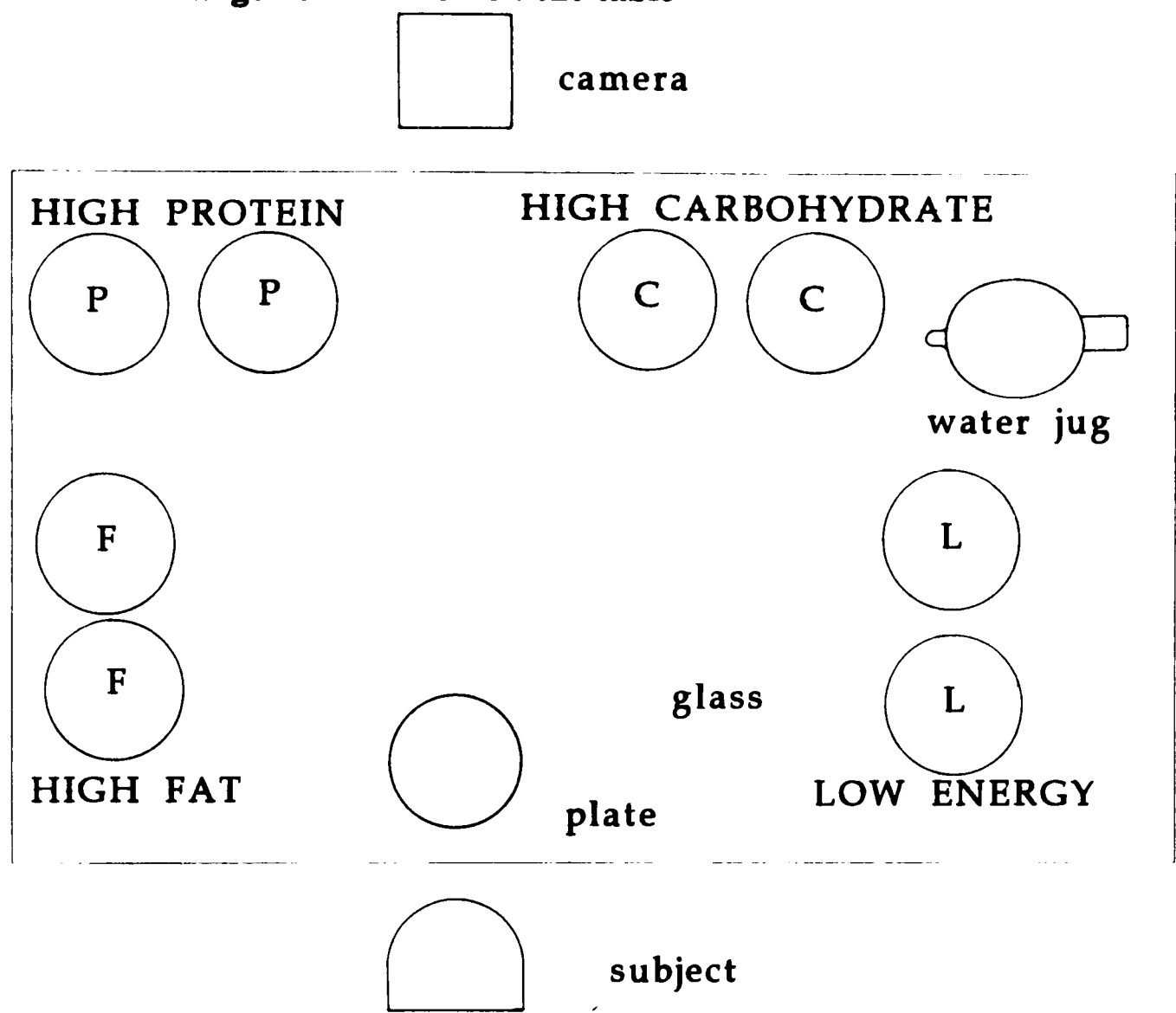
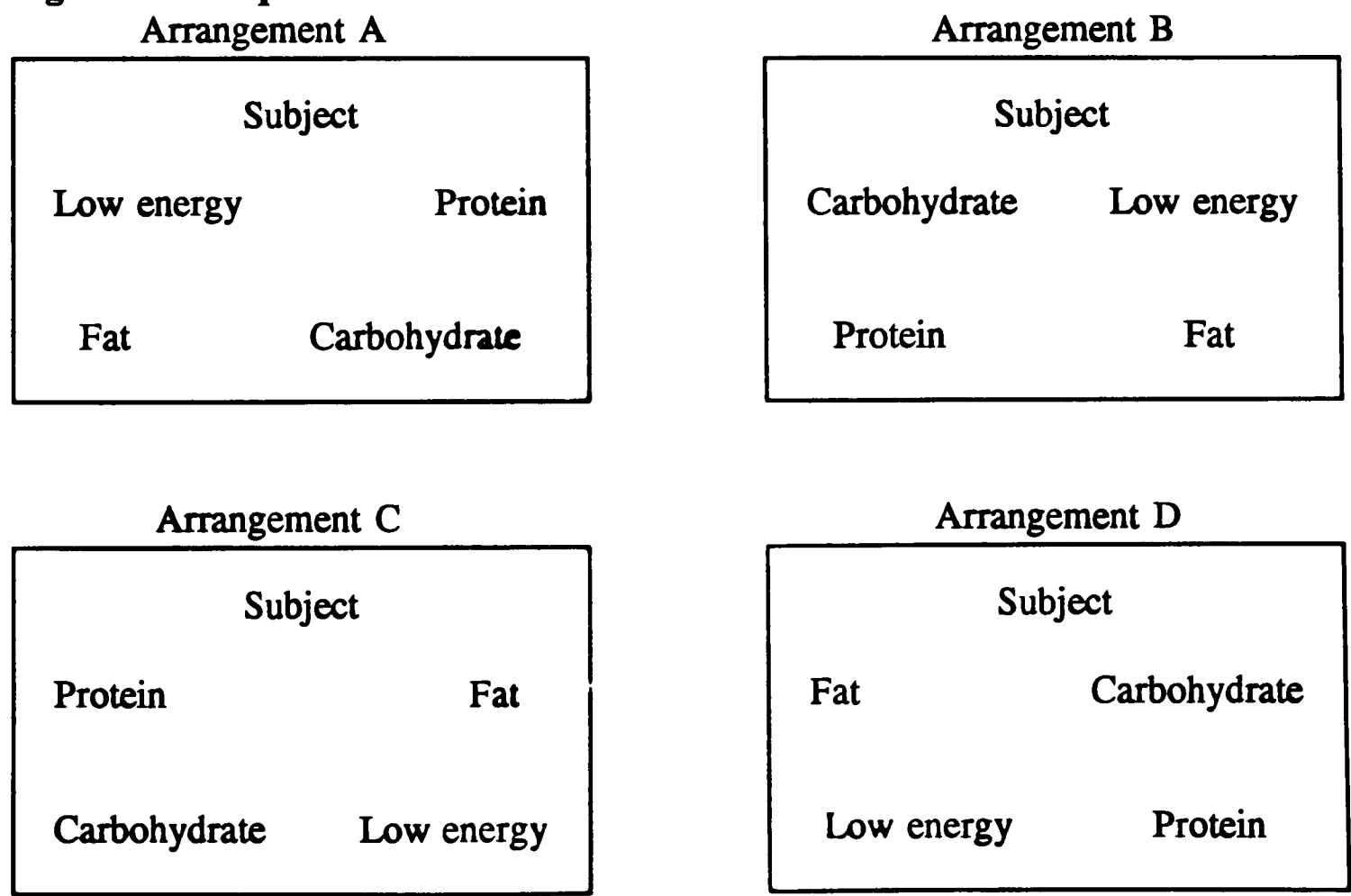


Figure 9.8 Sequence of rotation of foods



Data on energy value and macronutrient composition were taken from the packets, or for unprocessed foods, from McCance and Widdowson (Paul & Southgate, 1991). The conditions in the room were kept constant on each occasion and the meal was given in a place where the subject could not see other people eating. Drugs currently being taken by subjects and controls were recorded, as some are known to affect appetite. Each carer was asked about the intake of food during the rest of the day, to assess whether it was more, less or the same as usual, in order to see if there was compensation after the mixed meal. Normal controls were also contacted the next day to ask about their subsequent food intake.

The procedures for starting the meal, ending the meal and responding to behaviour during the meal were the same as described above for the 'biscuit meal'.

RESULTS

Energy intake

The mean energy intake at the first mixed meal are shown in figure 9.9 and table 9.7.

a) All reported hyperphagics

The mean intake of the reported hyperphagic group was 4097 kJ. Again the range of intake was large, ranging from two people who refused to start to others who ate more than an average day's intake for someone of this age group. The reported hyperphagic group ate significantly more than the normal elderly (t-test: $t = 2.76$, $df = 37$, $p = 0.009$) and they also ate more than the non-hyperphagic demented group (t-test: $t = 2.49$, $df = 37$, $p = 0.017$).

Figure 9.9

Figure 9.9 ENERGY VALUE (All reported hyperphagic)
Mixed meal 1

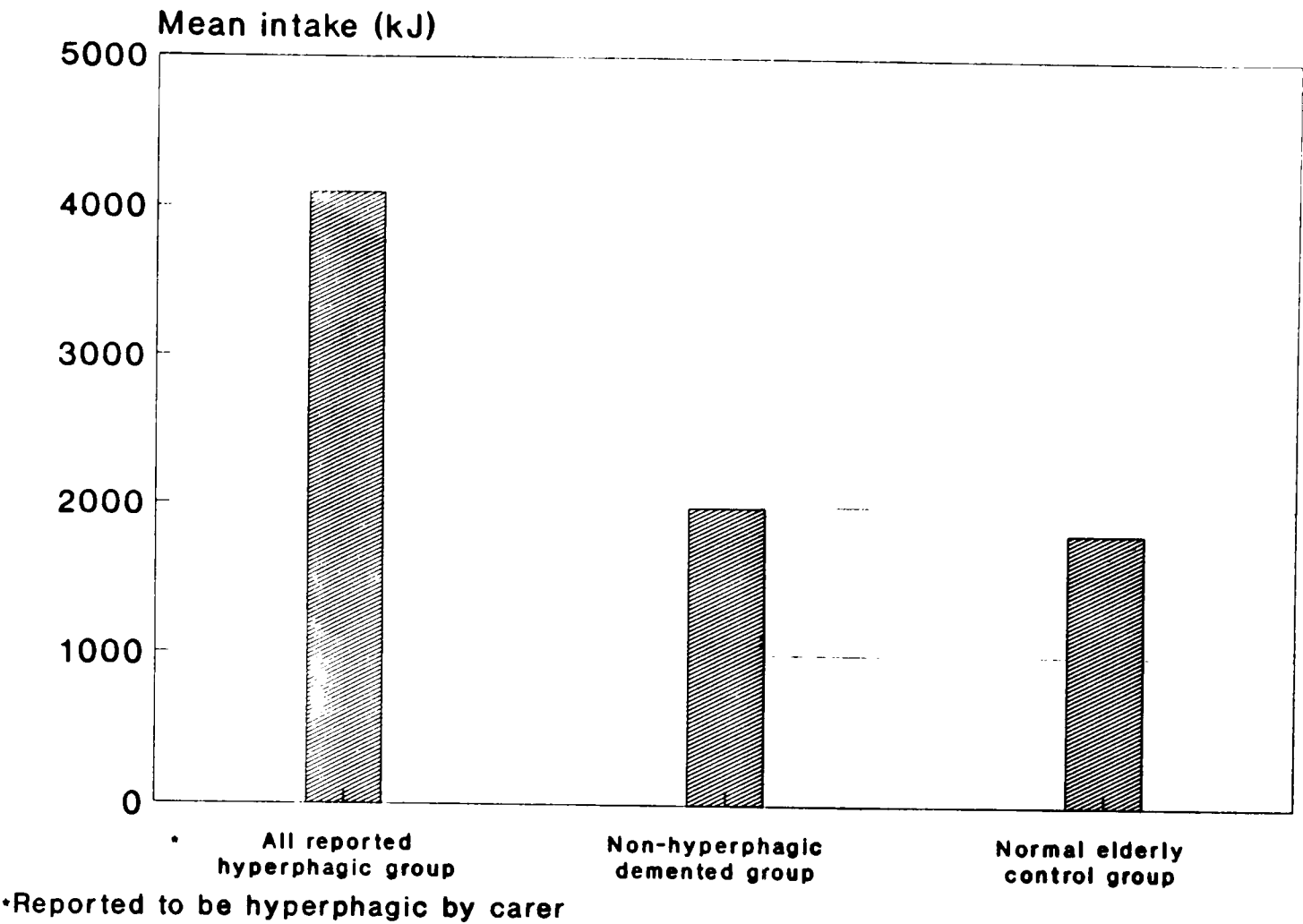


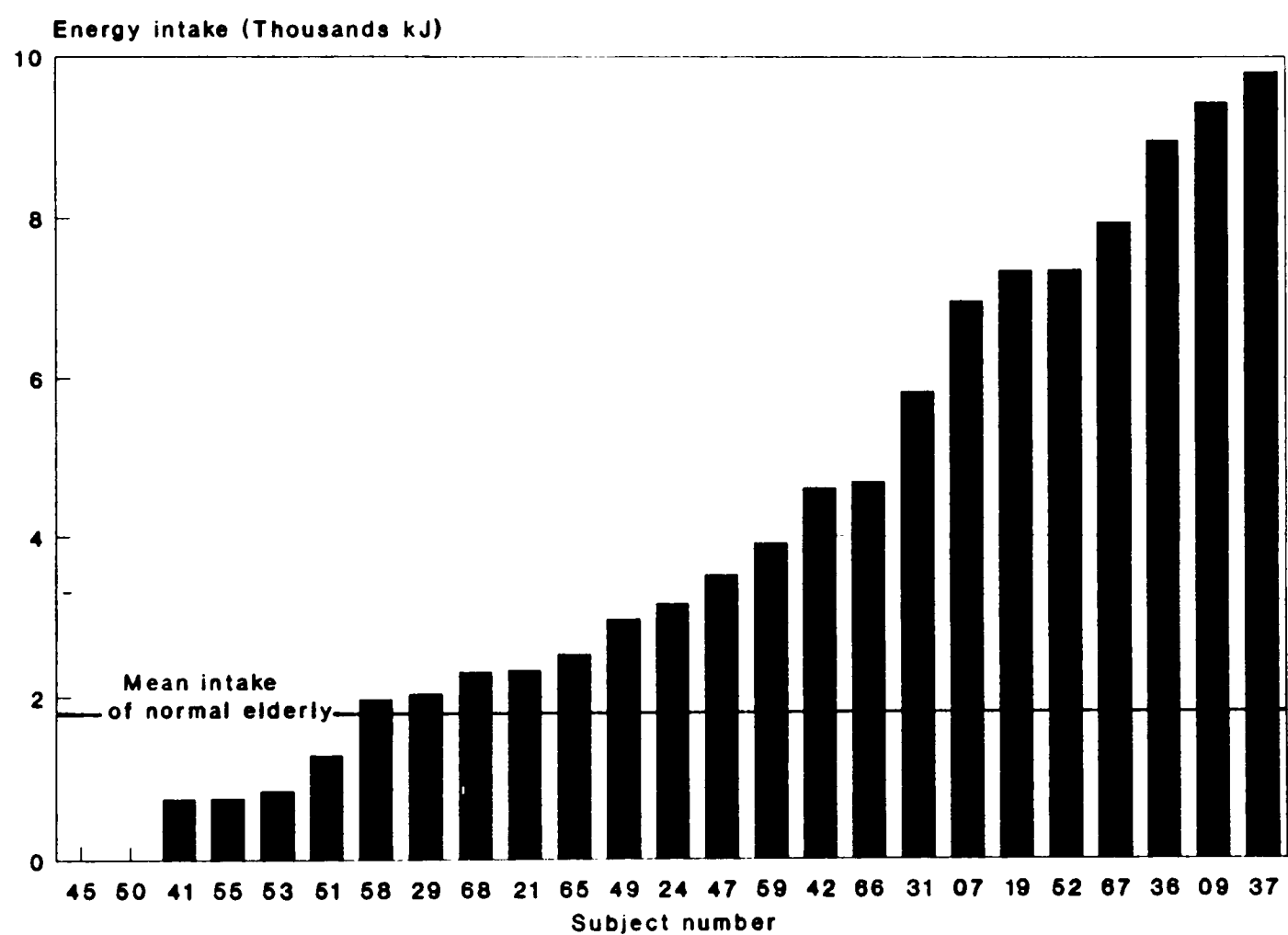
Table 9.7 Total energy value of mixed meal 1 (kJ) - All reported hyperphagics

SUBJECT GROUP	MEAN (kJ)
All reported hyperphagics	4097 (S.D. 3036; range 0-9813; n=25)
Non-hyperphagic demented controls	1987 (S.D. 1164; range 13-3999; n=14)
Normal elderly controls	1823 (S.D. 505; range 1127-2908; n=14)

Three of the reported hyperphagic demented group were stopped because they were still eating after 2 hours and two were stopped because they seemed to be uncomfortably full.

As was found with the biscuit meal, the amount eaten at the mixed meal by the reported hyperphagics varied greatly from individual to individual (figure 9.10).

Figure 9.10 MIXED MEAL - all reported hyperphagics



b) Demented non-hyperphagic control group

The amount eaten by the non-hyperphagic demented controls was very variable (mean 1987 kJ; S.D. 1164; range 13-3999). The time they spent eating was also highly variable with a mean of 49.9 minutes. One person, who was eating very slowly, was

stopped after two hours. The non-hyperphagic group did not eat a significantly different quantity of food from the normal elderly in terms of energy value (kJ) but they ate significantly less in terms of mass (g) the elderly eating a mean of 249 g and the non-hyperphagic controls eating 183 g (t test: $t = 2.3$, $df = 26$, $p = 0.03$). This reflected their small intake of low-energy foods (pear and cucumber) and slightly higher intake of high-fat foods.

c) Normal elderly controls

Although the normal elderly ate a similar amount to the non-hyperphagic demented on average, they were much less variable (mean 1823 kJ, S.D. 505, range 1127-2908) and they ate much more quickly (mean 17.6 minutes, range 9-29). None of the normal elderly group was stopped.

Compensation after the mixed meal

During the mixed meal the mean energy intake was about 150% that of the biscuit meal. In the two control groups, during the rest of the day, there was very little compensation after the mixed meal. Therefore, the mixed meal was presumably equivalent to the normal midday meal. Five people who were reported to be hyperphagic, but who did not eat excessively during the test meal, did eat more during the rest of the day. They seemed to be socially aware and either refused the mixed meal or were suspected of holding back out of politeness during the meal. They presumably compensated by eating more during their normal meal conditions.

Effect of neuroleptic drugs

The only drugs being taken which might have affected appetite were neuroleptics. At the mixed meal 10 out of 25 (40%) of the reported hyperphagics were on drugs in this category and 3 out of 14 (21%) of the demented control group were also taking such drugs. This was not a significant difference (chi-square after Yates' correction: 0.68, $p = 0.41$). In both groups there was a trend for the people taking these drugs to eat more but the difference was not significant except for the non-hyperphagic demented group (t-test: $t = 3.29$, $df = 4.5$, $p = 0.025$). None of the normal control group took drugs which might have affected their appetite.

TEST-RETEST RELIABILITY

AIM

To examine the test-retest reliability of the mixed meal.

METHOD

For test-retest reliability, the mixed meal was repeated, after an interval of at least 14 days, with a sample of all three groups of subjects and controls. The order and timing of the meals were that the first test meal was a biscuit meal, followed at least a week later by the first mixed meal. The retest meals were given at least a week after the first mixed meal. They were given in the same order i.e the second biscuit meal first with the second mixed meal at least a week afterwards.

Conditions were kept as identical as possible to reduce variables and the time interval was to prevent people from remembering how much they had eaten previously. Also,

in order to avoid jogging the memory of the normal group, the order of foods in the mixed meal was rotated on the second occasion in the order:

Meal 1	Meal 2
A	B
B	C
C	D
D	A

This rotation of the order of food was to eliminate any position effect in the choice of food.

RESULTS

Intra-subject reliability

Overall the test-retest reliability was high (Pearson correlation: 0.87; $p < 0.0005$). There was a highly significant correlation between the energy intake of the first and the second mixed meal in the hyperphagic group (Pearson correlation: 0.803, $p = 0.005$), see table 9.8 and figure 9.11. The sample sizes for the other two groups were small and correlations for the non-hyperphagic group (0.344) and the normal elderly (0.700) were not significant. The non-hyperphagic demented group were again the least reliable, both in the amount eaten by different individuals and in the amount eaten by the same individual on different occasions. The scatter graph (figure 9.12), however, shows that most individuals ate very similar amounts at the first and the second meal. Paired t-tests were carried out between each group (see table 9.9) and there was no significant difference in intake between the first and second mixed meals.

Figure 9.11 **RELIABILITY - Mixed meals 1 and 2**
Test-retest

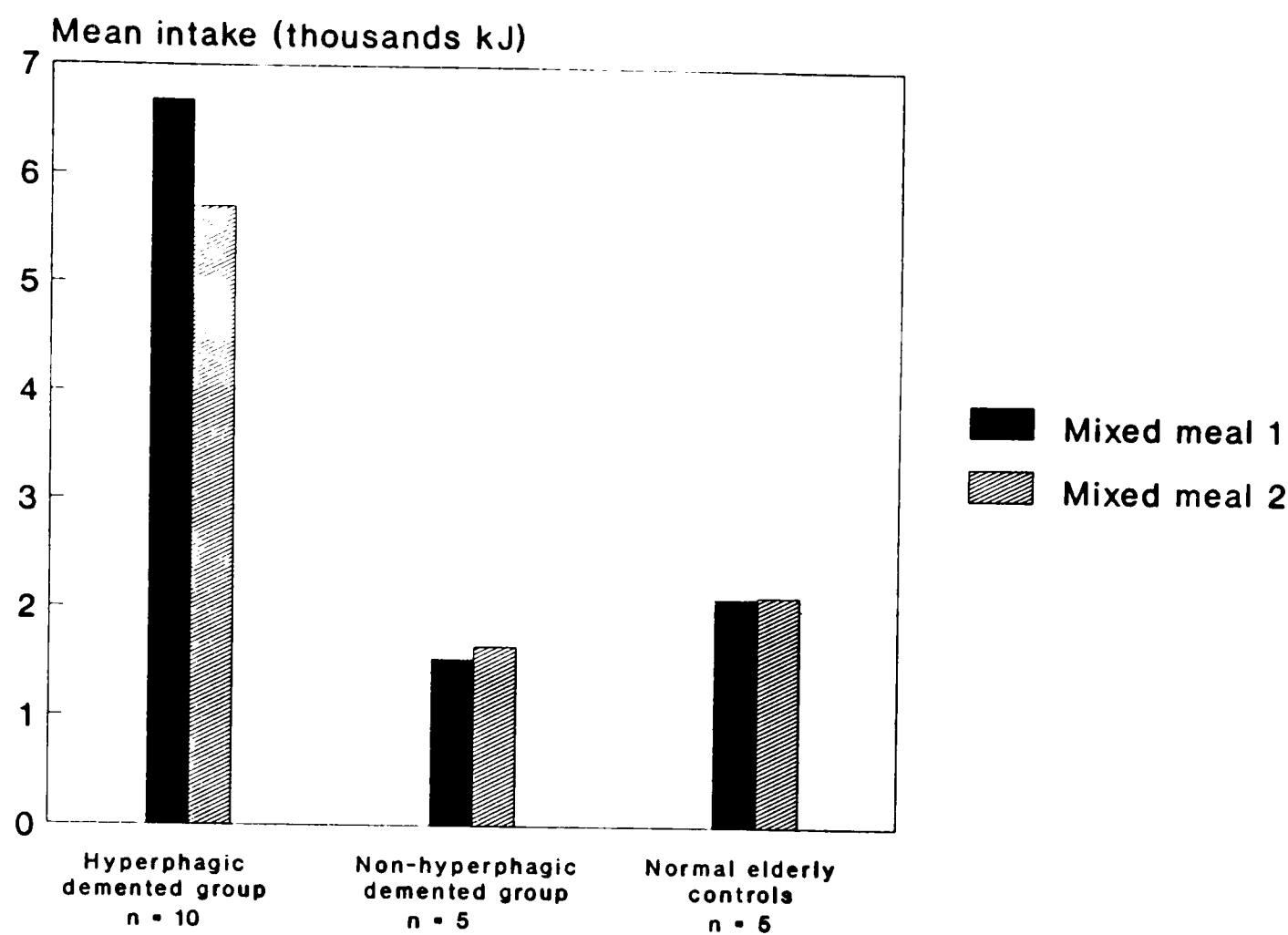


Table 9.8 Total energy intake of mixed meals 1 and 2

Comparison of 2 mixed meals by group		Mean (kJ)
Hyperphagic group (n = 10)		
Mixed meal 1	6683	(S.D. 2413; range 2973-9813)
Mixed meal 2	5703	(S.D. 3177; range 1409-11167)
Non-hyperphagic demented controls (n = 5)		
Mixed meal 1	1529	(S.D. 1028; range 13-2586)
Mixed meal 2	1645	(S.D. 478; range 904-2128)
Normal controls (n = 5)		
Mixed meal 1	2108	(S.D. 464; range 1804-2908)
Mixed meal 2	2120	(S.D. 379; range 1661-2594)

Figure 9.12 **CORRELATION OF MIXED MEALS**
Meal 1 and meal 2

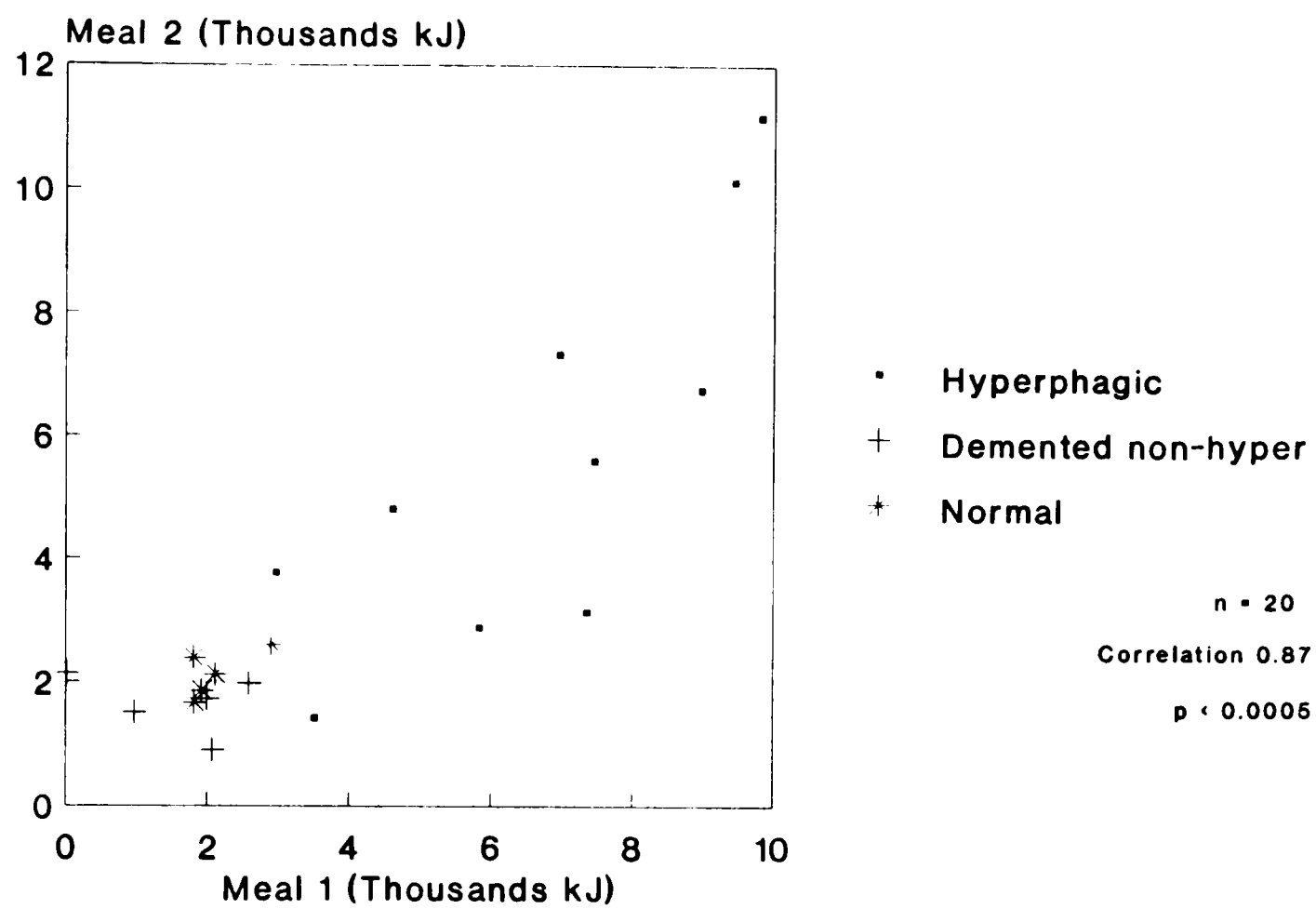


Table 9.9 **Intra-subject reliability - mixed meal 1 and 2.**
Correlation and paired t-test

Group	Correlation	t-test
Hyperphagic demented group (n = 10)	0.803 (p = 0.005)	1.63 (p = 0.137)
Non-hyperphagic demented controls (n = 5)	0.344 (p = 0.571)	0.20 (p = 0.848)
Normal controls (n = 5)	0.700 (p = 0.188)	0.08 (p = 0.940)
All groups (n=20)	0.869 (p <0.0005)	1.33 (p = 0.198)

COMPARISON OF ENERGY INTAKE OF THE TWO TYPES OF MEAL

METHOD

Having demonstrated that the reliability for both types of meal was good, a comparison was made between the intake and the reliability of the first digestive biscuit meal and the first mixed meal.

RESULTS

The energy intake at the two types of meal, in all three groups, was consistently higher during the first mixed meal than at the first biscuit meal; in general people ate nearly half as much again at the mixed meal (figure 9.13, table 9.10). The results for all three groups (reported hyperphagics, non-hyperphagic and normal elderly) are shown as a scatter graph for the energy intake at the two meals (figure 9.15).

As well as eating more at the mixed meal all three groups ate for a longer period of time during the mixed meal than the biscuit meal (see figure 9.14 and table 9.11).

Figure 9.13 ENERGY VALUE (All reported hyperphagic)
Digestive biscuit and mixed meal

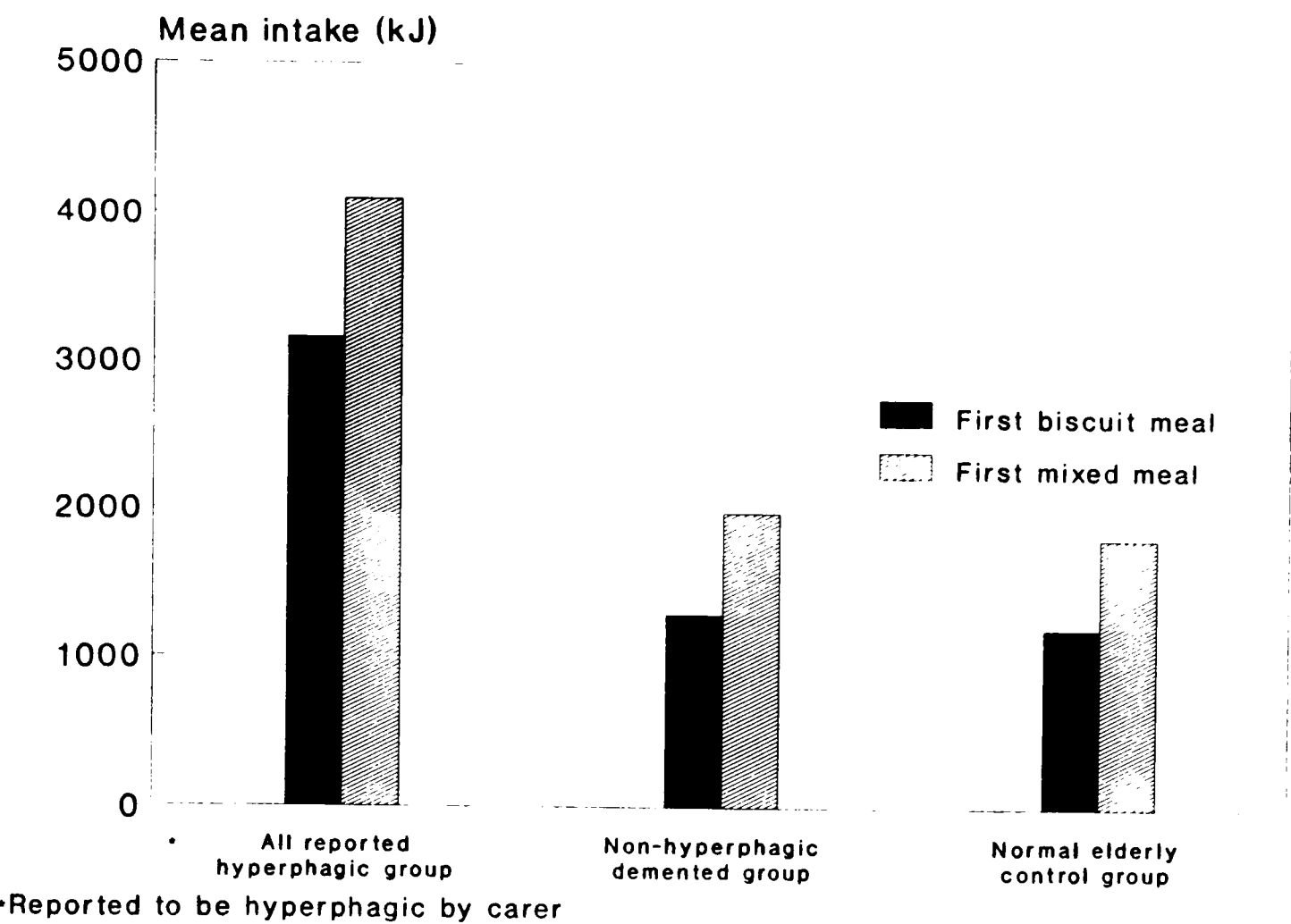


Table 9.10 Inter-meal reliability

Group	Digestive meal 1 (kJ)	Mixed meal 1 (kJ)
All reported hyperphagic group	3160	4097
Non-hyperphagic demented controls	1292	1987
Normal controls	1204	1823

Figure 9.14 MEAL TIME - first biscuit and mixed meal
 Time taken to eat meal (minutes)

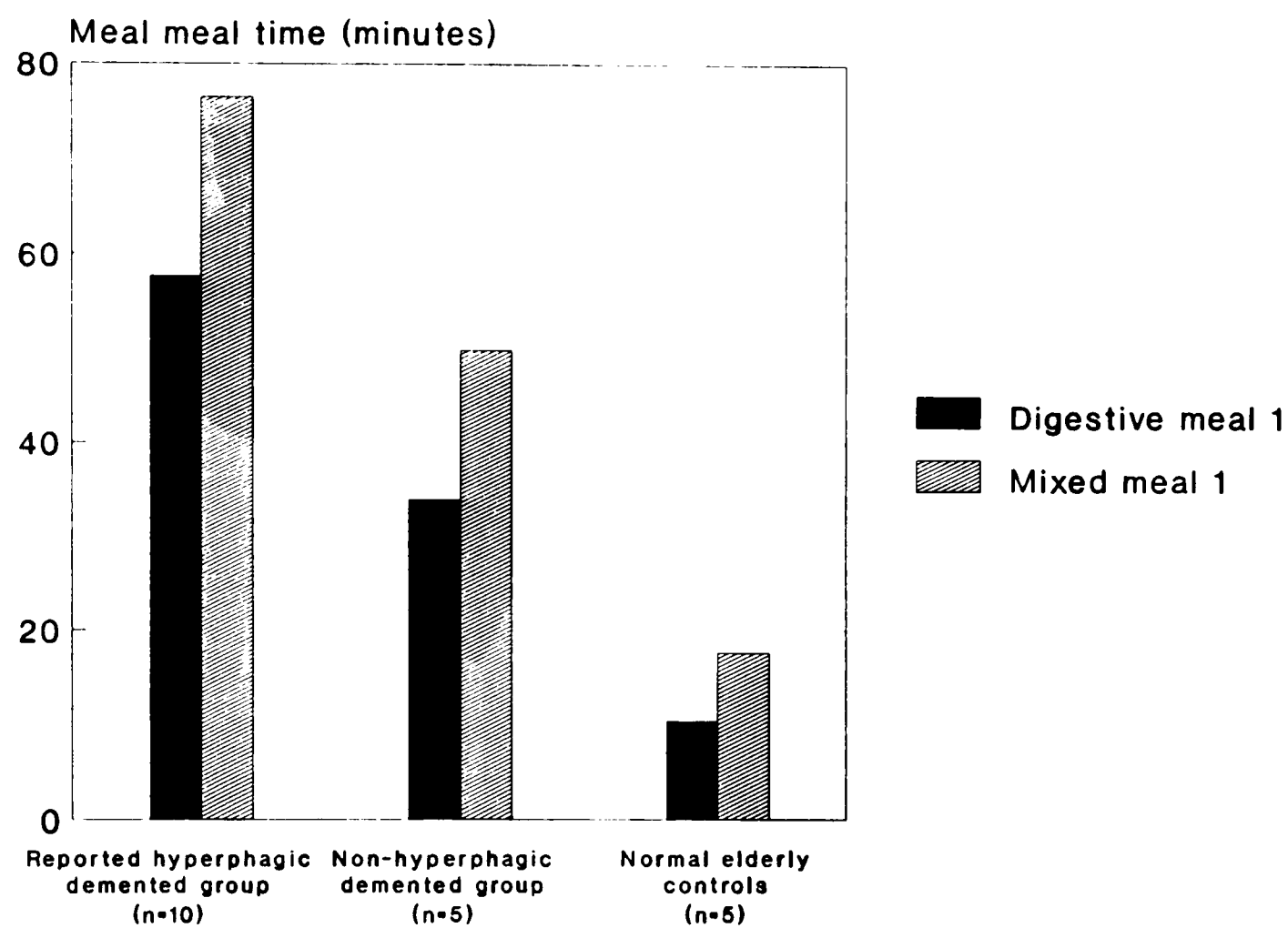
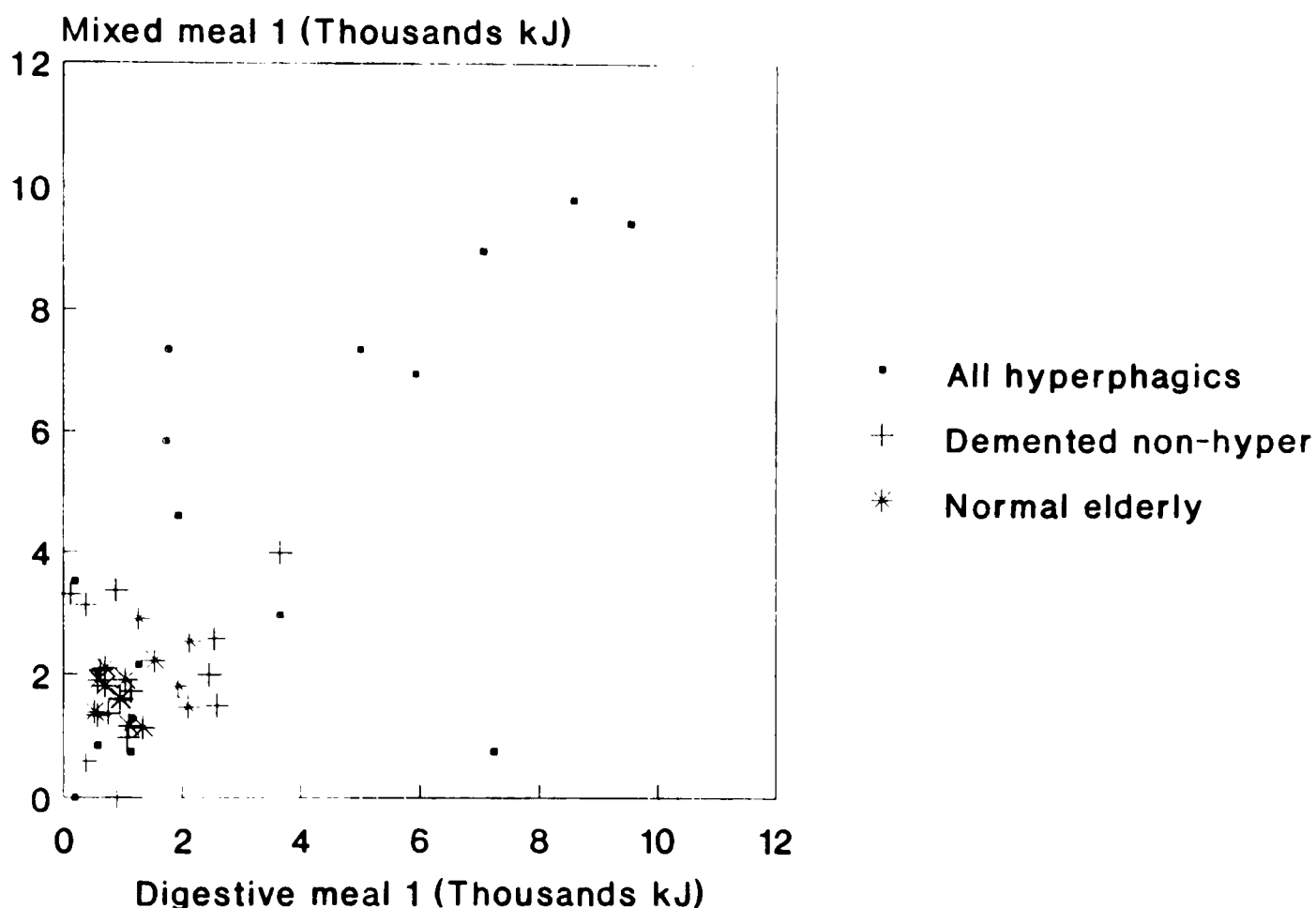


Table 9.11 Mean mealtime for the two types of meal

DIGESTIVE MEAL 1	
Subject group	Meal time in minutes
Hyperphagic group	57.7 (S.D. 36.9, range 5-121, n=18)
Non-hyperphagic demented	33.9 (S.D. 35.7, range 5-120, n=14)
Normal elderly controls	10.4 (S.D. 5.5, range 4-24, n=14)
MIXED MEAL 1	
Subject group	Meal time in minutes
Hyperphagic group	76.5 (S.D. 32.5, range 31-120, n=17)
Non-hyperphagic demented	49.9 (S.D. 42.4, range 2-120, n=14)
Normal elderly controls	17.6 (S.D. 6.8, range 9-28, n=14)

Figure 9.15 CORRELATION OF TWO MEAL TYPES
Biscuit meal 1 and mixed meal



EXPERIMENTAL DEFINITION OF HYPERPHAGIA USING THE MIXED MEAL

As in the biscuit meal, a threshold for hyperphagia for the mixed meal was defined by taking the mean of the normal control group plus three standard errors. This was chosen for the same reasons as given for the biscuit meal. For the mixed meal, the mean of the normal group was 1823 kJ and the standard error was 504.8 therefore 3337 kJ was taken as the threshold. People ate more at the mixed meal, this was predicted from the reasons given previously suggesting why the single food meal led to undereating in some people. The mean intake for the hyperphagic group was over 150% of the threshold for both meals whereas the mean for both control groups was under 60% of the threshold for both meals.

Using criteria, based on these thresholds (see page 121), the mean intake of the observed hyperphagic group at the first biscuit meal was 4239 kJ, representing a range of 1 - 55 biscuits. The mean intake at the first mixed meal was 5462 kJ - range 1900-9813 kJ (see tables 9.12 and 9.13 and figure 9.16).

Table 9.12 Comparison of energy intake during the two types of meal

Group	Biscuit meal Mean (kJ) Threshold 2824 kJ	Mixed meal Mean (kJ) Threshold 3337 kJ	Ratio Biscuit/mixed
Observed hyperphagic group (n=17)	4239	5462	1:1.29
N6on-hyperphagic demented controls (n=14)	1292	1987	1:1.63
Normal elderly controls (n=14)	1204	1823	1:1.51

Figure 9.16 ENERGY VALUE (Observed hyperphagics)
 Digestive biscuit and mixed meal

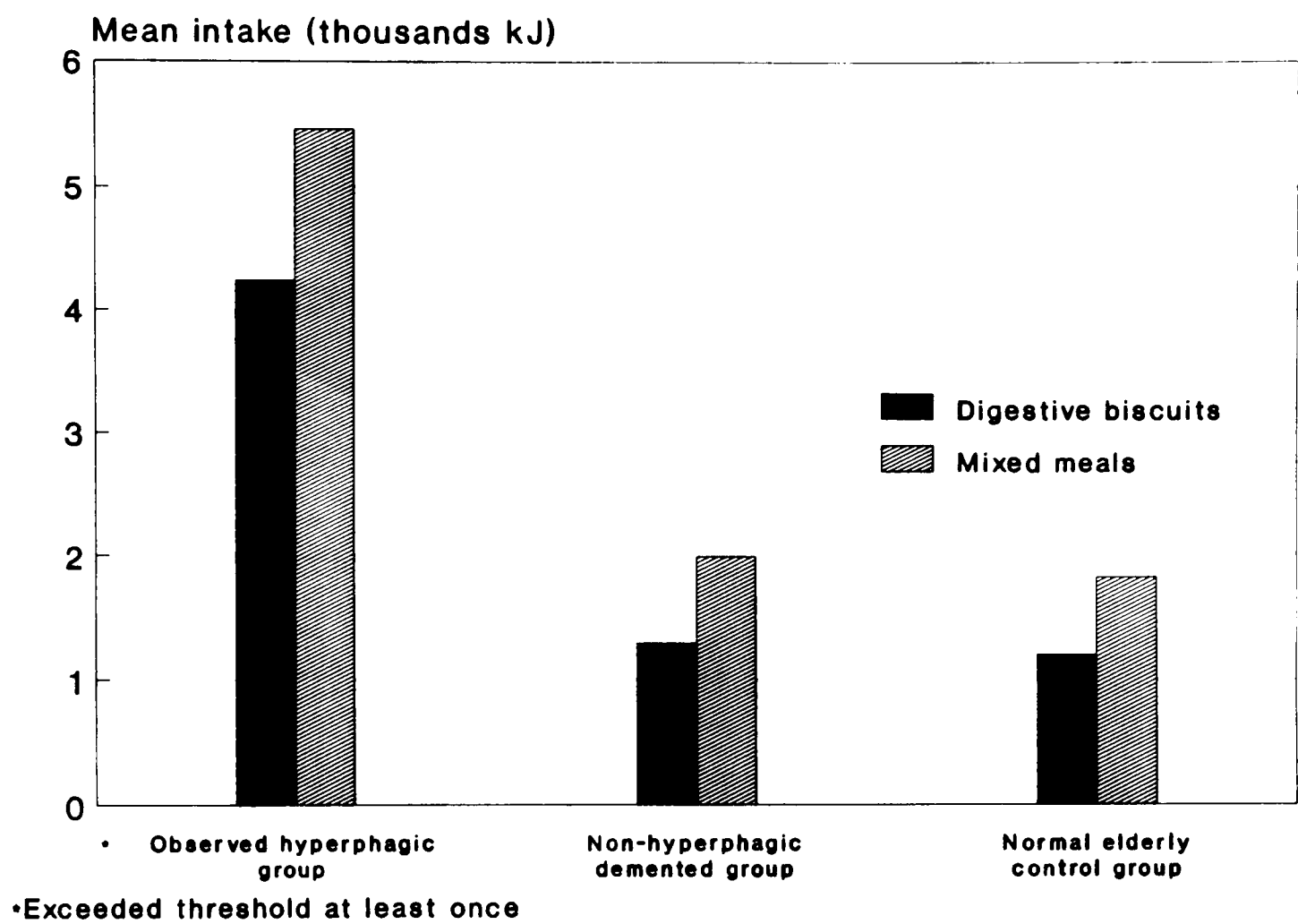


Table 9.13 Total energy value mixed meal 1 (kJ) -‘Observed hyperphagic group’

SUBJECT GROUP	MEAN (kJ)
‘Observed hyperphagic group’	5462 (S.D. 2688; range 1900-9813; n=17)
Non-hyperphagic demented controls	1987 (S.D. 1164; range 13-3999; n=14)
Normal elderly controls	1823 (S.D. 505; range 1127-2908; n=14)

a) Reported hyperphagic group

Twenty-five people, reported to be hyperphagic, had both types of meal. Twelve of them were classified as hyperphagic by the mixed meal but only nine by the biscuit meal. Five people, who did not exceed the threshold during first biscuit meal, were classified as hyperphagic by the first mixed meal and another three people exceeded the threshold for hyperphagia during the second mixed meal. Four of these ‘reclassified’ people had the highest MMSE in the reported hyperphagic group and seemed to be the most socially aware.

Reported hyperphagic, demented subject group
(Subjects reported by carers currently to show signs of hyperphagia.)

10/26 exceeded threshold of 2824 kJ at the first single food meal.
12/25 exceeded threshold of 3337 kJ at the first mixed food meal.

b) Non-hyperphagic demented controls

The person in the demented control group who, although reported to be non-hyperphagic, exceeded the threshold during the digestive meal also exceeded the threshold on the mixed meal. A second person in this group marginally exceeded the threshold during the first mixed meal.

Non-hyperphagic demented control group
(Matched controls with dementia who were reported by carers not to show signs of hyperphagia.)

1/14 exceeded threshold during the first single food meal
2/14 exceeded threshold during the first mixed food meal

c) Normal elderly group

None of the normal elderly were classified as hyperphagic by either meal (see table 9.14). They all were within the 2 standard errors of the mean on the digestive biscuit

meal and during the mixed meal only one man marginally exceeded 2 standard errors of the mean.

Table 9.14 Classification for hyperphagia on the proposed criteria for subjects having both the first biscuit and mixed meals

	Digestive biscuit meal 1		Mixed meal 1	
Group	Non-hyperphagic	Hyperphagic	Non-hyperphagic	Hyperphagic
All reported hyperphagic (n = 25)	16	9	13	12
Reported non-hyperphagic group (n = 14)	13	1	12	2
Normal elderly group (n = 14)	14	0	14	0

DISCUSSION - reliability of mixed test meal

The aim of the mixed meal experiment was to see if giving a more natural meal overcame some of the difficulties encountered during the biscuit meal. One disadvantage of a single food meal was that subjects may not have liked the type of food offered and another difficulty was that a plate of biscuits resembled a snack rather than a full meal, which may have prevented the more socially aware people from overeating when they were being observed.

As with the digestive biscuit meal two questions have been examined. The first is whether the energy intake at the mixed meal was reliable and the second question is what the relationship was between the carers’ report and amount eaten in a mixed meal.

Reliability of classification using a mixed meal

The same criterion for 'objective hyperphagia' was used for the mixed meal, as for the biscuit meal (i.e. the mean energy intake of the normal elderly group plus 3 standard errors). The classification of all ten people in the normal elderly and non-hyperphagic control groups, who were retested, was reliable as all ten were classified as non-hyperphagic on both mixed meals. In addition none of them exceeded the threshold during any of the other meals in the study.

All ten of the reported hyperphagic group who were retested were classified as hyperphagic on one of the mixed meals and six exceeded the threshold on both. The biscuit meal only classified six of the same ten people as hyperphagic, therefore it seemed that the mixed meal was more sensitive but less reliable when used to classify a hyperphagic group. The mixed meal, however, can be regarded as a valid measure of hyperphagia because all ten people who exceeded the threshold during one of these test meals also exceeded the threshold during at least one other meal in the study, showing that classification of hyperphagia using the mixed meal gave valid results.

The relationships between 'reported' hyperphagia and 'observed' hyperphagia using the biscuit and the mixed meal

When making a comparison of people who were rated hyperphagic at the digestive biscuit meal with those at the mixed meal it depends, of course, on where the threshold is set. The advantage of using normal controls as the yardstick for both meals is that the method is consistent.

a) All reported hyperphagics

(i) Positive confirmation of hyperphagia

Twelve of the 25 reported hyperphagics exceeded the threshold of 3337 kJ on the first mixed meal. The first two mixed meals classified seven people as hyperphagic who did not exceed the threshold during digestive biscuit meals. While they were observed during the biscuit meal, at least four of these seven, who were more socially aware, had appeared to have been restraining, as if they thought it inappropriate to eat a large number of biscuits. The other people who ate more at the mixed meal than the biscuit meal seemed to be borderline hyperphagics, during some meals they exceeded the threshold and during others they did not. As suggested by the biscuit meal, the hyperphagic group seemed to represent a continuum. At the severe end of the scale were five subjects who consistently ate more than the threshold at each of the first four meals, sometimes to the point where they had to be stopped.

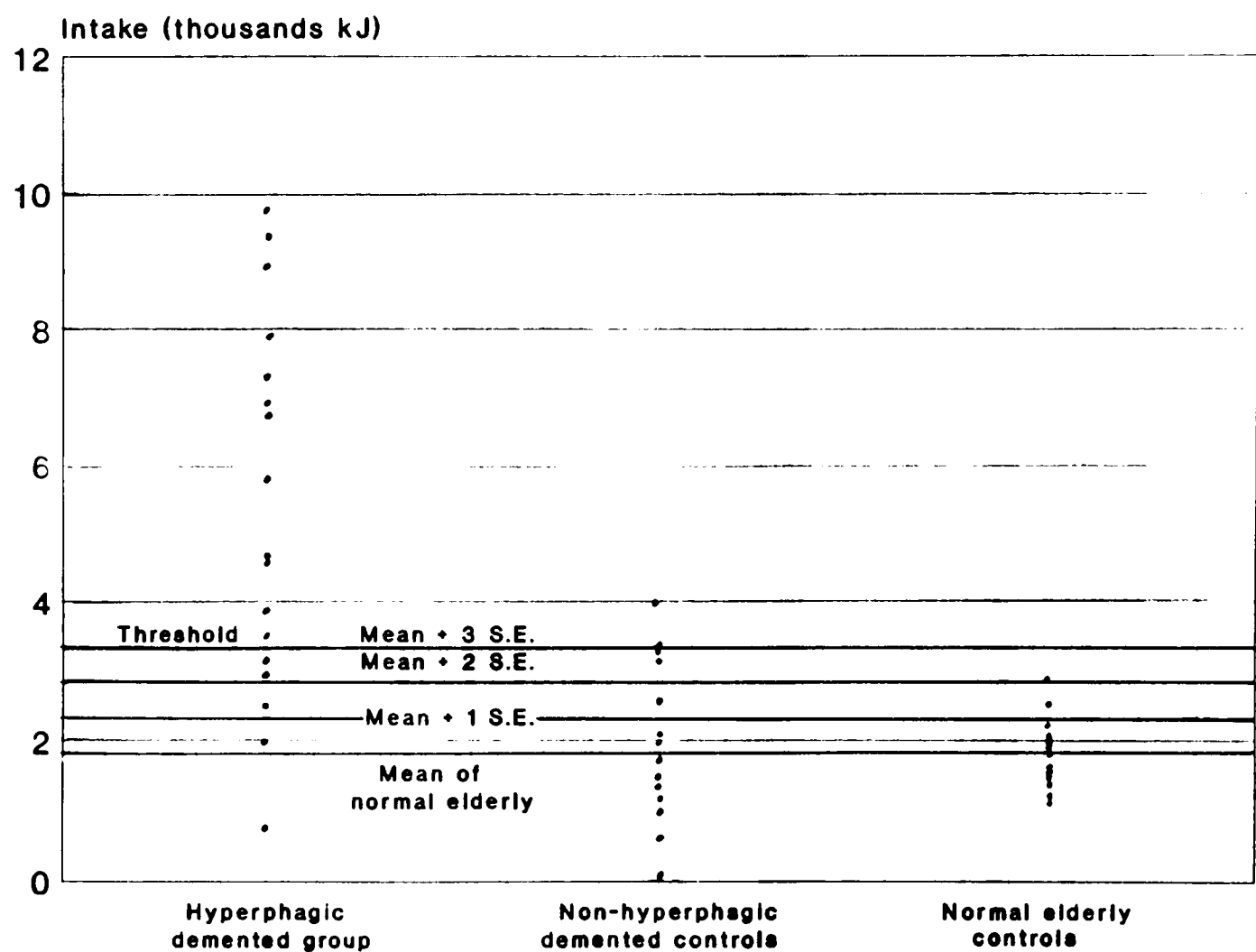
(ii) Negative results

Of the 25 people who were given a mixed meal, 13 did not exceed the threshold. One person, classified as hyperphagic by the first biscuit meal, did not exceed the threshold during subsequent mixed meals. The apparent reason seemed to be that she had passed the peak of the hyperphagia stage, and her eating behaviour had changed, rather than because the mixed meal was an unreliable method of assessing hyperphagia. The probable reasons for genuine hyperphagics not exceeding the threshold in test meals are listed on pages 113-114.

Like the biscuit meal lowering the threshold would not have had a marked effect (see figure 9.17). If the threshold was lowered to the mean of the normal elderly + 2 S.E. two more people would have been included, and by lowering it to mean + 1 S.E. one more would have been included (all three exceeded the threshold during their second mixed meal).

The results show that a group of people are clearly eating more than normal for this age group. Some, having already eaten a substantial breakfast and a mid-morning snack, ate more than the equivalent of a whole day's energy intake at one sitting (see table 9.15).

Figure 9.17 **Mixed meal intake (kJ)**



Eating in elderly control groups

Table 9.15 Estimated average requirements (EAR) (HMSO, 1991)

Group characteristics	Male		Female	
Age	65-74	75 +	65-74	75 +
Weight (kg)	71	69	63	60
Estimated energy requirements (MJ/day)	9.71	8.77	7.96	7.61
Estimated protein requirements (g/day)	37.2 g/day for 62 kg person over 50			

Whereas both the normal elderly and the non-hyperphagic controls ate less than one-third of the estimated average daily requirements for their age group, the mean intake of the hyperphagic group was more than two-thirds of their estimated average requirements and some ate considerably more than the requirements for the whole day during a single meal.

b) Non-hyperphagic demented controls

The non-hyperphagic group were more erratic, how much they ate seemed to depend on their mood, their concentration and restlessness. With all the demented subjects, whether reportedly hyperphagic or not, the end-point of the meal often seemed to be apparently arbitrary if, for instance, the person was distracted or walked away forgetting where they had been eating. The chance timing of the end-point of the meal determined the total intake (see Chapter 11).

However, the non-hyperphagic controls were apparently not driven to eat by hunger, as the hyperphagic group seemed to be, nor were they bound by the social conventions and expectations of the normal elderly. Although the test-retest reliability

was good, two of the 14 people in the reportedly non-hyperphagic group were classified as hyperphagic by the mixed meal. This was probably because they had developed a degree of hyperphagia but the amount of food they had access to was carefully controlled. Both were reported to be hyperactive. Both were severely demented and unable to ask or look for more food and neither had access to extra food, which is why carer's were unlikely to have seen signs of hyperphagia.

c) Normal elderly control group

The normal group were consistent in the amount they ate during both types of meal. None of the 14 normal elderly controls approached the threshold for hyperphagia during any of the meals. The arbitrary level, of the mean of the normal controls plus three standard errors, chosen to classify hyperphagia, was clearly reliable in separating the normal from the 'observed' hyperphagic group.

Validity of classification

The mixed meal is probably a more valid measure for confirming hyperphagic behaviour reported by carers although both the digestive biscuit meal and the mixed meal were able to identify an extreme group of people with dementia who overeat. As with the digestive biscuit meal, some subjects refused to participate but fewer people seemed to be restraining and they treated it as a normal meal and not as a snack. This seemed to indicate that the mixed meal resulted in fewer people with hyperphagia being misclassified as normal eaters. However, even for the mixed meal, this classification did not confirm all the carers' reports of overeating. This may partly be that the threshold is a stringent one and also that the subjects, for a variety

of reasons do not overeat under experimental conditions. Carer's reports only seemed to be reliable predictors of hyperphagia if they had enough contact with the person and there was an opportunity for the subject to have access to extra food or to be able to ask for more. Sometimes nursing home staff had not noticed that, for people who they reported as hyperphagic, the overeating stage had ended.

For all three experimental groups, a major difference between the two types of meal was that on average all groups ate more of the mixed meal than they did at the single food meal. This confirms experiments investigating sensory specific satiety in young people, which showed that eating a single food soon results in satiety for that food, whereas a variety of foods stimulates the appetite (Rolls *et al*, 1981).

It also seemed that this meal was a better indicator of normal food intake as the quantity of food eaten during the rest of the day was the same as usual in a larger proportion of people after the mixed meal than after the biscuit meal. This indicates that the buffet-style mixed meal has a greater similarity to a normal midday meal. The mixed meal is a valid, if less stringent, measure of hyperphagia than the biscuit meal.

Definition of 'observed' hyperphagic group

A definition of hyperphagia is an excessive consumption of food in comparison with someone of the same age and sex. People who were described by this definition were recruited first from carers' reports and the validity of their report was tested by direct observation. Although the experimental setting probably excluded some people who

were genuinely hyperphagic, it did provide a sufficiently large group to allow an experimental investigation of hyperphagia. Therefore, for the purposes of future experiments, subjects were included in the experimental hyperphagic group on the basis of the carers' report and if they exceeded the threshold on at least one of the first three test meals. This group of people were the observed hyperphagic, demented group used for the experiments described in the rest of the thesis. Together with the closely matched control groups, they took part in further experiments to characterise the changes which occur both in dementia and in hyperphagia.

Chapter 10 MACRONUTRIENT AND FOOD CHOICE: HYPERPHAGIA, DEMENTIA AND AGEING

AIM

1. To investigate whether the choice of macronutrients (protein, fat and carbohydrate), in those who are hyperphagic, is significantly different from the two control groups.
2. To investigate whether the ratio of sweet to savoury food intake is affected by age, by dementia and in hyperphagia.

INTRODUCTION

The question arises, in those who are hyperphagic, whether the preferred macronutrient intake is abnormal. This is important in a full description of the phenomenon and in addition it could shed light on the underlying mechanisms.

Neurotransmitters and food choice

From human and animal studies, there is evidence that macronutrient intake is controlled by neurotransmitters in the brain and that macronutrient intake, in turn, influences the synthesis of some neurotransmitters. Meal size and macronutrient composition can affect subsequent cognitive performance (Rogers & Lloyd, 1994). A high carbohydrate meal, at least when eaten in the morning, is followed by an

increase in brain 5-HT (Fernstrom & Wurtman, 1971) whereas a high protein meal is not. The relative intake of carbohydrate is increased in a number of situations: carbohydrate-craving obesity (Wurtman, 1988a), seasonal affective disorder (Wirz-Justice & Richter 1979), premenstrual syndrome and behaviour disturbance following smoking withdrawal. In people with carbohydrate-craving obesity, food rich in carbohydrate and low in protein were chosen. It is suggested that the foods obese people choose affect mood and behaviour, making them feel less sad, more energetic and more sociable. Obesity has been described (Wurtman & Wurtman, 1992) as a disease of mood, where 'appetite control is sacrificed to affective state'. Low 5-HT may be a common mechanism in all these conditions.

In rats, brain 5-HT depletion is followed by a 20-30% reduction in protein intake (Ashley *et al.*, 1979). People with bulimia nervosa were also found to have a relatively low intake of protein (Walsh *et al.*, 1992). These authors asked patients with bulimia nervosa and normal controls to binge. Although people with bulimia ate more overall, unexpectedly the percentage intake of carbohydrate and fat was very similar in the two groups. However, the mean energy value of protein, as a percentage, was significantly lower in the bulimic group ($12.1 \pm 4.1\%$) than in normal controls ($15.0 \pm 3.3\%$; $p = 0.01$).

Changes in food choice in the elderly

There are conflicting accounts of energy and macronutrient intake in the normal elderly. Garry *et al.* (1989) found that in a group of normal elderly, daily energy intake decreased by 12 kcal a year in men and 4 kcal a year in women. The decrease

in protein intake was also greater in males and it was this macronutrient which decreased most with age. Wurtman (1988b) found that healthy elderly people ate fewer sweets and starchy food snacks than the young and they ate a similar quantity of protein. These results were found to conflict with a supermarket business survey which reported that the elderly ate more carbohydrate than the young, at the expense of protein. Wurtman suggested this could result from mild depression. A Swedish report found that the elderly ate too much fat but sufficient protein for individuals who were in good health (Nordström *et al.*, 1988).

Anorexia is common in the elderly (Morley & Silver, 1988; Morley *et al.*, 1989) and Blundell (1988) suggested that undereating is the result of a weak or incomplete interpretation of the metabolic signals which bring about satiation. He considers that undereating in the elderly is more likely to be due to a dysregulated system than to a single pathological mechanism.

Changes in food choice in dementia

Mungas and colleagues (1990) carried out a brief telephone survey on the food consumption and preference of people with dementia as well as some behavioural measures. They contacted the carers of 45 patients with Alzheimer's disease or vascular dementia and 43 normal controls. From the answers to the questionnaire they found that patients with dementia had a clear preference for sweet foods, whether they were high or low in fat. Carers reported that they needed to restrict sweet foods for 51% of the patients. Based mainly on simple yes/no answers to single questions, Mungas and colleagues also found that a preference for sweet foods

was significantly related to an increase in appetite but not to change in weight or to the presence of disinhibited behaviour. They suggested that this change in preference was the result of disinhibited behaviour abolishing the normal control which curbs the urge for taste gratification, although sweet preference was not necessarily associated with other disinhibited behaviour and did not relate to degree or duration of dementia. There was a trend for a greater increased preference for sweets in those with higher MMSE scores and in males rather than in females.

These results were confirmed by other more searching, semi-structured interviews with carers. Morris and colleagues (1989) found increased preference for sweet food in 24% of a cohort of 33 demented subjects. In the MRC study (see Chapter 7) 29% of people with dementia had an increased preference for sweet food and 57% would eat more sweet food than premorbidly if it was available. The reported evidence is strong but, until now it has not been confirmed experimentally.

There could be several spurious reasons for the reported increase in liking for sweet food. It could be chance, because when people are searching for food, the most accessible foods happen to be sweet, for example biscuits, chocolate or fruit. It could also be that if people are still hungry at the end of a meal and want more to eat, they are likely to be given more of the sweet food which traditionally ends the meal. Sweet puddings are often easier to eat than meat dishes if people have problems with teeth or swallowing. However, there is strong reported evidence that during meals savoury food is rejected in preference for sweet foods.

One possible mechanism to account for the sweet-craving may result from a lack of 5-HT (see Chapter 6). As 5-HT induces carbohydrate satiety its lack is likely to result in overconsumption of carbohydrate and a consequent weight gain. Lack of 5-HT is also associated with carbohydrate craving and compulsive eating disorders in dementia (Cooper & Mungas, 1992).

Chung-A-On *et al.* (1985) measured the food intake of 29 in-patients with severe dementia and 35 healthy controls. The intake of tryptophan was the same in both groups but women with dementia ate significantly less protein than the matched normal elderly controls. A second study by the same team (Thomas *et al.*, 1986) using a smaller cohort reported that men with dementia also had a significantly lower protein intake. All the men and 85% of the women ate less than the recommended daily amount of energy. For the demented subjects in these studies, this was presumably based on standard hospital food without a choice of food items. In both males and females with dementia, the mean concentrations of both total and bound tryptophan were significantly lower than controls. Although the reasons were unclear, it confirmed previous reports of low plasma tryptophan in dementia (Lehmann, 1979; Shaw *et al.*, 1981), and showed it was not due to a lower dietary intake.

Apart from these data there is no information concerning macronutrient intake in AD, when subjects are given a free choice of foods, and no data relating hyperphagia to macronutrient intake or other aspects of food choice.

Developing the choice of foods

In order to be able to study macronutrient intake, it was first necessary to find a variety of foods which had varying macronutrient content and, as far as possible, were of equal palatability. The foods also needed to fulfil the criteria, listed in the previous chapter, for suitability for use with demented subjects.

a) **Pilot work** - The first trials were made with 12 food types with a range of different macronutrient types. The twelve plates of food were arranged in a semi-circle, equidistant from the subject. In other respects the procedure was similar to the digestive biscuit meal.

The foods used in the pilot study were:

High protein:	slices of cheese and half of a hard-boiled egg
High carbohydrate:	brown bread sandwiches with a little margarine, (non-sweet), digestive biscuits (slightly sweet), pieces of chocolate and custard cream biscuits (high-sugar)
High fat:	cold grilled cocktail sausages
Low-energy:	tomato (non-sweet), cucumber; slices of banana, orange, apple (sweet)

This mixed meal was successful in principle but several modifications were found to be necessary. It was difficult to arrange twelve separate dishes within easy reach so it was decided to use only eight foods in the final study, two from each of the four groups above. Some of the foods were unsuitable, for example chocolate and custard cream biscuits were too palatable, tempting people who were not hyperphagic to eat large quantities. To make the results less skewed, digestive biscuits (with normal sugar content) were substituted instead. Orange could cause coughing and apple

slices caused choking in some subjects with badly-fitting dentures. Substituting pear avoided both these hazards.

b) Main study - Eight foods were chosen and tested. Two foods were chosen for each of the macronutrient classes (as listed below). For each class, the food was chosen to have a predominant percentage of the relevant macronutrient. Two low-energy foods were also chosen. For all four classes the aim was to provide a contrast of colour, texture and sweet or savoury taste. The ideal was to have foods that were equally attractive so that choice was likely to be related to macronutrient content rather than palatability. Very sweet foods were avoided, as they were felt to be too palatable and might override satiety signals, but there was a choice of sweet or non-sweet carbohydrate food as well as sweet and non-sweet, low-energy foods.

The eight foods were all judged, by a sample of five normal controls, to be palatable but no one food markedly more attractive than the others. When tested with demented people, there were no significant problems and some of the food from each category was sampled.

Foods for main study

HIGH PROTEIN

Ham 4 slices Sainsbury's Premium Honey Roast Ham rolled up tightly to make them easy to handle and to make the standard unit look similar in size to the other food portions.

Cheese 8 slices Sainsbury's low-fat (14%) cheddar - 17 g a slice.

HIGH CARBOHYDRATE

Bread with a little margarine (non-sweet) 4 slices of Sainsbury's brown medium-sliced bread (23 slices per loaf), each slice spread with 4 g Flora margarine. Made into sandwiches and crusts trimmed to give 8 sandwiches each weighing 15 g.

Digestive biscuits (sweet) 8 Sainsbury's small Sweetmeal (Digestive) biscuits (not low-sugar) 250 g pack.

HIGH FAT

Pork sausage 8 Sainsbury's Premium Pork Cocktail sausages, grilled as instructed on the packet.

Thick cheese and butter sandwich 8 sandwiches prepared from 2 slices of Sainsbury's thin-sliced white bread (27 slices per loaf) spread evenly with 44 g Sainsbury's slightly salted, blended butter and 2 triangular portions of Sainsbury's Cheese Spread. The sandwich was trimmed of crusts until it weighed 120 g and then cut into 12 portions of 10 g each.

LOW-ENERGY FOODS

Pear (sweet) A medium-sized pear peeled, cored and cut longitudinally into 8 equal slices.

Cucumber (non-sweet) A length of peeled cucumber, weighing 100 g (approximately), cut into 8 equal thick slices.

Subject groups

The three subject and control groups were:

a) 17 hyperphagic demented subjects who had been reported as hyperphagic by their carer. The criterion for hyperphagic subjects was the 'objective standard' given in the last chapter (i.e. a consumption of, either (1) more than 2824 kJ for a digestive

Macronutrient content of foods for main study

Food item (main macronutrient)	Macronutrient content (%)		
	Protein	Fat	Carbohydrate
Ham	20.5	5.6	0.7
Cheese	29.0	14.0	0.2
Bread and margarine	7.6	9.6	43.6
Biscuit	5.7	23.9	69.0
Cheese and butter sandwich	7.5	33.3	23.3
Sausage	13.4	31.2	10.7
Pear	0.3	0	10.6
Cucumber	0.6	0.1	1.8

biscuit meal or (2) more than 3337 kJ for a mixed meal, during at least one of the first test meals).

- b) 14 non-hyperphagic demented controls matched individually for age, sex, cognitive ability and diagnosis.
- c) 14 normal elderly controls matched individually for age and sex.

This chapter describes how the food choice of these three experimental groups was examined, by analysing the foods which were selected during the first mixed meal, (described in the previous chapter). The analysis investigated macronutrient choice, the ratio of sweet to savoury foods and also the types and range of foods selected by the three groups. The reliability of these food choices was examined. Finally, data presented in detail later (in Chapter 12) were used to investigate the effect of age, dementia and hyperphagia on macronutrient and sweet/savoury food choice.

A. MACRONUTRIENT CHOICE

METHOD

The eight foods described above, were given *ad libitum*, in a mixed meal (the method is described in the last chapter). Subjects and controls were given a free choice, to select as much of any of the foods as they liked. The choice of macronutrients was calculated for each of the meals eaten and the choices of the three groups were compared. The macronutrient content and sweet/savoury content of the meal was analysed using the 'Weight-watcher' program, originally devised by Andrew Leech for use with the Automated Food Dispenser.

From observations during pilot work it seemed that food choice may be unreliable in some subjects with hyperphagia. Some people were observed to take food from one particular area on the table regardless of what the food was. One explanation is that because of their cognitive deficit or because of sensory deterioration they are unable to discriminate between food types. As a result, subjects may choose food primarily on the basis of its position on the table, perhaps because it is nearest the hand they eat with or it might be due to left-side spatial neglect. To eliminate this confounding factor, the arrangement of food types on the table was rotated for each consecutive person given a test meal. Also for each repeat mixed meal with the same person, the position of foods on the table for that person was rotated in the same sequence (see Chapter 9). This balancing of meal order should eliminate the effect of position from the means of each group's results. For each individual, the results of repeat meals should show whether food choice was random, by macronutrient type or was chosen by the position of the food on the table.

The focus of the analysis is the first mixed meal to examine macronutrient intake and the second mixed meal to examine reliability of the macronutrient intake. For each group the test-retest reliability was calculated for food choice and total intake of each macronutrient during the mixed meals.

RESULTS

When macronutrient intake was calculated, as a percentage of total intake, the normal group ate the highest proportion of protein (18.5%, 334 kJ). The non-hyperphagic demented group ate less protein both as a percentage of the total (15.4%) and in total energy (314 kJ). Although the hyperphagic group consumed more protein when measured in kJ (mean intake 680 kJ), they had a lower percentage intake than either of the other two groups (12.3%). The macronutrient intake for the three experimental groups for the first meal is shown in tables 10.1, 10.2, 10.3 and figures 10.1 and 10.2. An independent t-test to compare the means of the percentage intake of protein showed that the normal elderly ate a significantly greater percentage than the hyperphagic group ($t = 3.5$, $df = 29$, $p = 0.002$). The differences in carbohydrate and fat as a percentage did not reach significance. Although the non-hyperphagic demented were intermediate between the other two groups for each of the macronutrients, eating less protein and more fat and carbohydrate than the normal elderly, the differences, as a percentage, were not significant.

Predictably, the people in the hyperphagic group ate more of each of the three macronutrients than either of the two control groups in terms of energy value (independent t-test: $p < 0.003$ in each case).

Reliability

At the second meal, a similar difference was found between the normal elderly (16.8% protein) and hyperphagic group (12.6% protein), suggesting that this difference in the percentage of protein intake is reliable, especially in the normal control group (figure 10.3). Expressed as a percentage of the total intake there was a significant correlation between protein intake at the two meals (Pearson correlation: 0.462, $df = 21$, $p = 0.03$). When energy values (kJ) were compared there was a significant correlation between all three macronutrients eaten at meal 1 and meal 2 (Pearson correlation: $df = 21$, protein $p = 0.001$, fat $p < 0.0005$, carbohydrate, $p < 0.0005$).

The data suggest that percentage intake for each of the three macronutrients can be ranked, with the hyperphagic group and the normal elderly at the extremes and the non-hyperphagic demented group in the middle.

The reliability of macronutrient intake was good. Using paired t-tests for all three experimental groups, there was no significant difference in the protein, fat or carbohydrate food intake, between the first and second mixed meals (at the $p \leq 0.05$ level), as a percentage of the total food intake.

Table 10.1 Food choice - mixed meal 1

Food item (main macronutrient)	Mean intake per meal in each group -					
	Hyperphagic demented group		Non- hyperphagic demented controls		Normal elderly controls	
	g	(%)	g	(%)	g	(%)
Ham (protein)	32.7	(7.0)	15.8	(8.7)	35.4	(14.2)
Cheese (protein)	32.7	(7.0)	17.6	(9.6)	14.8	(5.9)
Bread and margarine (non-sweet carbohydrate)	69.0	(14.7)	42.8	(23.4)	35.6	(14.3)
Biscuit (sweet carbohydrate)	91.0	(19.4)	18.6	(10.2)	7.9	(3.2)
Cheese and butter sandwich (fat)	76.7	(16.4)	21.2	(11.6)	24.9	(10.0)
Sausage (fat)	53.4	(11.4)	29.2	(16.0)	20.0	(8.0)
Pear (sweet low-energy)	86.4	(18.4)	25.8	(14.1)	79.5	(31.9)
Cucumber (non-sweet low-energy)	27.0	(5.8)	11.7	(6.4)	31.4	(12.6)

B. SWEET/SAVOURY CHOICE

METHOD

Several studies, cited above, found a reported increase in sweet-food liking in people with dementia. An analysis was made to compare the ratio of sweet food chosen by each of the three experimental groups. The intake of sweet foods (biscuits and pear) and non-sweet foods (ham, cheese, bread and margarine, cheese sandwich and cucumber) was calculated using the ‘Weight-watcher’ program. The reliability was tested by comparing the consumption of sweet food at the two meals. Sweet food was measured as total energy value of biscuits and pear eaten (kJ) and as the mass

Figure 10.1 Macronutrient choice - mixed meal 1

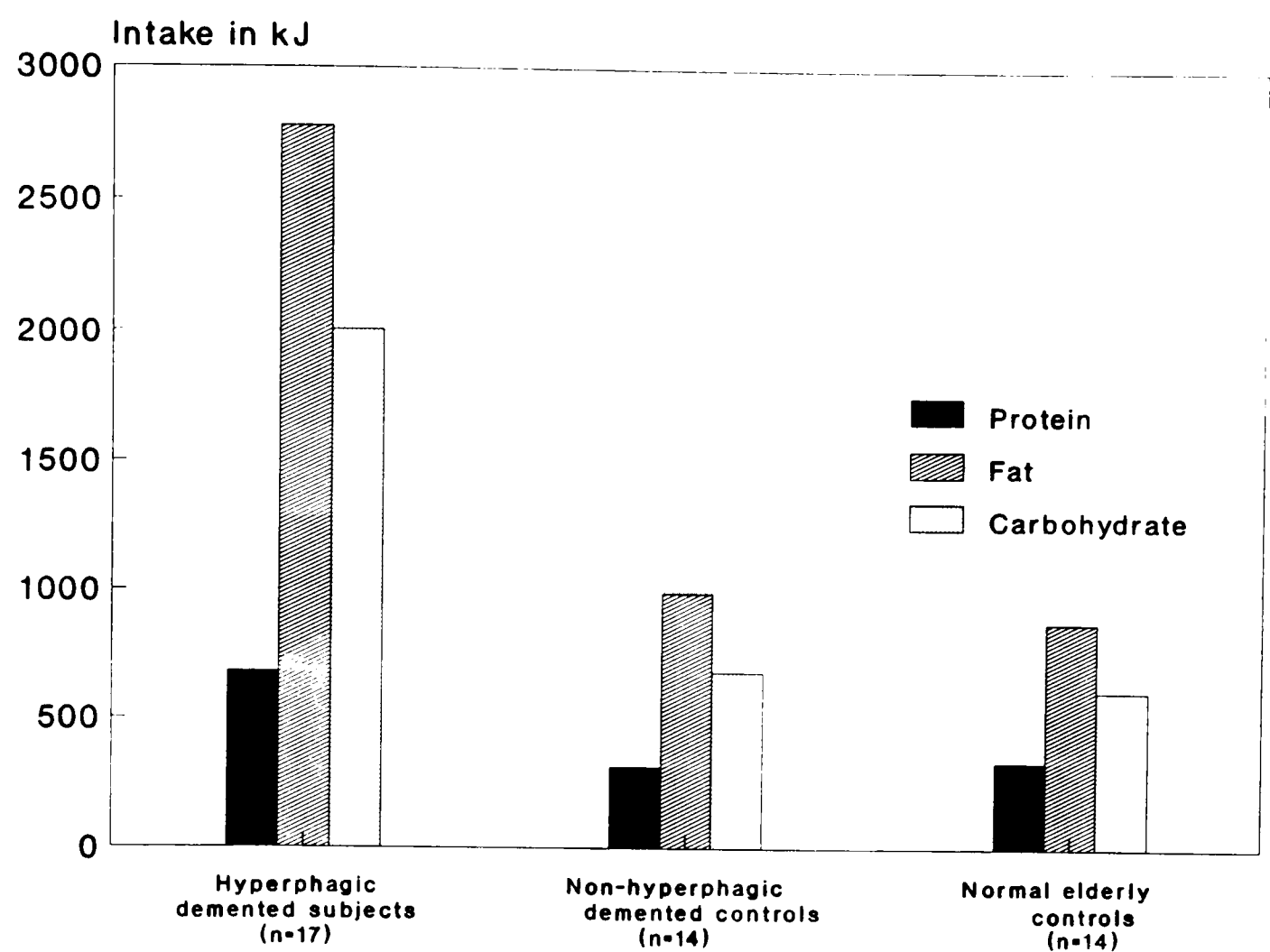


Table 10.2 Mean macronutrient consumption at mixed meal 1 (kJ)

PROTEIN		
Group	Mean (kJ)	
Hyperphagic demented	680	(S.D. 392, n=17)
Non-hyperphagic demented controls	314	(S.D. 218, n=14)
Normal elderly controls	334	(S.D. 122, n=14)
FAT		
Group	Mean (kJ)	
Hyperphagic demented	2777	(S.D. 1553, n=17)
Non-hyperphagic demented controls	990	(S.D. 600, n=14)
Normal elderly controls	878	(S.D. 346, n=14)
CARBOHYDRATE		
Group	Mean (kJ)	
Hyperphagic demented	2006	(S.D. 985, n=17)
Non-hyperphagic demented control	684	(S.D. 486, n=14)
Normal elderly controls	611	(S.D. 165, n=14)

Figure 10.2 **Macronutrient choice - mixed meal 1**
Percentage of total meal

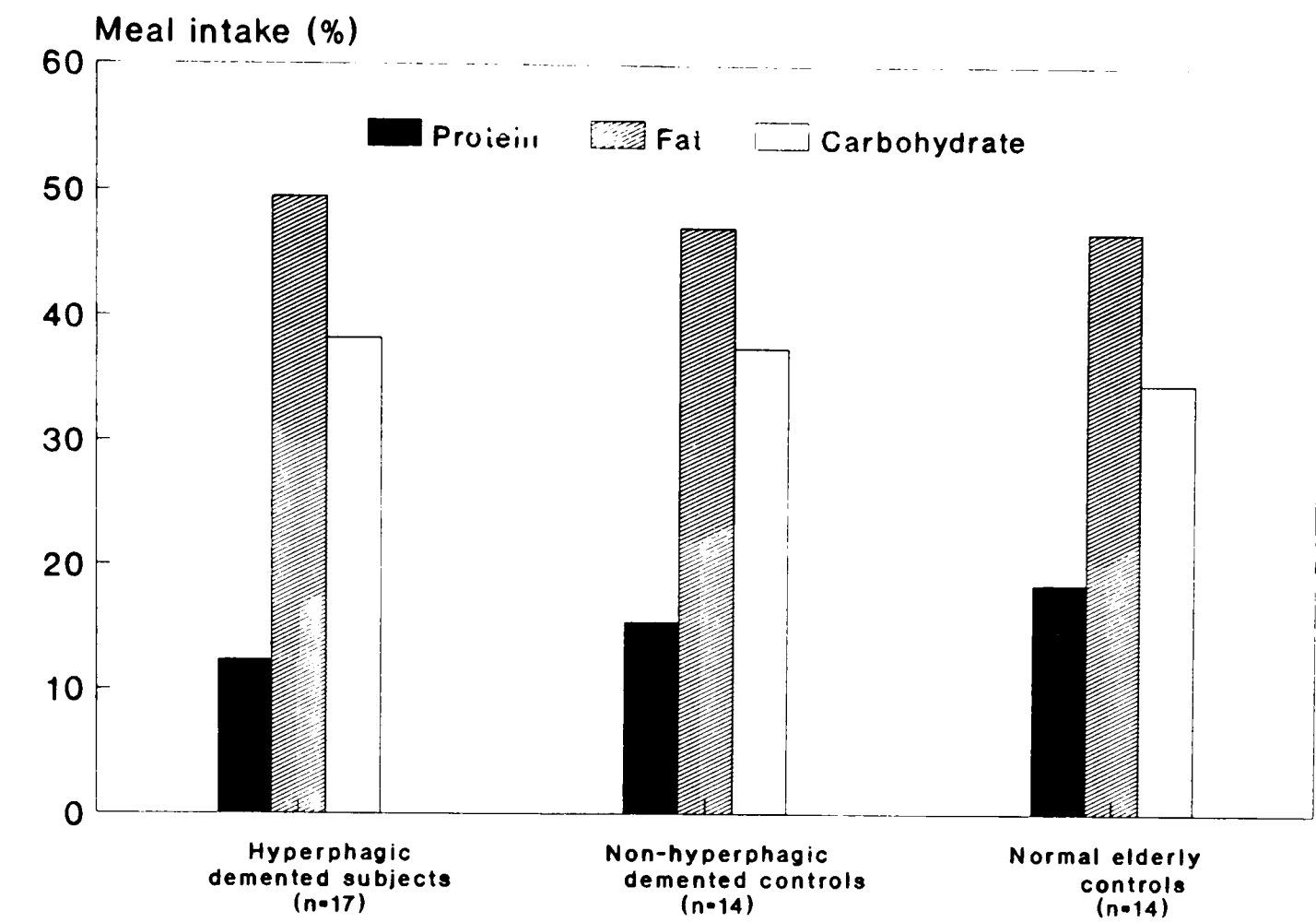
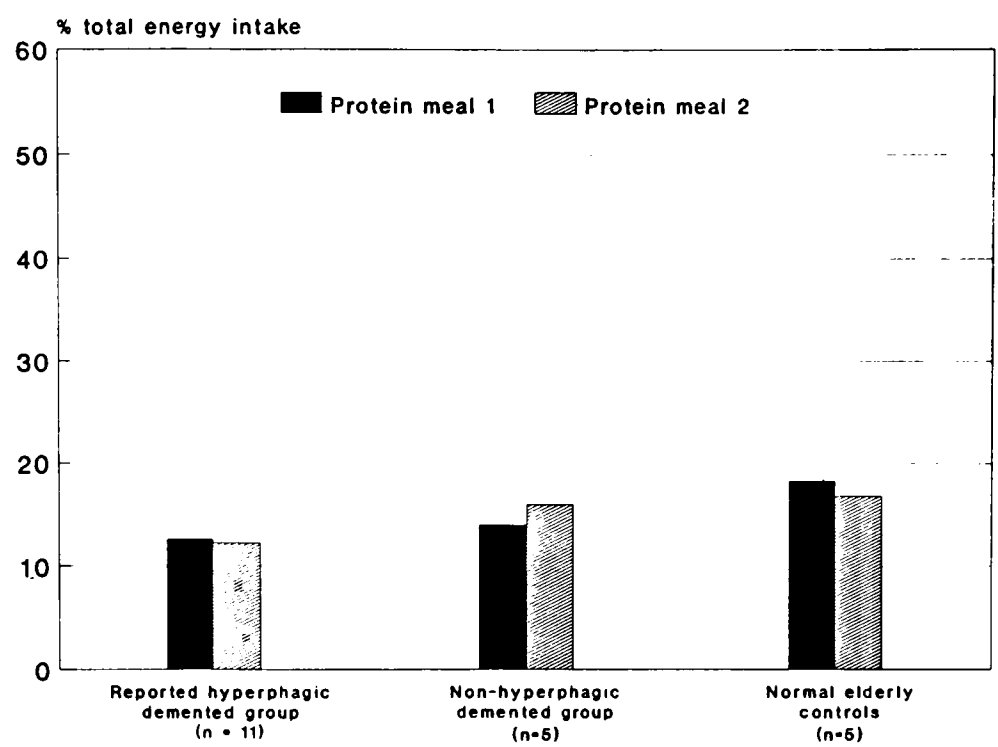


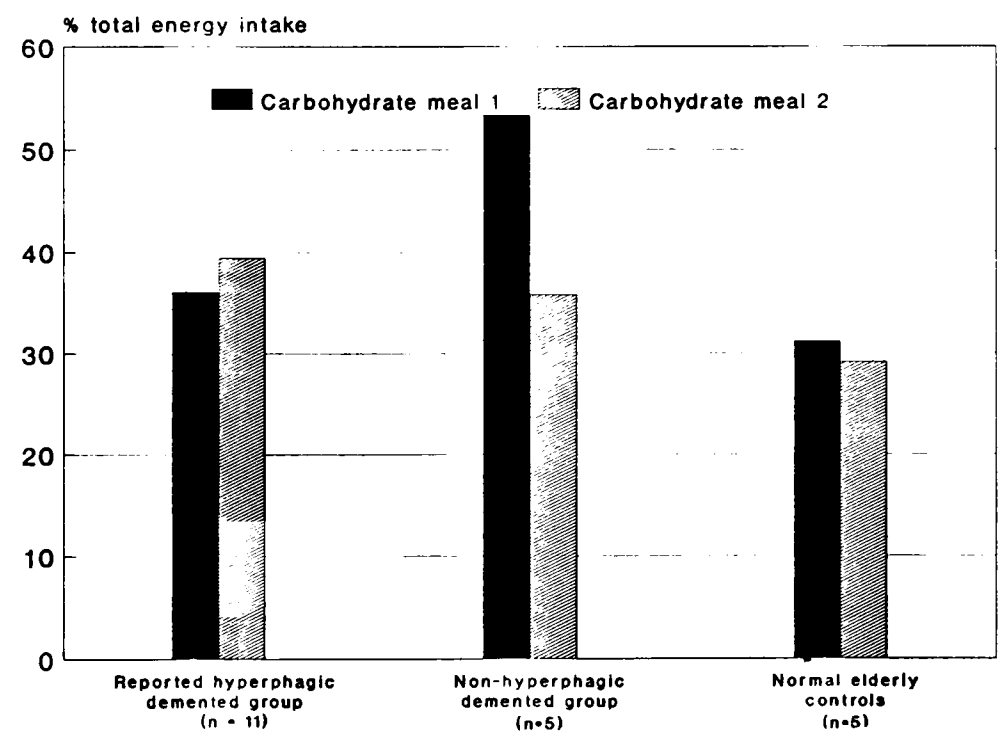
Table 10.3 **Mean macronutrient consumption at mixed meal 1 (%)**

PROTEIN		
Group	Mean (%)	
Hyperphagic demented	12.3	(S.D. 4.4, n=17)
Non-hyperphagic demented controls	15.4	(S.D. 7.7, n=14)
Normal elderly controls	18.5	(S.D. 5.6, n=14)
FAT		
Group	Mean (%)	
Hyperphagic demented	49.5	(S.D. 7.6, n=17)
Non-hyperphagic demented control	47.1	(S.D. 16.4, n=14)
Normal elderly controls	46.8	(S.D. 8.3, n=14)
CARBOHYDRATE		
Group	Mean (%)	
Hyperphagic demented	38.2	(S.D. 8.2, n=17)
Non-hyperphagic demented control	37.5	(S.D. 20.4, n=14)
Normal elderly controls	34.7	(S.D. 10.1, n=14)

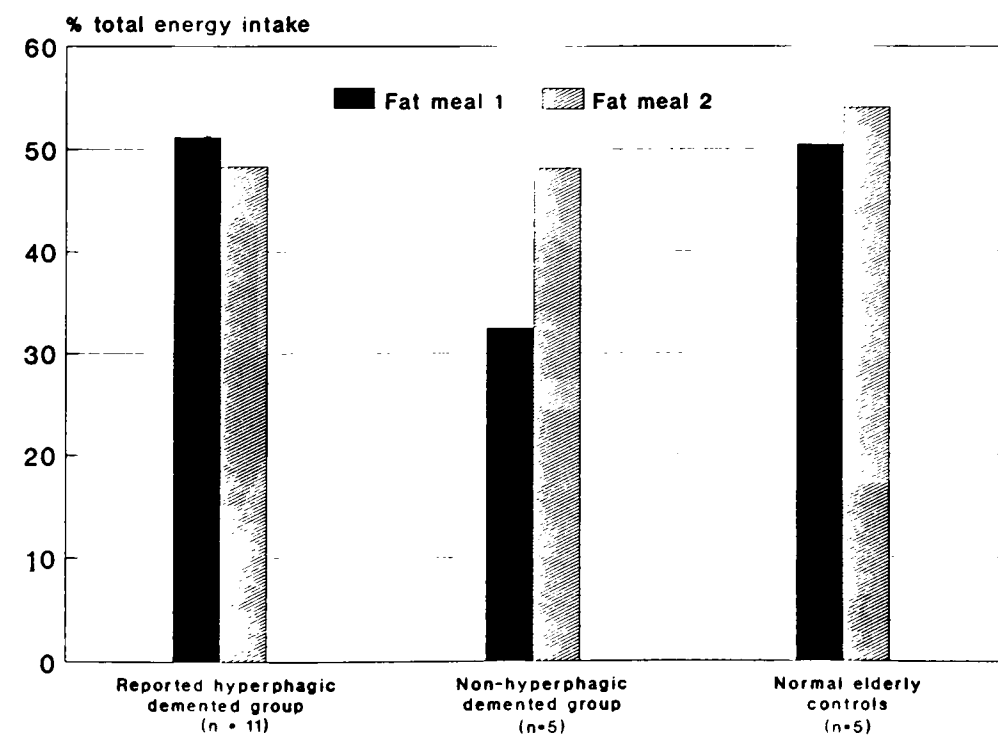
Figure 10.3 Protein reliability - test-retest



Carbohydrate reliability - test-retest



Fat reliability - test-retest



of sweet food eaten (g). Both were calculated as a total and as a percentage of total intake, to obtain the ratio of sweet to savoury foods chosen. Reliability was tested by comparing the sweet/savoury food choice at the first and the second mixed meal.

RESULTS

There was a clear pattern, with the hyperphagic group at one extreme and the normal elderly at the other and the non-hyperphagic in the middle. When the mean total energy value of sweet food was compared for the three groups (table 10.4 and figure 10.4), using independent t-tests, the hyperphagic group were shown to eat significantly more than either of the other two groups ($p < 0.003$). The non-hyperphagic demented group was very variable, eating more sweet food than the normal elderly, but the difference was not significant.

As a percentage of total intake the hyperphagic demented ate more than twice as much sweet food as the normal elderly (table 10.5 and figure 10.5). Using an independent t-test, the difference in the mean percentage of sweet food eaten by the hyperphagic group (34.8%) and the normal elderly (16.0%) was highly significant ($t = 3.4$, $df = 27.4$, $p = 0.002$). The differences between the non-hyperphagic demented group and either of the other two groups were not significant at the $p \leq 0.05$ level.

Reliability

The reliability of sweet/savoury choice was good. For all three experimental groups, there was no significant difference in the sweet food intake, between the first and

Figure 10.4 Sweet/savoury choice - mixed meal 1

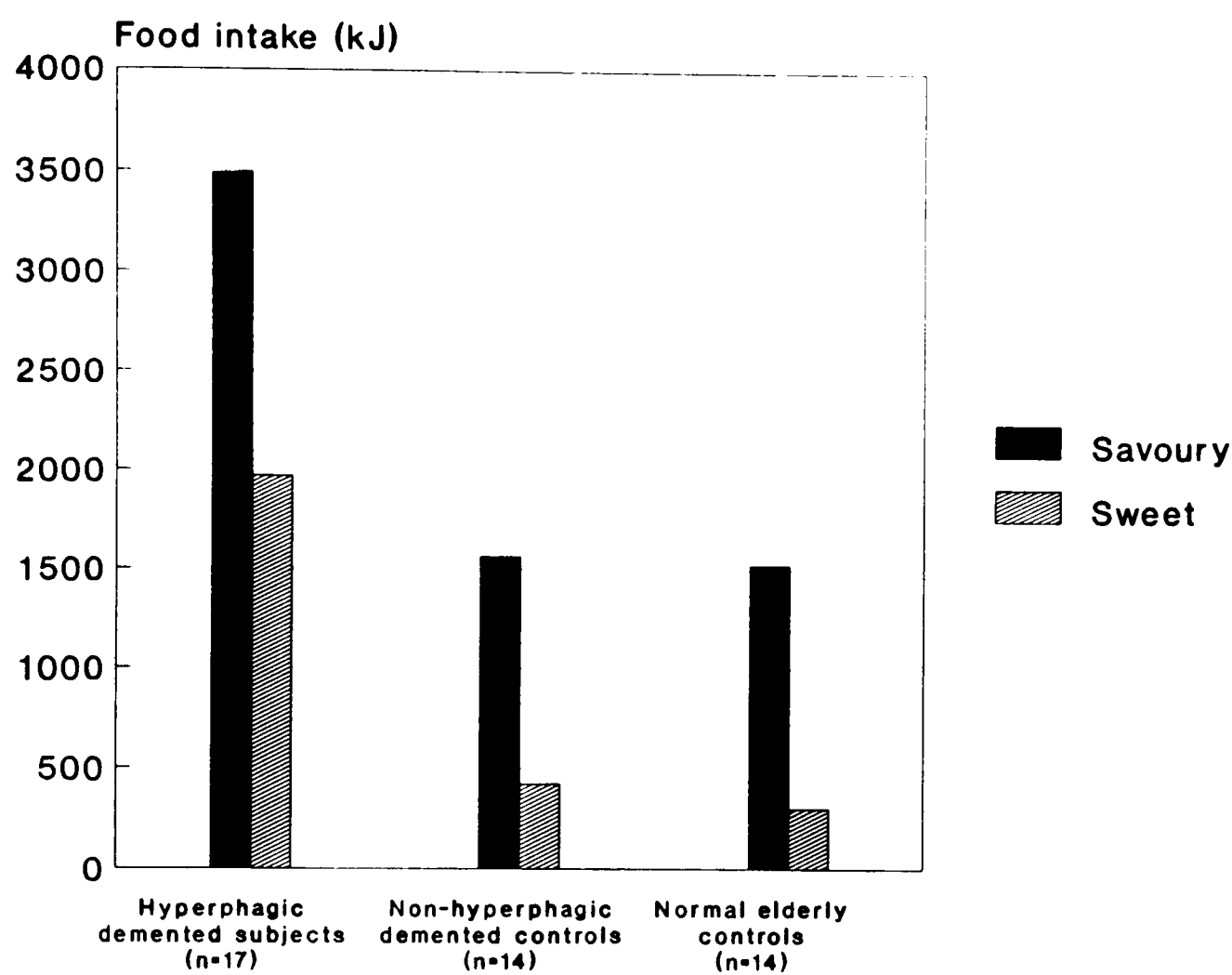


Table 10.4 Mean sweet/savoury food choice at mixed meal 1 (kJ)

SWEET FOOD		
Group	Mean (kJ)	
Hyperphagic demented	1972	(S.D. 1703, n=17)
Non-hyperphagic demented control	421	(S.D. 606, n=14)
Normal elderly controls	300	(S.D. 279, n=14)

SAVOURY FOOD		
Group	Mean (kJ)	
Hyperphagic demented	3491	(S.D. 1917, n=17)
Non-hyperphagic demented control	1565	(S.D. 1042, n=14)
Normal elderly controls	1522	(S.D. 464, n=14)

Figure 10.5 Sweet choice (%) - mixed meal 1
 Percentage of total meal

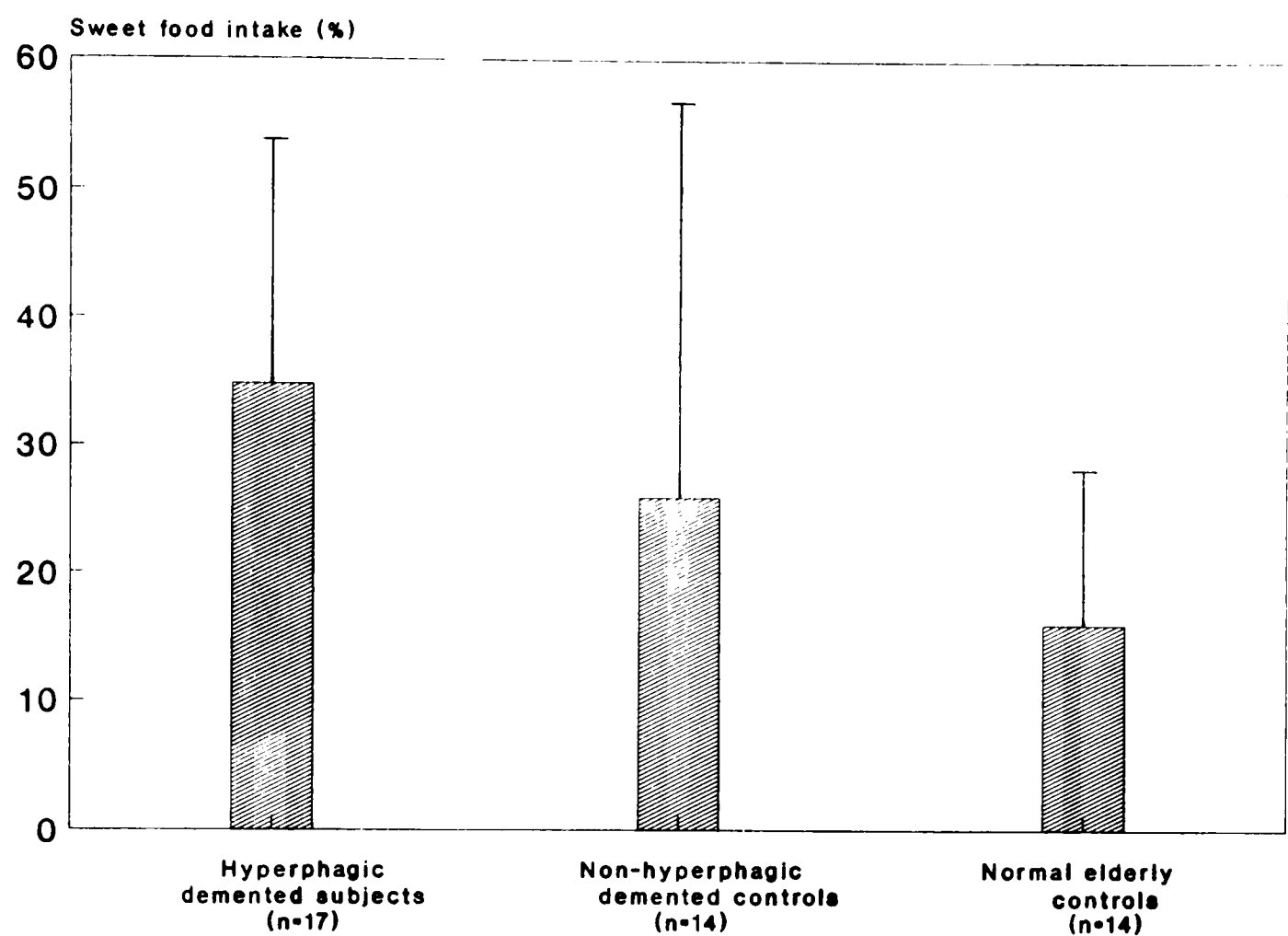


Table 10.5 Mean sweet/savoury food choice at mixed meal 1 (%)

SWEET FOOD		
Group	Mean (%)	
Hyperphagic demented	34.8	(S.D. 19.0, n=17)
Non-hyperphagic demented control	25.9	(S.D. 30.9, n=4)
Normal elderly controls	16.0	(S.D. 12.0, n=14)

Figure 10.6 **Sweet choice (%) - reliability**
Percentage of total meal

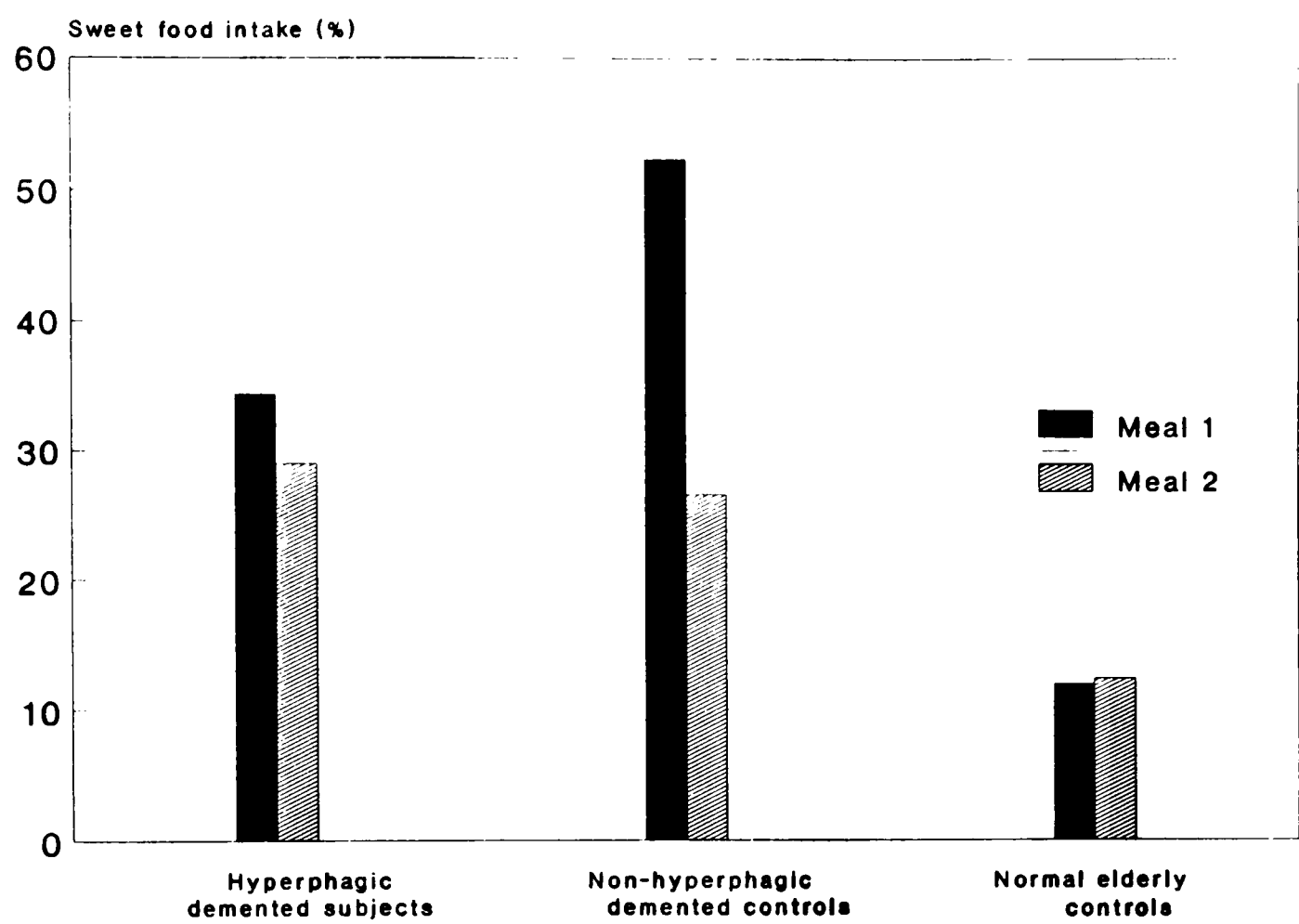


Table 10.6 The reliability of sweet/savoury choice (kJ)

Group	Meal 1	Meal 2
Hyperphagic demented subjects (n = 11)	2168 kJ	2122 kJ
Non-hyperphagic demented controls (n = 5)	649 kJ	494 kJ
Normal elderly group (n = 5)	253 kJ	248 kJ

Table 10.7 The reliability of sweet/savoury choice (%)

Group	Meal 1	Meal 2
Hyperphagic demented subjects (n = 11)	34.4%	29.0%
Non-hyperphagic demented controls (n = 5)	52.4%	26.6%
Normal elderly group (n = 5)	12.0%	12.4%

second mixed meals (at the $p \leq 0.05$ level), either in terms of kJ or percentage sweet food intake (see tables 10.6 and 10.7 and figure 10.6).

C. CONSUMPTION OF LOW-ENERGY FOODS

METHOD

A comparison of the quantity of low-energy foods eaten (i.e. pear and cucumber) was made between the three groups. This was measured by total mass and by percentage mass of the whole meal.

RESULTS

Both demented groups ate a smaller percentage of low-energy food (especially the non-sweet cucumber) than the normal elderly. The results are summarised in figure 10.7 and table 10.8.

When the low-energy food was calculated as a percentage of total intake, the two demented groups were not significantly different from each other but both the hyperphagic demented and the non-hyperphagic demented ate a significantly lower percentage of low-energy food (pear and cucumber) than the normal elderly (t-test: $p = 0.001$ and $p = 0.007$ respectively). When cucumber and pear were considered independently both the hyperphagic demented and the non-hyperphagic demented ate a significantly lower percentage of cucumber than the normal elderly (t-test: $p < 0.0005$ and $p = 0.003$ respectively). The difference in percentage mass of pear eaten was not significant at the $p \leq 0.05$ level.

Figure 10.7 LOW ENERGY FOOD - mass as % meal
Mass of pear and cucumber

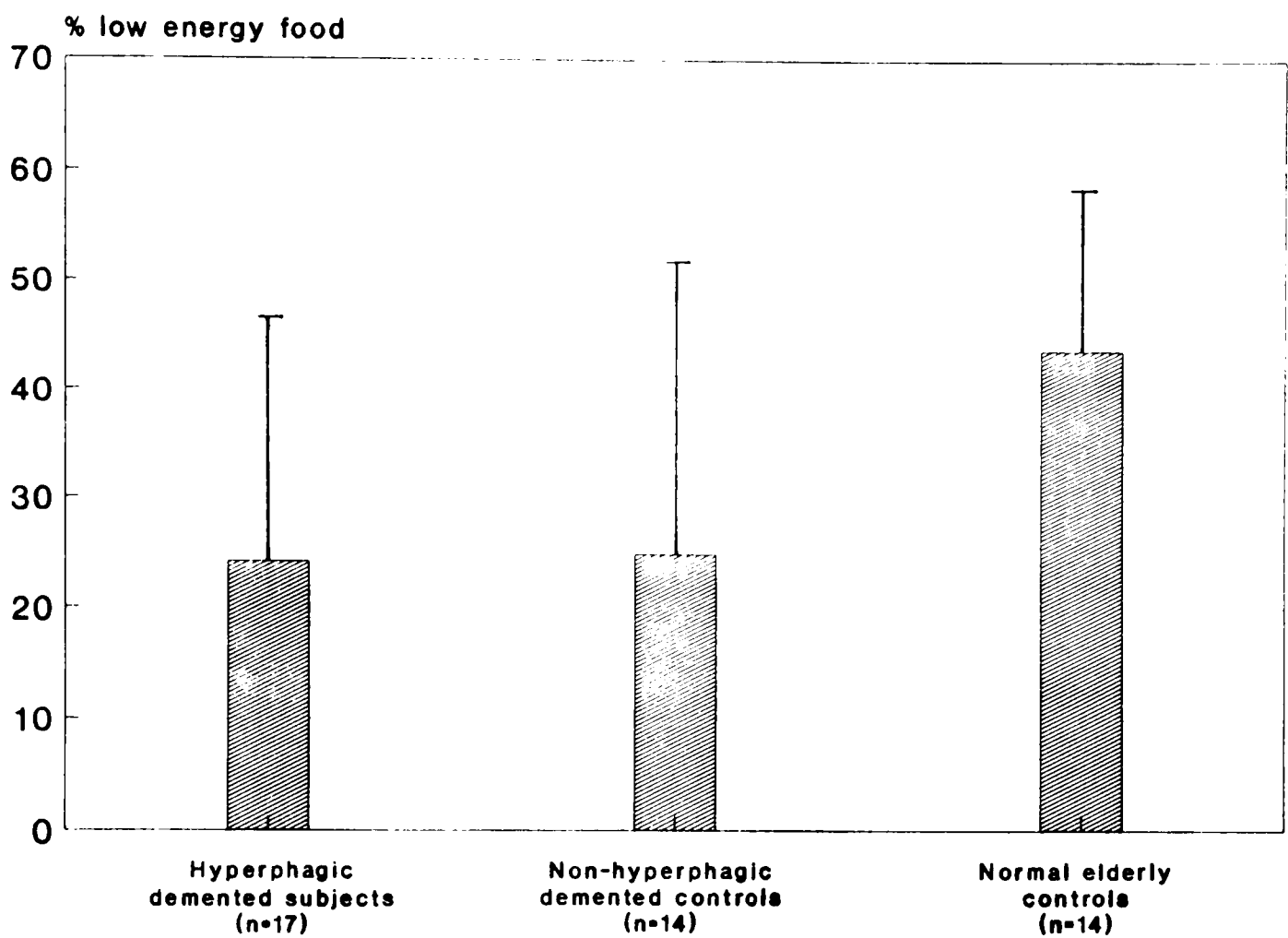


Table 10.8 Consumption of low-energy foods - Mixed meal 1

a) LOW-ENERGY FOODS - total intake in grams		
Group	Cucumber (g)	Pear (g)
Hyperphagic demented	27.0	86.4
Non-hyperphagic demented control	11.7	25.8
Normal elderly controls	31.4	79.5

b) LOW-ENERGY FOODS - percentage of mass of whole meal		
Group	Cucumber (%)	Pear (%)
Hyperphagic demented	4.38	19.75
Non-hyperphagic demented control	5.38	19.49
Normal elderly controls	12.55	31.19

Reliability

There was high test-retest reliability for the percentage intake of the low-energy foods. For all three experimental groups, there was no significant difference (at the $p \leq 0.05$ level) in the intake of both pear and cucumber (when calculated as a percentage mass of the total intake), between the first and second mixed meals.

D. RANGE OF FOODS CHOSEN

METHOD

In order to investigate whether the range of food types chosen differed between the three groups, the number of different types of food, sampled during meal 1, was noted (e.g. one person might choose four of the eight types during the course of the meal and another might eat some of all eight). The means for the groups were compared to see if there was a significant difference in the number of types of food sampled. Reliability was investigated by comparing the first two mixed meals.

RESULTS

The normal elderly group usually chose foods in a 'conventional' order. They ate savoury food first, such as protein foods, cucumber and sandwiches, then pear and/or biscuits at the end of the meal. The demented groups tended to choose a less wide range of foods, often alternating between sweet and savoury foods. Apart from the people who chose food according to the position on the table, the people with dementia ate more of just one or two types of food, mainly carbohydrate foods, cheese, sandwiches or pear.

The normal controls chose a wider range of food items, eating a mean of 6.6 of the eight different food types during the first mixed meal (see table 10.9). The non-hyperphagic, demented group chose a mean of 4.9 types. The difference between these groups was significant (t-test; $t = 2.68$, $df = 22.8$, $p = 0.013$). The hyperphagic demented were intermediate, eating significantly more types than the non-hyperphagic group ($t = 2.03$, $df = 23.7$, $p = 0.05$). The difference between the hyperphagic group and the normal elderly was not significant.

Table 10.9 Range of food eaten in mixed meal 1.

Group	No of meals	Mean no of food types
Hyperphagic demented subjects	17	6.2 (S.D. 1.4)
Non-hyperphagic demented controls	14	4.9 (S.D. 1.9)
Normal controls	14	6.6 (S.D. 1.3)

Reliability

The reliability of range of food sampled was good (see table 10.10). For all three experimental groups, there was no significant difference in the number of foods eaten, between the first and second mixed meals (at the $p \leq 0.05$ level).

Table 10.10 Reliability of range of food eaten in mixed meals 1 and 2.

Group	Mixed meal 1	Mixed meal 2
Hyperphagic demented subjects (n = 10)	6.2	6.2
Non-hyperphagic demented controls (n = 5)	4.2	4.8
Normal controls (n = 5)	7.2	7.4

E. THE EFFECT OF AGE ON FOOD CHOICE

METHOD

In order to investigate the effect of age on food choice, the macronutrient and sweet/savoury content of three consecutive test mixed meals were examined. These meals were given during an experiment to investigate satiety (described in detail in chapter 12). The meals were given to three groups of normal adults, 12 aged 23-30, six aged 40-47 and 9 of the normal elderly controls aged over 50 years (range 55-82). Each of the three mixed meals was preceded an hour earlier by a preload each with a different energy value, as part of the satiety experiment. One preload was 200 ml water and the other two were milkshakes, which were apparently identical, but one had an energy value of 660 kJ and the other 1870 kJ. The macronutrient intake for test meals and the ratio of sweet to savoury food were calculated as described in part A of this chapter.

RESULTS

(i) Macronutrient choice - (% of total intake)

The results concerning protein intake are summarised in table 10.11.

Table 10.11 Percentage protein intake

Group	No preload	Low preload	High preload
Young group (n=12)	20.2	20.1	20.4
Middle-aged (n=6)	24.9	24.9	24.5
Normal over 50 (n=9)	18.1*	16.4	17.3

* denotes that the majority of meals in this group were not eaten within the same month as the preload meals, therefore eating may have changed in the meantime.

As can be seen, the preload condition does not appear to have any effect on the percentage protein intake and analysis shows no significant difference between the three preload conditions for any of the three age groups. Taking the two younger groups together (i.e. the under 50s) the results showed that they ate a higher proportion of protein (21.8% over all three preload conditions) than the older group (17.3%). This difference was significant at the $p \leq 0.05$ level. When the under 50s were divided into two groups, the youngest 12 (mean age 24.9; range 21-30) and the oldest 6 (mean age 44.2; range 40-47), the protein intake for the younger subgroup, aggregated over the three preload conditions, was not significantly different from either of the other two groups but the middle-aged group ate significantly more protein than the elderly group (t-test: $t = 2.66$, $p = 0.026$) - see table 10.12.

Table 10.12 Percentage protein intake (mean of three meals)

Group	Age range	Mean of three preload meals
Young group age (n=12)	21-30	20.2 %
Middle-aged (n=6)	40-47	24.8 %
Normal elderly (n=9)	over 50	17.3 %

The differences between fat and carbohydrate intake with age was not significant at the $p \leq 0.05$ level.

(ii) Sweet food intake - (% of total intake)

The results are summarised in tables 10.13 and 10.14. There was no significant difference in percentage of sweet food eaten between the three preload conditions. When the three preload meals were combined, the young group ate a significantly greater proportion of sweet food across the three conditions as a percentage of total

intake, than the middle-aged group (t-test: $t = 2.54$, $p = 0.022$). The elderly ate more sweet food than the middle-aged but the difference was not significant at the $p \leq 0.05$ level.

Table 10.13 Percentage sweet food intake

Group	No preload	Low preload	High preload
Young (n=12)	20.3	19.0	20.6
Middle-aged (n=6)	11.6	9.8	7.7
Normal over 50 (n=9)	19.0*	19.6	16.6

* denotes that the majority of meals in this group were not eaten within the same month as the preload meals, therefore eating may have changed in the meantime.

Reliability

Test-retest reliability was calculated from the food intake during the test meals following the water and low-energy preloads. For all three age groups, there was no significant difference in the percentage of sweet foods eaten, between the two test meals (at the $p \leq 0.05$ level).

Table 10.14 Reliability of sweet food eaten in two test meals.

Group	Meal following water preload (%)	Meal following low-energy preload (%)
Young (n = 12)	20.3	19.0
Middle-aged (n = 6)	11.6	9.8
Normal elderly (n = 9)	19.0	21.1

DISCUSSION

The results presented in this chapter suggest five main conclusions,

1. People with hyperphagia eat less protein, as a proportion of total food intake, than

normal elderly. The results for the demented non-hyperphagic group lie between those for the other two groups.

2. There is a significant increase in the proportion of sweet food eaten in those with dementia compared with the normal elderly. The hyperphagic group ate the highest proportion of sweet food, significantly more as a proportion of the meal, than eaten by the normal elderly. The non-hyperphagic demented group was again intermediate.

3. There are changes in normal ageing in macronutrient choice. When the young group were compared with the middle-aged group, the young ate less protein as a proportion of the meal and more sweet food. The normal elderly ate less protein, both as an absolute quantity and as a proportion of the whole meal, than either the young groups and they ate a greater proportion of sweet food than the middle-aged group.

4. The changes in food choice seen in dementia appear to be an exaggeration of the changes seen in normal ageing. Furthermore, the changes seen in the hyperphagic group are still more of an 'exaggeration' than those seen in the non-hyperphagic demented group.

5. Dementia affects the range of foods chosen. In the normal elderly, a wider range of foods was usually chosen, with a fairly even spread between the eight types. In both demented groups the choice of foods was usually narrower with a lower proportion of high-protein foods (ham and cheese) and low-energy food (pear and

cucumber) being chosen. The lack of social conventions over eating, in the demented groups, was reflected in the choice and order of foods chosen.

Food choice in dementia

Given that there seems to be a reliable and marked difference in macronutrient intake and sweet food selection in people with dementia who are hyperphagic, the question arises as to whether the difference is due to dementia or hyperphagia.

The differences between the normal elderly and the demented groups are mainly a decrease in protein intake and an increased in liking for sweet food. The change in sweet food intake in both demented groups confirms the validity of carers' reports in this study, the MRC study and other surveys of people with dementia (Morris *et al.*, 1989; Mungas *et al.*, 1990). The reduction in protein adds weight to the rather inconsistent results of Chung-A-On *et al.* (1985) and Thomas *et al.*, (1986). In spite of the close matching there seems to be a consistent difference between the non-hyperphagic demented group and hyperphagic group as the proportion of sweet food chosen is greater in the hyperphagic group than the non-hyperphagic demented group, also the proportion of protein food eaten by the hyperphagic group is even less than the non-hyperphagic demented group. Because of the matching, these differences cannot be related to sex, age, type of dementia or degree of dementia therefore it may reflect a more extreme change in one particular aspect of the changes causing dementia for example the underlying neurotransmitter deficiency in a particular area of the brain (see below).

POSSIBLE MECHANISMS FOR CHANGE IN FOOD CONSUMPTION AND CHOICE

1. Change in diet might contribute to dementia

The radical suggestion has been made that diet might cause (or at least contribute to) dementia (Lehmann, 1979; Lehmann *et al.*, 1981). A suggested mechanism is that decreased 5-HT is thought to contribute to some of the detrimental changes in dementia. The amino acid tryptophan, the precursor of 5-HT, is obtained from dietary protein. Plasma tryptophan decreases in the elderly and the effectiveness of tryptophan uptake decreases with age (Curzon, 1985). Low fasting tryptophan concentrations, both protein-bound and consequently plasma fractions, were found in patients with senile dementia (Lehman, 1979; Thomas *et al.*, 1986). However, they found that low plasma tryptophan was not due to lack of dietary intake although it could be the result of malabsorption. As plasma albumin was also low it could be that the lower concentration of bound tryptophan was limited by the availability of albumin for binding. If, as the findings of the hyperphagia study suggest, protein intake is low when people with dementia choose their own diet, this could contribute to low levels of tryptophan.

As tryptophan is needed to make 5-HT, a primary dietary lack, or a failure to absorb tryptophan, might contribute to dementia. Although it has not been reliably confirmed, a limited improvement, in a few subjects in pilot studies, was reported after increasing tryptophan levels in the diet (Lehman, 1979; Shaw *et al.*, 1981). It is not clear that this is relevant to individuals who eat normally but, in the case of malabsorption, a condition similar to that found in dieting women may apply

(Anderson *et al.*, 1990), where dieting was found to reduce plasma total tryptophan and also the ratio of tryptophan to competing neutral amino acids. Therefore dieting was assumed to reduce the supply of tryptophan to the brain and, in women, it was shown to have an effect on brain 5-HT function. It is possible that poor nutrition could exacerbate dementia. However there is no good evidence that it is a primary cause. Dementia in general, and AD in particular, has many causes (see Chapter 1). The changes in eating and food choice are likely to be primarily a result of the dementia rather than its cause.

2. The reduction of 5-HT in dementia may affect diet

As already stated, because of neuronal damage, brain 5-HT is low in AD, and reduced 5-HT has been associated, amongst other symptoms, with hyperphagia, low mood, irritability and carbohydrate craving.

The macronutrient composition of each meal can affect plasma tryptophan in two ways (Fernstrom *et al.*, 1979). First, a reduction in dietary protein increases the ratio of plasma tryptophan to the sum of the other large neutral amino acids (LNAA). These LNAA are abundant in dietary protein so their concentration in the plasma varies directly with the protein content of the diet. As tryptophan competes with these amino acids for the transport mechanism across the blood-brain barrier, increasing the ratio favours the entry of tryptophan into the brain. Secondly, carbohydrate meals stimulate the secretion of insulin which facilitates transport of branched-chain amino acids into skeletal muscle. This reduces the amino acids which compete with tryptophan to enter the brain. For example, when insulin was injected

into fasting rats, plasma tryptophan increased 30-40% (Wurtman, 1978). However, the effect of macronutrients seems to vary with different experimental conditions. Most of these experiments involve non-human animals, pure macronutrients and pre-meal fasting. In more natural conditions, and in humans, protein or carbohydrate meals may not alter neurotransmitter synthesis (Teff *et al.*, 1989).

There are marked parallels between hyperphagia in dementia and hyperphagia induced by hypothalamic lesions in the ventro-medial hypothalamus, whether caused by tumours or experimental lesions (Anand & Brobeck, 1951; Reeves & Plum, 1969; Celesia *et al.*, 1981). Delayed termination of eating, preference for sweet foods and choice of high-fat and carbohydrate food, together with a severe reduction in protein intake are all compatible with a reduction of 5-HT (Leibowitz & Shor-Posner, 1986). Increased intake of carbohydrate and low-protein diet could hypothetically increase the availability of 5-HT, at least in a highly dysfunctional system, where the blood-brain barrier, hypothalamic neurones as well as plasma albumin are known to be abnormal.

If, in dementia, reduction in 5-HT does influence diet, it might be predicted that the hyperphagic group are a sub-group with lower levels of 5-HT. The change in food choice towards less protein and more sweet foods could be a consequence of this reduced 5-HT. Furthermore, the effect of these dietary changes is likely to act in such a way as to increase 5-HT, therefore serving a useful function. Indeed they might ameliorate some of the other possible effects of low 5-HT on mood and behaviour. Increased carbohydrate intake might alleviate the unpleasant symptoms,

such as dysphoria and irritability, caused by low brain 5-HT. This may account for the preference for sweet foods. It is tempting to speculate that overeating, a low-protein and high-sweet food diet might be a form of self-medication giving a greater feeling of well-being, counteracting the unpleasant effects of low 5-HT.

3. Olfaction

The increased consumption of sweet food might be a result of the deterioration in the ability to recognise and identify odours (Schiffman *et al.*, 1990). If the sense of smell deteriorates, people might prefer to eat food which stimulate the taste cells. Loss of the sense of smell might account for carers reports of some people with dementia eating substances such as soap and faeces as well as the reported preference for sweet foods and the less frequently reported preference for salty foods.

4. Taste

Although there is an age-related change in taste thresholds, especially for salt, sweet and sour tastes (Coward, 1989), this is not likely to account for the change in taste preferences shown in these experiments.

5. Stress reduction

The anxiety and depression shown by many people suffering from AD may be alleviated by mediation of opioid pathways. This may account for the preference (typical of stress-related feeding) for foods rich in carbohydrate and sweetness, which is seen in people with dementia in these test meals. Blass (1991) demonstrated that the calming effect of sucrose, as well as glucose, in human newborn babies is

characterised by short latency and long duration. He showed that sucrose can also have an analgesic effect and also that tasting fats, polysaccharide and sugars has a calming effect on distressed rats and human infants.

6. Depression

A large proportion of people with dementia show signs of depression (Zubenko *et al.*, 1990). Lack of 5-HT is associated with dysphoric mood and irritability. People with dementia choose sweet foods preferentially and, as sweet foods are normally associated with foods rich in carbohydrate, they could alleviate this low mood by increasing 5-HT synthesis (Wurtman & Wurtman, 1989), the resulting feeling of well-being if aggressive feelings and depression were reduced might condition future food choice. Booth (1989) suggests depressed people may crave snack foods and "it could become increasingly tempting to eat and to keep eating certain foods in certain circumstances after they had been paired with sensual pleasure, distraction from distress, or sheer sedation". This is less convincing in dementia because of cognitive impairment.

7. Hypoglycaemia

Sugar-craving may relieve distress caused by hypoglycaemia. Glucose regulation has been shown to be abnormal in Alzheimer's disease (Fisman *et al.*, 1988).

8. Change in needs

Reduction in protein intake might reflect reduced need. Muscle protein content diminishes by almost 45 % between 25 and 75 years of age. Sources disagree about whether protein requirements and turnover decrease with age (Kritchevsky, 1992) although elderly people seem to require more protein per kilogram of body weight than young people (Lipschitz, 1992). This reduction in protein need might account for the reduction in intake with increased age, but not in hyperphagia, where the total protein intake is often higher (as opposed to the percentage of protein in the diet).

In the normal elderly, energy requirements decrease by about a third over the age of 70 (HMSO, 1991) and the basic metabolic rate decreases by a quarter from 26 - 76 years. This makes the high total energy intake in hyperphagia seem to be even more extreme.

SUMMARY

There is a marked change in macronutrient choice and in the intake of sweet food in people with dementia, which is even more extreme in the hyperphagic group. The decrease in the proportion of protein and increased intake of sweet foods may have many contributory causes but further work needs to be done to investigate metabolic disturbances and the role of neurotransmitters.

Chapter 11 MICROSTRUCTURE OF EATING IN HYPERPHAGIA

AIMS

To examine the microstructure of eating of hyperphagic subjects and to use microstructural measures to examine the mechanisms controlling the onset and termination of eating.

INTRODUCTION

Microstructure and its measurement

The 'microstructure' of a meal can be defined by many different methods which involve measuring the rate and pattern of eating within a meal. They include parameters such as latency before eating starts, the number of bites or mouthfuls, average bite-size, chewing rate throughout the meal, number of chews per mouthful, chews per unit time, intra-meal pauses, time spent drinking and rate of ingestion (Bellisle & Le Magnen, 1981). Other methods of measuring the microstructure of a meal have been used to give evidence for control mechanisms, for example the 'edogram', which is a continuous recording of chewing, swallowing and pausing. A trace is obtained by attaching devices, such as a strain gauge, to the head and connecting them to an oscillograph (Bellisle & Le Magnen, 1980). Measurements vary widely between individuals but remain stable for each person over years. These measures reveal more than overall food intake and the patterns of eating might have a diagnostic value in assessing eating disorders and provide a tool for understanding

systems involved in the modulation of food consumption (Bellisle, 1989).

Normal microstructure

Normal-weight adults consume more during the first half of a meal, that is the rate of intake slows during the course of the meal (Kissileff *et al.*, 1982; Kissileff & Thornton, 1982). The cumulative rate of food intake can be measured using a Universal Eating Monitor (Kissileff *et al.*, 1980) which is a table with an inbuilt electronic balance, linked to a computer. At the beginning of a meal eating rate is fast and chewing activity is reduced compared with the end of a meal. An increase in palatability of food accelerates feeding patterns, mainly because chewing time, the number of chews per standard bite and the average duration of pauses during the meal decrease (Bellisle, 1989). Also, with increased palatability, meal size and duration increase and larger mouthfuls of food are taken. The quantity of water and the number of sips increase during the course of the meal.

Models of control of food intake

In normal, non-obese subjects Kissileff *et al.* (1982) found the cumulative food intake curve (I) was best described by a quadratic equation. In the equation:

$$I = a + bt + ct^2$$

t represents time; the linear coefficient *b* reflects the initial rate of eating or facilitation and the quadratic coefficient *c* is a measure of the degree of deceleration in intake, it therefore provides a measure of the inhibiting process. They assumed that the intercept with the y-axis (*a*) was not important because of experimental error with the apparatus used. From their analysis, they deduced that two opposing

processes appeared to control food intake; the initial rate of eating reflecting hunger and the rate of deceleration reflecting satiety (see Chapter 5). They also found a difference between the sexes, the curves for men appearing to rise more sharply and decelerate more rapidly than those for women. The reason for this difference between the sexes is not clear but they suggest it might be due to physiological or personality differences.

Although the quadratic equations described most features of food intake, meals ended more abruptly than the quadratic model predicted, and this was especially true in women. They suggest, that if this model is correct, there could be three reasons for this abrupt termination of the meal. One reason could be the effect of sensory specific satiety; that is, in a single food meal, true termination of eating has not occurred, only relative inhibition to the food that was given (Rolls *et al.*, 1981). Evidence in favour of this is that they found that the presentation of a different food stimulated further food intake. A second reason is that subjects may have learned to anticipate the discomfort, which would occur if they continued to eat, and therefore they stop eating before the point predicted in their quadratic model. The third reason is that cognitive factors, such as concern about eating or thoughts about what subjects have to do after the meal, might cause them to stop earlier than the predicted point. The higher restraint scores in women could relate to the larger (but not significant) difference in women between theoretical and actual duration of a meal.

Rogers (1993, 1994) interprets cumulative intake with a more complex graphical model (figure 11.1). This differs from Kissileff *et al.* (1982), principally in

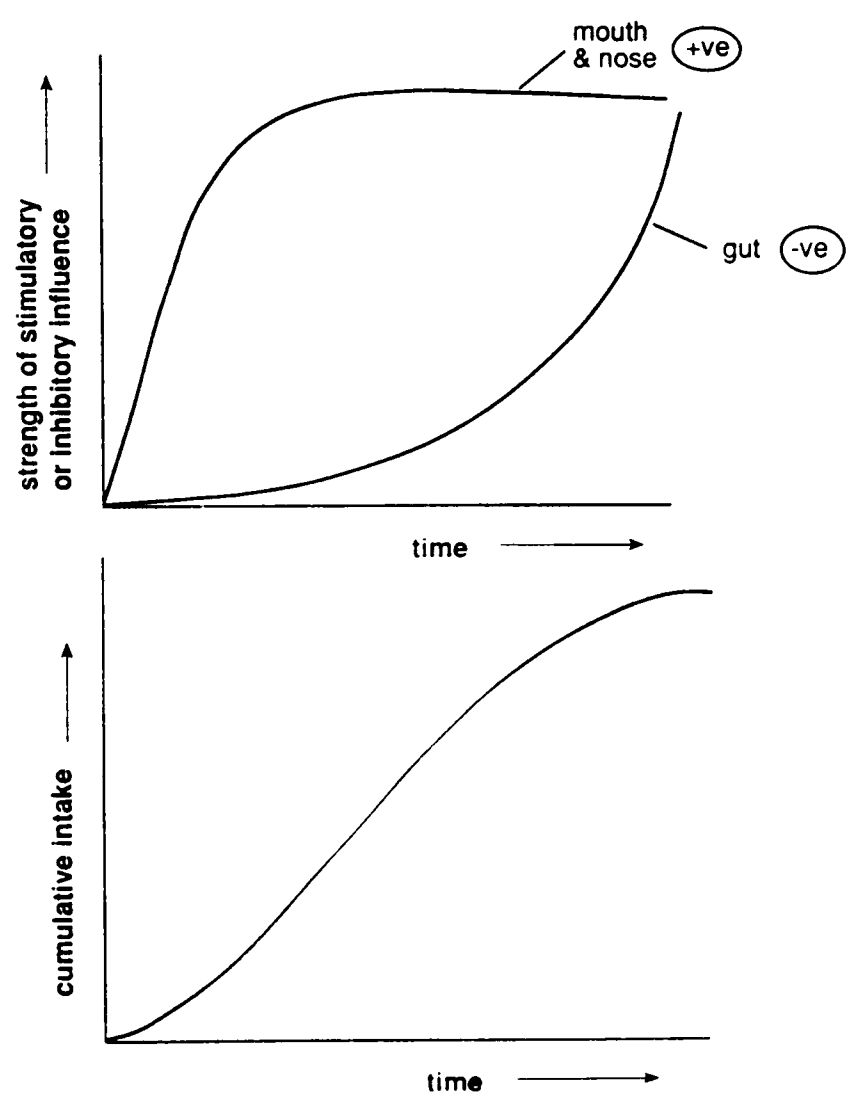
postulating that once eating begins, there is positive feedback initially rather than a straight line excitatory component proposed by Kissileff and colleagues. The balance is between positive feedback, arising from the quality of strong sensory signals caused by contact with food which stimulates further food intake (palatability), and negative feedback due to gastric satiety signals. This initial acceleration in the rate of eating is recognised by the French in their saying, 'L'appetit vient en mangeant' (Appetite comes with eating). There are behavioural data to support this positive feedback. Wiepkema (1971) observed a large increase in the length of successive feeding bouts in mice at the start of a spontaneous meal, whereas the length of the non-feeding intervals did not change in the early part of the meal. It was shown to be dependent on palatability because when the standard food was adulterated with a bitter substance the early increase in feeding-bout length was greatly reduced. Palatable food enhanced feeding (positive feedback) but bitter food markedly inhibited feeding (Wiepkema, 1971). When the positive and negative feedback elements are combined (see figure 11.1), it gives a sigmoid cumulative intake curve for normal subjects instead of a simple quadratic proposed by Kissileff and colleagues.

Microstructure changes with normal ageing

Hungry newborn babies consume 80% in the first half of a meal and only 20% in the second half. This deceleration becomes less marked with age until, in the healthy elderly, 81.4% have a near-linear cumulative intake curve (Meyer *et al.*, 1980). The lack of deceleration, indicating satiation, suggests either that internal regulation becomes weaker in the elderly or that eating is controlled by habit (as in some other patterns of behaviour in the elderly). Anorexia and weight loss are commonly found

in the elderly (Morley & Silver, 1988). This is partly a result of diseases associated with ageing but there is probably an increased satiety effect of CCK in the elderly (Morley *et al.*, 1989). From their work with ageing rodents, they found that increased activity of CCK was possibly due to decreased degradation of CCK or to increased receptor or post-receptor sensitivity. Also there is a decreased effectiveness of the opioid feeding system. In elderly humans, less acute senses of taste and smell diminish the pleasure in eating.

Figure 11.1. Hypothetical model of positive and negative feedbacks operating on eating during a meal.
Top: stimulatory and inhibitory effects of sensory and gut-mediated signals.
Bottom: resulting cumulative amount of food eaten across the meal (Rogers, 1993).



Microstructure of eating in bulimia nervosa and obesity

People with bulimia nervosa usually have a slower rate of food intake (measured as energy in unit time) during normal meals compared with normal controls (Hetherington *et al.*, 1993). In Hetherington's study the eating rate of normal controls was 188.8 kJ/min (45.1 kcal/min), whereas the eating rate of subjects with bulimia nervosa was 139.8 kJ/min (33.4 kcal/min). Eating behaviour of people with bulimia nervosa is more disturbed than normal controls when rated on the Eating Behavior Rating Scale (EBRS, Wilson *et al.*, 1989; see Appendix III). The most frequent behaviour ratings were for eating low-energy foods, expressing distaste, picking at foods, eating abnormally slowly, more negative affect especially during high-energy meals, a long latency period before eating started and an absence of sensory specific satiety (Hetherington & Rolls, 1989; Hetherington *et al.*, 1993). When unable to purge they ate for longer but excessively slowly (Hetherington *et al.*, 1993). During binge meals, when purging follows, people with bulimia eat excessive amounts very quickly (Walsh, *et al.*, 1992).

Obese people, in test meals with highly palatable food, ate less and ended earlier than lean subjects. They ate more quickly, however, as if they were relatively more stimulated than the lean subjects i.e. making fewer chewing movements, spending less time chewing each food unit and with fewer pauses during the meal. They also spent more time drinking (Bellisle & Le Magnen, 1981). Unlike normal weight controls, obese people and people with weight problems did not decelerate in the second half of the meal (Meyer & Pudiel, 1972; Meyer *et al.*, 1980; Bellisle and Le Magnen, 1981; Westerterp-Plantenga *et al.*, 1990, 1992). This may be due to previous high

deprivation, palatability of food or failure of the satiety mechanism. As they eat less than lean people during test meals, satiation sensations may not have developed enough to alter the pattern of eating before they stopped eating. Meyer and colleagues suggest that internal signals are strong for normal-weight people e.g. filling of stomach, blood-sugar levels, insulin levels, but external signals are more important for obese people e.g. taste, usual mealtime, availability and appearance of food.

MICROSTRUCTURE IN THE HYPERPHAGIC DEMENTED GROUP

AIM

The aim of this study was to see if there was a failure of the normal mechanism controlling satiation in subjects who demonstrate hyperphagia. This was examined by comparing the change in the rate of ingestion through the meal.

INTRODUCTION

It was expected that in those who are not hyperphagic, the rate of ingestion would decrease towards the end of the meal, as the subject became satiated (Kissileff *et al.*, 1982). If the mechanism controlling satiation were disrupted in subjects who were hyperphagic, it was predicted that the rate of ingestion would remain constant even throughout a lengthy meal. In some people it might increase, as Meyer *et al.* (1980) found that one hyperphagic, demented, elderly person even showed positive curves i.e. more was consumed in the second half of the meal. If hyperphagia is driven by hunger it might be predicted that the latency period would be short, and the eating rate would be rapid i.e. mouthfuls would be large and frequent.

Measuring microstructure in demented subjects

Measuring the microstructure of eating in people with dementia using the standard methods is usually impractical. Most recording methods are unsuitable, for example food dispensers are too complex, a table with an inbuilt balance relies on people leaving the plate in position and eating without jogging the apparatus. Electronic monitoring devices, to measure chewing and swallowing, are unlikely to be tolerated by people who do not understand their purpose and even observing facial expression is difficult as the face is often mask-like. The only previous study of microstructure of people with dementia used a liquid-food dispenser (Meyer *et al.*, 1980). This was only found to be suitable for people with mild dementia. Direct observation, during a normal style of meal, using a videorecording to analyse microstructure seemed the only feasible method.

Before microstructure is analysed, definitions need to be specified to ensure that ratings are reliable. The definitions adopted for this study are given in table 11.1.

Table 11.1 Operational definitions used in analysis of microstructure in the elderly

(a) LATENCY The time, in seconds, from the subjects being presented with food until taking the first mouthful.
(b) LOADING RATE The rate of food intake measured as mouthfuls per unit time. Two mouthfuls were rated if loading was separated by two or more bites or if the hand was taken away from the mouth in between. Eating a crumb or licking was not counted as a mouthful.
(c) CHEWING RATE Chewing was timed from the closure of the mouth after ingestion or when the hand was moved away from the face. Each distinct jaw movement was counted as one chew. Chewing rate was standardly measured by timing the period taken for 20 chews. Pilot work showed, however, that chewing rate is almost constant over short periods of time, so that the period chosen for measurement is not critical.
(d) INGESTION (ENERGY CONSUMPTION) RATE Ingestion rate was measured in kJ ingested per minute. From the videorecording an estimate was made of the food portions eaten during each 5-minute interval. If the size of the piece of food eaten could not be seen accurately, the mouthful was estimated by dividing the unit by the number of loads taken to eat it, for example if a person took four mouthfuls to eat a biscuit, each bite was counted as a quarter if there was no obvious difference between the bites. Some studies have measured 'local eating rate' which is the rate at which food is disposed of (i.e. chewed and swallowed) once it enters the mouth (Rogers & Blundell, 1979). This was too difficult to measure in most people with dementia as chewing movements were prolonged beyond the point where the mouth seemed to be empty.
(e) ANALYSIS OF EATING BEHAVIOUR The Noldus Observer Program is designed to record the frequency and duration of behaviour when it is being observed directly. It was used to record eating behaviour during a meal while watching videorecordings. The types of behaviour were keyed into the program as they occurred and were rated as mutually exclusive; loading ended as chewing started and the next load, drinking or 'other' behaviour marked the end of chewing. CHEWING and LOADING were rated as described above. DRINKING was rated as starting when the glass was raised to the lips and ending when it was replaced on the table or another activity intervened. OTHER included any activity, while sitting, not listed above including empty chews, talking or looking about. WALKING started when a person got up and moved out of view. Walking was rated even if eating was occurring at the same time.
END OF THE MEAL The definition of the end of the meal was when the last mouthful had been chewed until:- (i) the mouth appeared to be empty (automatic chewing movements are not counted if the food appeared to have been swallowed or if chewing continued for an inappropriate length of time); (ii) the subject started to drink water and the mouth appeared to be empty afterwards; (iii) the subject got up and did not return to eat again within a reasonable time, i.e. 5 minutes unless there were extenuating circumstances e.g. visit to lavatory.

RELIABILITY OF METHODS USED TO MEASURE MICROSTRUCTURE

1. INTER-RATER RELIABILITY

METHOD

To test for inter-rater reliability, a second observer (Kathy Gedling) and I watched, and rated independently, the first 15 minutes of videorecordings of six digestive biscuit meals and seven mixed meals. Two tapes, for each type of meal, were chosen at random from each of the three groups (hyperphagic demented, non-hyperphagic demented and normal controls plus one extra normal control mixed meal).

Reliability was measured for:-

- a) latency before first mouthful - times were rated as concordant if within 2 seconds;
- b) number of mouthfuls taken (excluding crumbs or licking);
- c) timing of each mouthful - times were rated as concordant if within 2 seconds;
- d) proportion of food item eaten during each mouthful - ratings were concordant if the second rater's estimate of the proportion of food item was within 20% of my rating;
- e) in addition, for the digestive biscuit meal, the total intake was estimated and for mixed meals identification of the type of food eaten was rated.

RESULTS

a) Latency

Both raters rated latency to within 1 second in all 13 meals.

In each of the tables below the total scores for different measurements of microstructure are listed for the three groups. The scores, made by each observer, are given as a ratio (rater 1:rater 2) with the percentage concordance in brackets after.

b) Mouthfuls rated

Group	Digestive biscuit meal	Mixed meal
Hyperphagic group	52:56 (93%)	79:78 (99%)
Non-hyperphagic demented controls	16:16 (100%)	61:60 (98%)
Normal controls	52:52 (100%)	134:134 (100%)

c) Timing of each mouthful

Group	Digestive biscuit meal	Mixed meal
Hyperphagic group	55:56 (98%)	76:78 (97%)
Non-hyperphagic demented controls	16:16 (100%)	60:60 (100%)
Normal controls	51:52 (98%)	134:135 (99%)

d) Proportion of food item eaten during each mouthful

Group	Digestive biscuit meal	Mixed meal
Hyperphagic group	45:56 (80%)	51:78 (65%)
Non-hyperphagic demented controls	10:16 (63%)	45:60 (75%)
Normal controls	42:52 (81%)	140:152 (92%)

e) Estimated intake

Group	Digestive biscuit meal
Hyperphagic group	9.5:9.63 (99%)
Non-hyperphagic demented controls	4.1:3.38 (82%)
Normal controls	14.0:14.0 (100%)

Group	Mixed meal - food identification	
Hyperphagic group	76:78	(97%)
Non-hyperphagic demented controls	60:60	(100%)
Normal controls	138:152	(91%)

The results show that inter-rater reliability for all items and all groups was high.

2. INTRA-RATER RELIABILITY

METHOD

To test intra-rater reliability, my ratings, from the same 13 tapes, were compared with the original ratings which had been made either during the meal or from videorecordings shortly after the meal. The same criteria were used as for inter-rater reliability.

RESULTS

a) Latency

Both sets of rating for latency to within 1 second in all 13 meals.

In each of the tables below the total scores for different measurements of microstructure are listed for the three groups. The scores, during each rating session, are given as a ratio (rating 1:rating 2) with the percentage concordance in brackets afterwards.

b) Number of mouthfuls taken (loads)

Group	Digestive biscuit meal	Mixed meal
Hyperphagic group	56:58 (97%)	78:78 (100%)
Non-hyperphagic demented controls	16:16 (100%)	59:60 (98%)
Normal controls	52:52 (100%)	132:134 (99%)

c) Timing of each mouthful

Group	Digestive biscuit meal	Mixed meal
Hyperphagic group	56:56 (100%)	76:78 (97%)
Non-hyperphagic demented controls	16:16 (100%)	59:59 (100%)
Normal controls	52:52 (100%)	133:134 (99%)

d) Proportion of food item eaten during each mouthful

Group	Digestive biscuit meal	Mixed meal
Hyperphagic group	56:56 (100%)	78:78 (100%)
Non-hyperphagic demented controls	16:16 (100%)	53:58 (91%)
Normal controls	52:52 (100%)	141:141 (100%)

e) Estimated intake

Group	Digestive biscuit meal
Hyperphagic group	9.6:10.0 (96%)
Non-hyperphagic demented controls	3.0:3.2 (96%)
Normal controls	14.0:14.0 (100%)

Group	Mixed meal - food identification
Hyperphagic group	78:78 (100%)
Non-hyperphagic demented controls	54:59 (100%)
Normal controls	133:152 (88%)

The results show that intra-rater reliability was high for all items and all groups; and was slightly higher than inter-rater reliability.

3. INTRA-SUBJECT RELIABILITY

METHOD

To examine test/retest reliability of the microstructure during meals, the following comparisons were made:

- a) Time spent eating during first two biscuit and mixed meals.
- b) Eating rate during the entire meal (total kJ divided by total meal time).

RESULTS

a) Meal time

Both demented groups ate for a significantly longer time (on average) than the normal elderly at the first biscuit and mixed meals (t-test: hyperphagic group $p < 0.0005$ for both meals; non-hyperphagic group $p = 0.02$ and 0.009 respectively). There was no significant difference in meal time between the two demented groups. The test-retest data showed that the time taken for each type of meal was reliable between meals, especially for the normal elderly (figure 11.2 and table 11.2).

b) Ingestion rate

When a paired t-test was carried out using the test-retest data there was no significant difference between the two meals for ingestion rate in any of the three groups and the correlation between the overall ingestion rates (eating rate) for meal 1 and meal 2 was highly significant (see figure 11.3 and table 11.3). Overall there was a high correlation in the eating rate between the two digestive biscuit meals (Pearson correlation: 0.738 , $p < 0.0005$).

Figure 11.2

Time taken for meals
Biscuit meal 1 and mixed meal 1

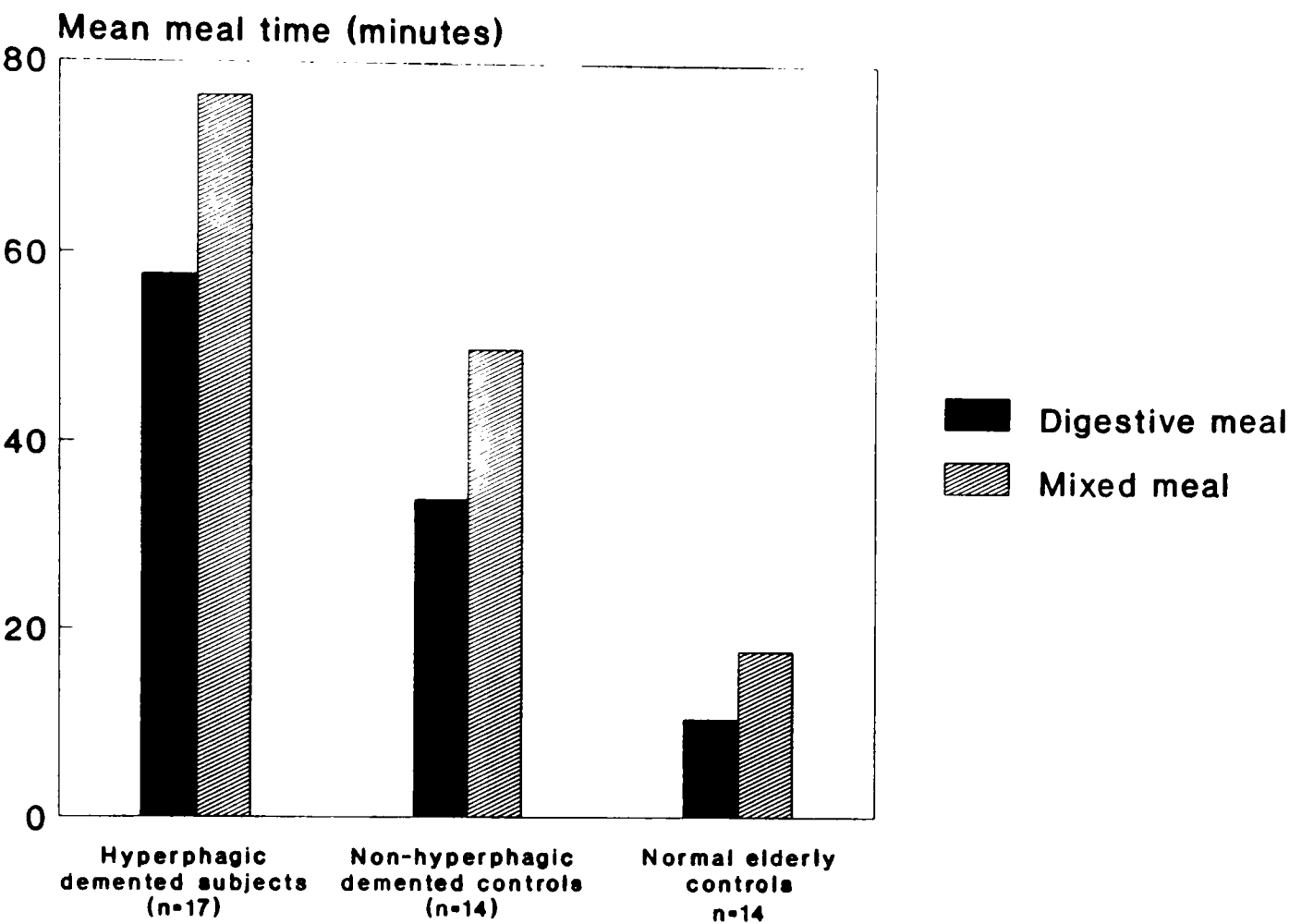


Table 11.2 Reliability of meal time for digestive biscuit meals 1 and 2

DIGESTIVE MEAL 1	
Subject group	Meal time in minutes
Hyperphagic group	58.7 (S.D. 37.0, range 5-120, n=10)
Non-hyperphagic demented	33.8 (S.D. 29.3, range 8-69, n= 5)
Normal elderly controls	11.8 (S.D. 7.2, range 6-24, n= 5)

DIGESTIVE MEAL 2	
Subject group	Meal time in minutes
Hyperphagic group	65.5 (S.D. 36.5, range 21-120, n=10)
Non-hyperphagic demented	28.8 (S.D. 21.6, range 6-58, n= 5)
Normal elderly controls	12.0 (S.D. 8.6, range 5-24, n= 5)

Test/retest reliability of overall eating rate

DIGESTIVE BISCUIT MEALS 1 and 2	Pearson correlation
Hyperphagic group (n=10)	0.955 (<i>p</i> < 0.0005)
Non-hyperphagic demented controls (n=5)	0.565 (<i>p</i> = 0.321)
Normal elderly controls (n=5)	0.888 (<i>p</i> = 0.044)
All groups (n=20)	0.916 (<i>p</i> < 0.0005)

Figure 11.3 **RELIABILITY - test-retest**
Eating rate (kJ/minute)

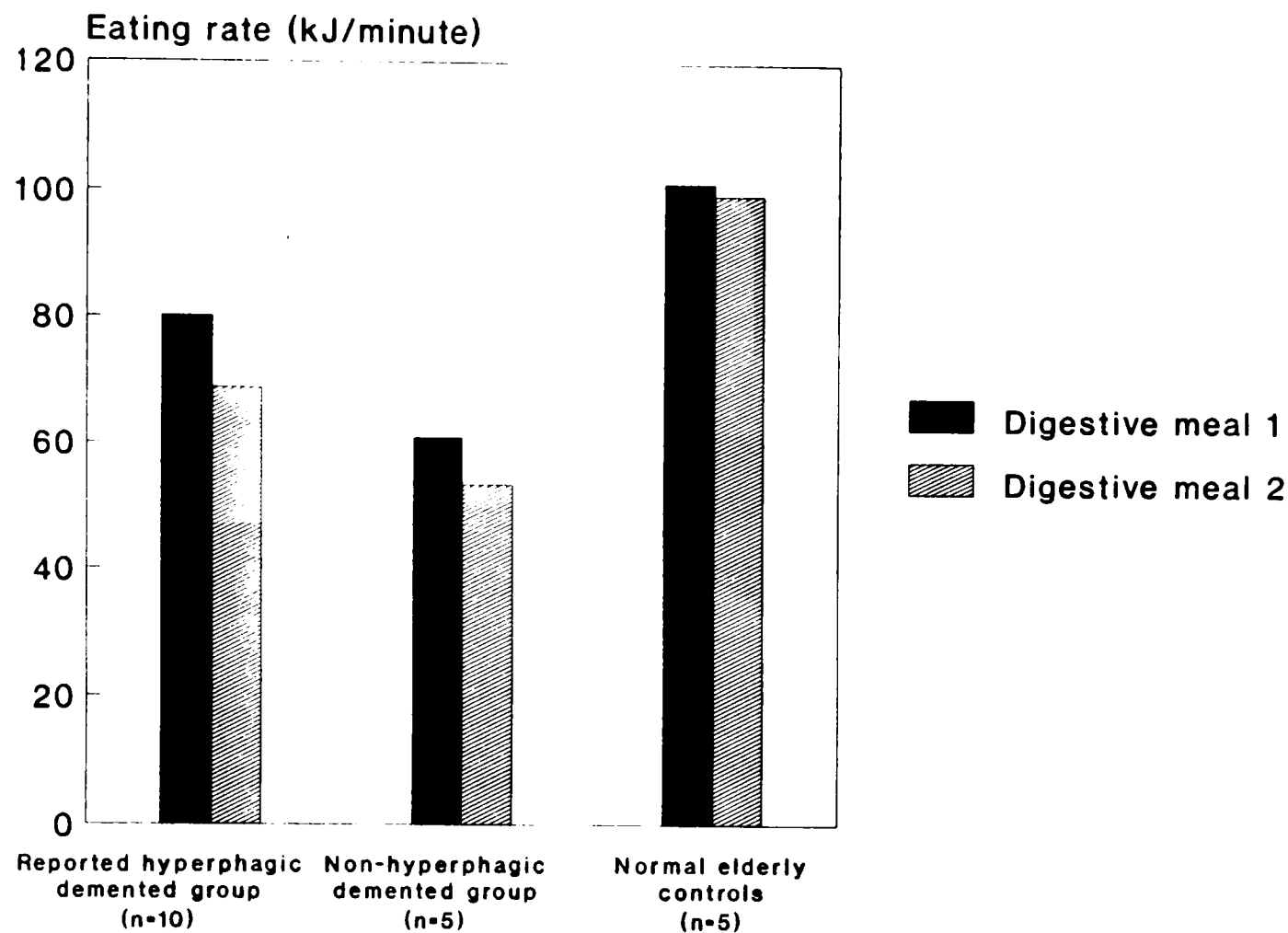


Table 11.3 Test-retest reliability of ingestion rate (biscuit meals 1 and 2)

DIGESTIVE MEAL 1	
Subject group	kJ/minute
Hyperphagic group	80.2 (S.D. 47.6, range 32-180, n=10)
Non-hyperphagic demented	61.0 (S.D. 31.2, range 36-114, n= 5)
Normal elderly controls	101.5 (S.D. 13.5, range 80-117, n= 5)
DIGESTIVE MEAL 2	
Subject group	kJ/minute
Hyperphagic group	68.8 (S.D. 34.9, range 24-128, n=10)
Non-hyperphagic demented	53.4 (S.D. 37.1, range 21-155, n= 5)
Normal elderly controls	99.6 (S.D. 24.6, range 78-140, n= 5)

Test/retest reliability of overall eating rate

DIGESTIVE BISCUIT MEAL 1 and 2	Pearson Correlation
Hyperphagic group (n=10)	0.698 (<i>p</i> =0.025)
Non-hyperphagic demented controls (n=5)	0.901 (<i>p</i> = 0.037)
Normal elderly controls (n=5)	0.305 (<i>p</i> = 0.617)
All groups (n=20)	0.738 (<i>p</i> < 0.0005)

ANALYSIS AND DETAILED DESCRIPTION OF THE MICRO-STRUCTURE OF EATING AND THE CHANGES IN RATE OF EATING DURING THE MEAL

METHOD

Although both the biscuit meals and the mixed meals were shown to be reliable for the overall aspects of microstructure, for example total eating time and eating rate (see above), the microstructure of the *ad libitum* low-sugar digestive biscuit meal was analysed for the detailed microstructure of eating. To ensure uniformity, the results of the biscuit meal were used so that differences in texture or palatability did not affect microstructure parameters. Chewing rate for example is known to vary with the texture of the food (Christensen, 1984) and increased palatability decreases chewing time and increases the size of mouthfuls (Bellisle, 1989).

For each of the three groups of subjects and controls, the following measurements were made, using videorecordings of the first single-food meal.

a) Latency

Latency period before eating started was measured in seconds. No initial instructions were given to the demented groups in order to estimate the intensity of their hunger. As with the other meals, a prompt was given if eating had not started after 2 minutes.

b) Loading rate

The overall loading rate for the whole meal for each of the three groups was compared. Loading rate was measured in three ways (i) mouthfuls eaten in unit time,

(ii) mass eaten in unit time and (iii) the numbers of mouthfuls taken in each five-minute period of the digestive biscuit meal. These data were plotted on a graphically to see if loading rate changed during the course of the meal.

c) Chewing rate

Chewing rate was measured at 5-minute intervals throughout the meal. For people who ate for less than 15 minutes the chewing rate was measured every 2 minutes. Chewing, after the first mouthful of each 5-minute interval was timed if the mouthful was chewed more than 10 times. A mouthful of less than 10 chews was ignored and the next mouthful was rated. If there were ≥ 10 and < 20 chews, the time for 20 chews was extrapolated. If no new mouthful was taken within the 5-minute period, chewing was timed from the beginning of the period (if it was occurring regularly).

d) Ingestion rate

The energy value of food ingested, during each 5-minute interval, was estimated from the videorecording. The overall eating (ingestion) rate was calculated (total kJ intake/total meal time). The mean size of mouthful was also calculated, by dividing the total mass of biscuit eaten by the number of loads. The cumulative total of food eaten was calculated and plotted on a graph. The shape of the curve was examined to see if it showed a linear, accelerating or decelerating ingestion rate during the course of the meal. Each person's cumulative intake curve was tested to see how well the data fitted a quadratic equation and R^2 (the coefficient of determination) was calculated in order to measure the goodness of fit and indicate the percentage variance accounted for by the equation.

e) Analysis of eating behaviour

Different activities during each quarter of the meal were analysed using the Noldus Observer Program to calculate the time spent loading, chewing, drinking, walking and 'other' activities (see table 11.1 for definitions). The total time for the meal was divided into 4 equal periods and the program run for each quarter. Afterwards, the quarter-meal intervals were each subdivided into four to give a more detailed breakdown of activities. Intra-meal pauses were calculated by totalling 'other' behaviour from data from the Observer program.

The Eating Behavior Rating Scale (Wilson *et al.*, 1989, see Appendix III) was developed as a measure of eating pathology in anorexia nervosa. The scale was later adapted to assess the eating pathology in bulimia nervosa (Hetherington *et al.*, 1993). In the present study it was used to assess eating abnormalities during both types of meal.

RESULTS

a) Latency

The results are summarised in table 11.4 and figure 11.4. Because of some atypical cases, where people were reluctant to start eating, the results were skewed and did not follow a normal distribution. The median, rather than the mean, was taken as the best summarising measure for each group. Several people in the hyperphagic group started to eat before they were seated.

The hyperphagic demented group had a significantly shorter latency than the non-

hyperphagic group (t-test: $t = 2.9$, $df = 29$, $p = 0.007$). There was much greater variability in latency in both groups with dementia compared with the normal controls. The hyperphagic group had a slightly shorter latency than the normal elderly controls as well, although this difference was not significant. The hyperphagic group was more variable.

The non-hyperphagic demented controls were significantly slower than the normal elderly in starting the first digestive biscuit meal (t-test: $t = 2.7$, $df = 25$, $p = 0.01$) and the first mixed meal (t-test: $t = 2.6$, $df = 26$, $p = 0.01$). In the non-hyperphagic demented group, latency varied from 0 to several minutes with many individuals needing to be prompted to start, sometimes through apparent lack of interest in the food, sometimes because they were not sure what they were supposed to be doing.

b) Loading rate

(i) Mouthfuls eaten (loads) in unit time

The loading rate for both demented groups was significantly slower than for the normal elderly. An analysis of variance (ANOVA) showed that there was a significant difference in loading rate between the groups (ANOVA: $F [2,41] 14.2$, $p < 0.00005$). Using independent t-tests, the non-hyperphagic demented controls were shown to be significantly slower than the normal elderly ($t = 6.3$, $df = 24.5$, $p < 0.0005$). The loading rate of the hyperphagic demented group was significantly slower than the normal elderly ($t = 3.3$, $df = 28.9$, $p = 0.002$) but faster than the non-demented controls ($t = 2.1$, $df = 27.0$, $p = 0.045$). The normal elderly took

Figure 11.4 LATENCY - Digestive biscuit meal

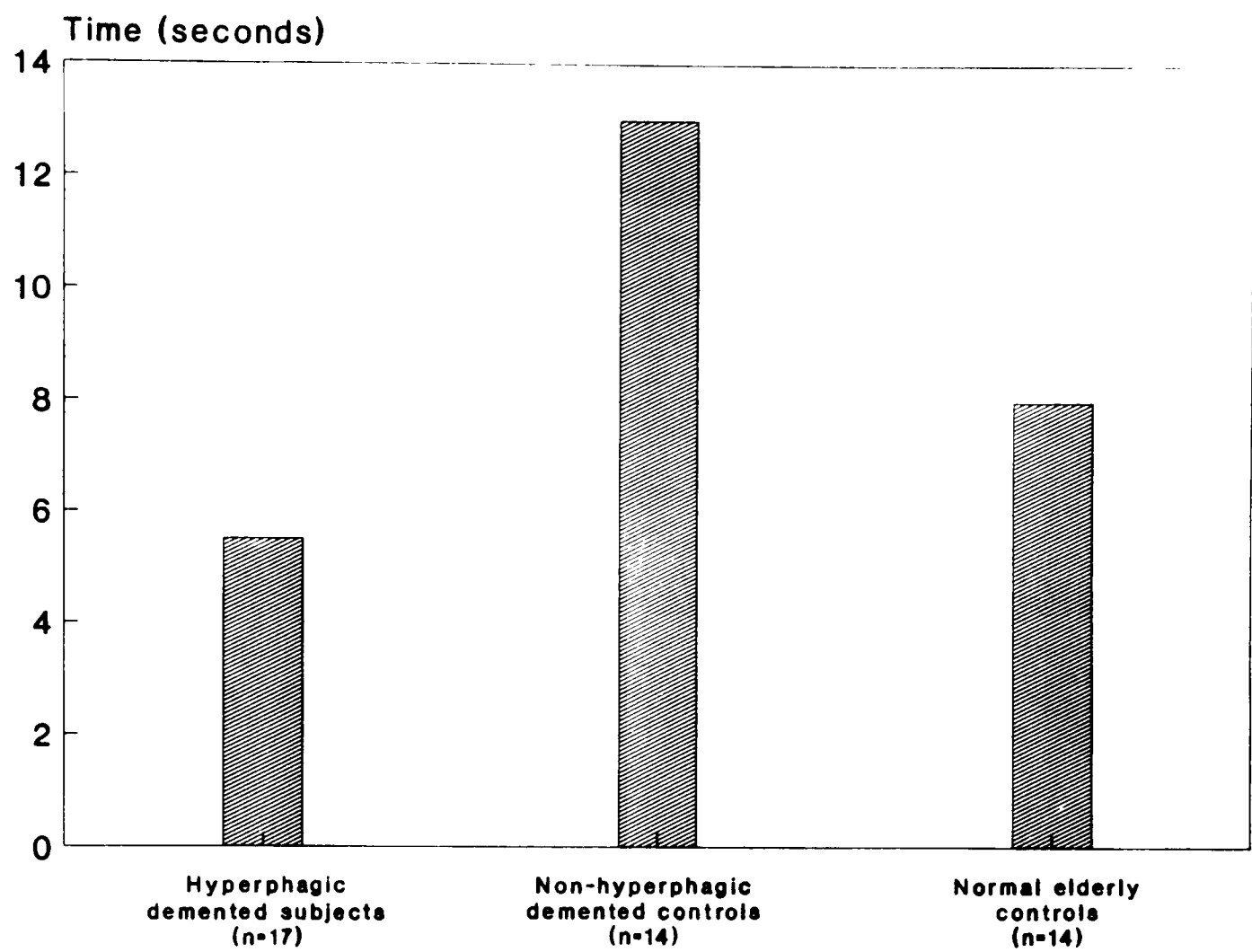


Table 11.4 Latency period

DIGESTIVE BISCUIT MEAL 1	Median and interquartile range (IQR) in seconds		
Hyperphagic group	5.5	(IQR 2-15,	n=18)
Non-hyperphagic demented controls	13.0	(IQR 7-150,	n=13)
Normal elderly controls	8.0	(IQR 6-15,	n=14)

the most frequent mouthfuls and the non-hyperphagic demented had the slowest rate (see table 11.5).

Table 11.5 Loading rate

DIGESTIVE MEAL 1	
Subject group	Mean loads/minute
Hyperphagic group	1.8 (S.D. .97, range 0.7-4.4, n=17)
Non-hyperphagic demented	1.2 (S.D. 0.6, range 0.5-2.3, n=13)
Normal elderly controls	2.8 (S.D. 0.7, range 1.7-4.3, n=14)

(ii) Mass eaten in unit time

The difference between the groups was highly significant (ANOVA: $F [2,43] 12.6$, $p < 0.00005$). The normal elderly ate the greatest mass in unit time; this was significantly more than the hyperphagic group ($t = 2.9$, $df = 26.2$, $p = 0.008$) and very much faster than the demented controls ($t = 5.0$, $df = 23.1$, $p < 0.0005$). The hyperphagic group ate significantly more quickly than the non-hyperphagic demented group ($t = 2.4$, $df = 30$, $p = 0.02$). See table 11.6.

Table 11.6 Mass eaten in unit time

DIGESTIVE MEAL 1	
Subject group	Mean mass (g)/minute
Hyperphagic group	3.9 (S.D. 2.0, range 1.5-9.0, n=18)
Non-hyperphagic demented	2.5 (S.D. 1.6, range 1.0-6.1, n=14)
Normal elderly controls	6.1 (S.D. 2.3, range 3.8-12.2, n=14)

(iii) Change in loading rate during the course of the meal

The loading rate in a few of the hyperphagic group showed signs of slowing in meals which lasted for more than an hour. Irregularities, mainly in the non-hyperphagic demented group, were due to other activities which replaced eating. Prompts were often needed to see if the person had finished eating or still wanted some more.

The normal elderly ate steadily and consistently and there was no evidence of slowing towards the end of the meal. When the two demented groups were compared, the people with hyperphagia were significantly faster eaters than the non-hyperphagic controls, who were matched for cognitive ability.

c) Chewing rate - changes during the course of the meal

Chewing rate varied between individuals but was moderately constant for each person throughout the meal. There was no systematic change in chewing rate during the course of the meal for any of the three groups and in particular no slowing down at the end of the meal (see figures 11.5 a-c).

Figure 11.5 a

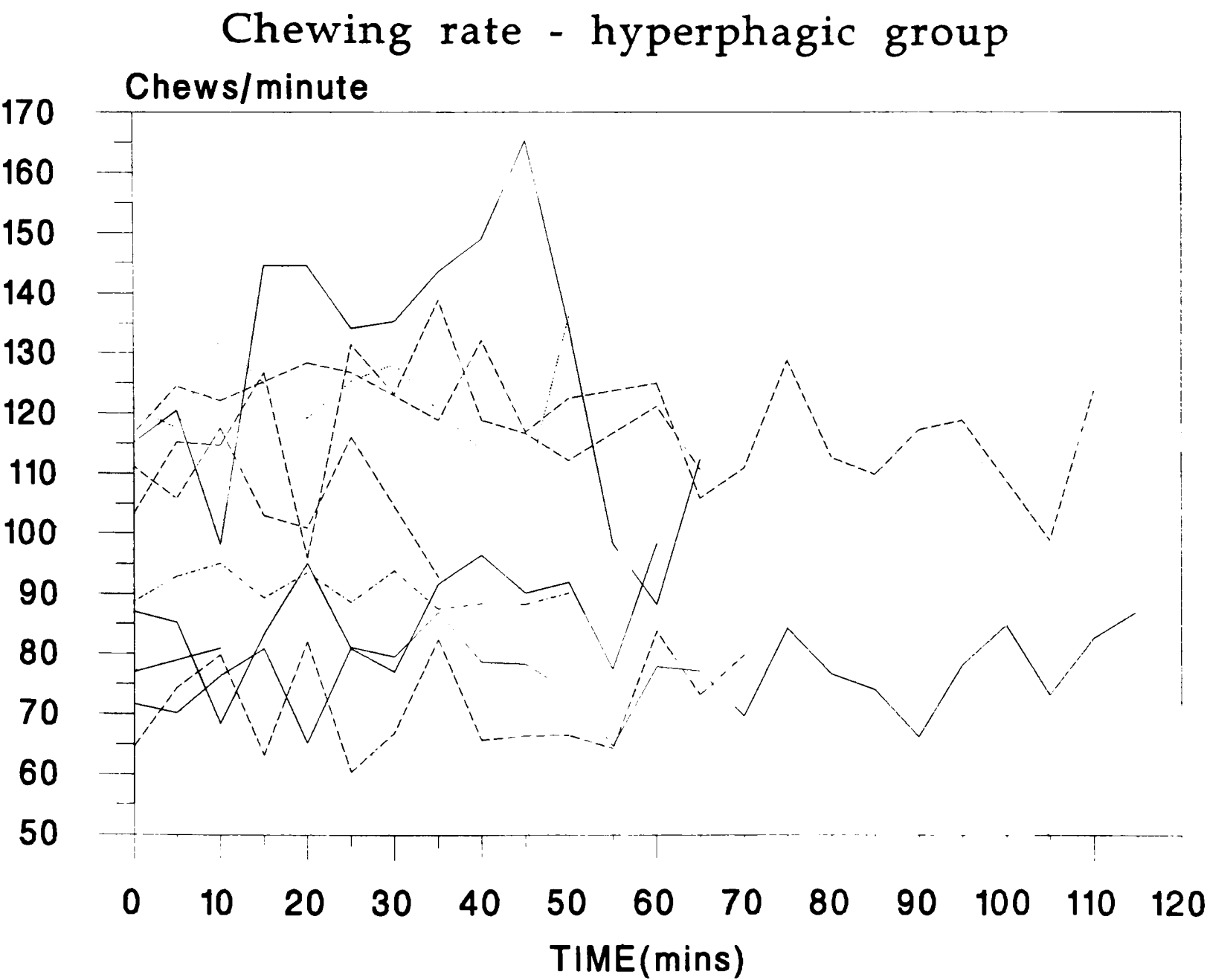


Figure 11.5 b Chewing rate - non-hyperphagic demented group

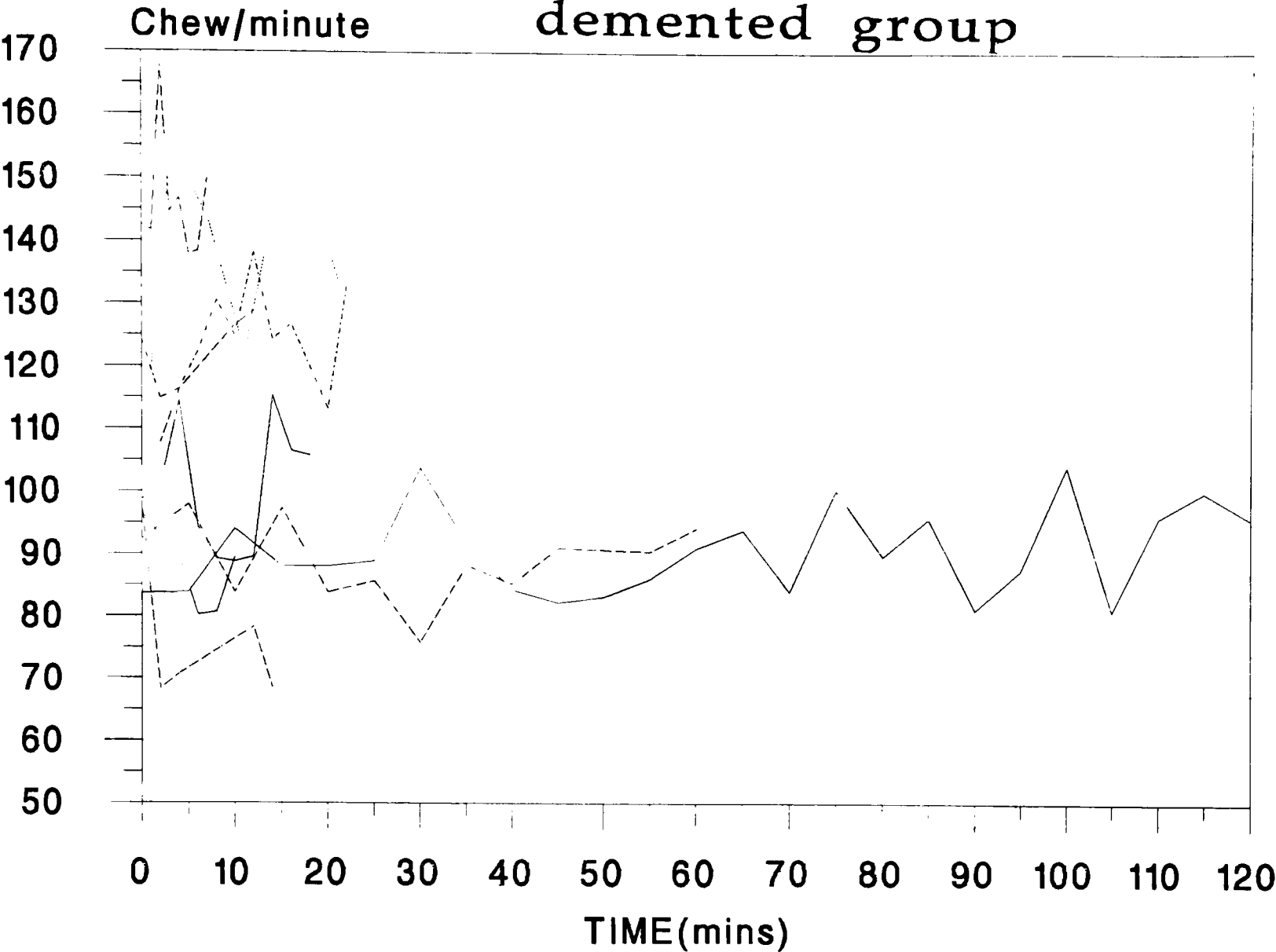
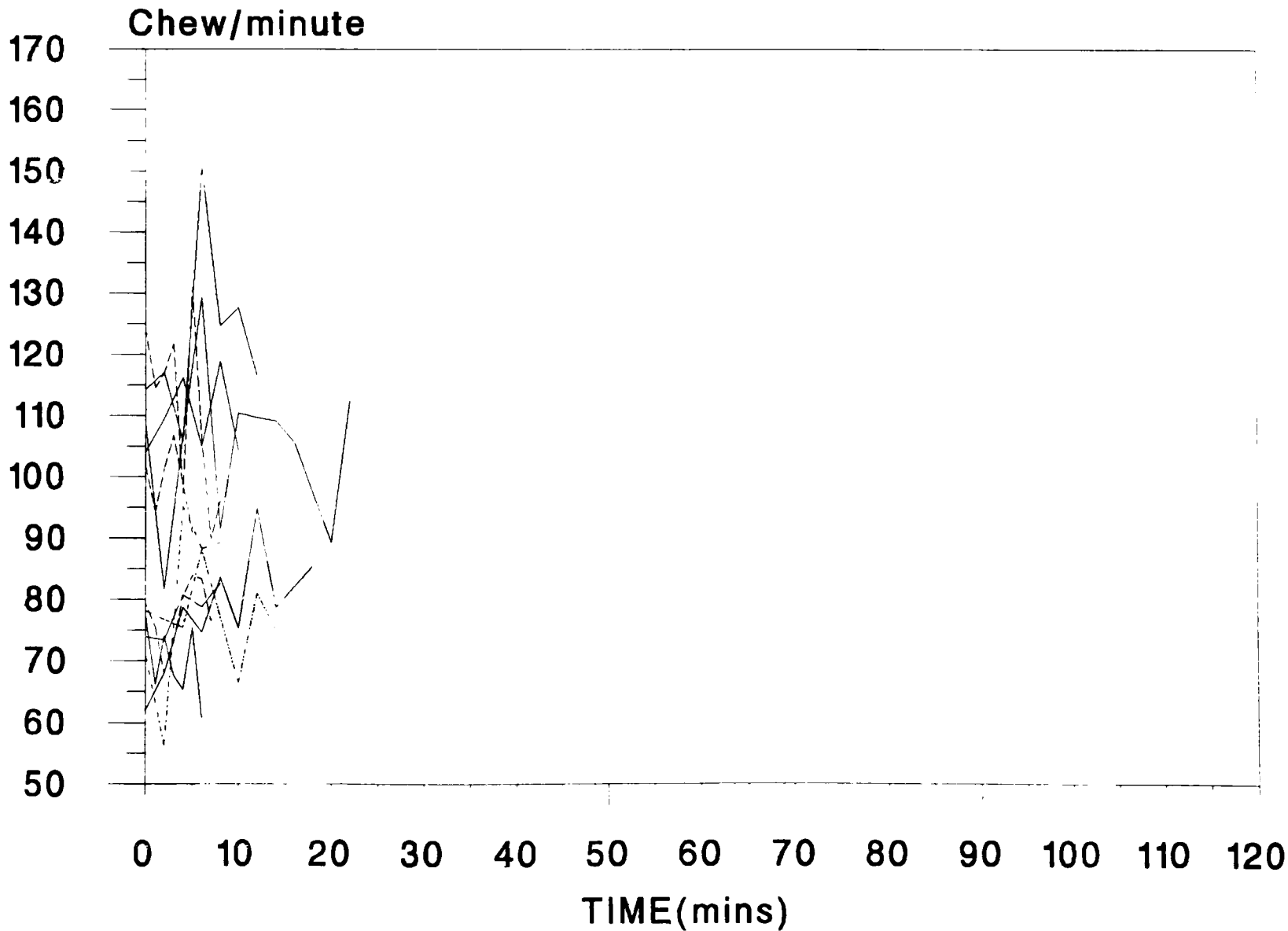


Figure 11.5 c Chewing rate - normal elderly group



d) Ingestion (energy consumption) rate

(i) The overall ingestion rate

The normal elderly had a significantly faster eating rate than both the hyperphagic group ($t = 2.8, df = 25.0, p = 0.01$) and the non-hyperphagic group ($t = 4.8, df = 22.6, p \leq 0.0005$). This appeared to be because their coordination was better than the two groups with dementia and they were not as easily distracted as the non-hyperphagic group. The hyperphagic group ate significantly faster than the non-hyperphagic demented ($t = 2.4, df = 30, p < 0.03$). The reliability data (table 11.3) show a very stable pattern with the normal elderly controls having the fastest eating rate, the non-hyperphagic demented controls eating more slowly at about half this rate and the hyperphagic group being intermediate.

(ii) Mean size of mouthful

The mean size (measured in grams) of each mouthful (load or bite-size) is given in table 11.7 below. The difference between groups is not significant.

Table 11.7 Mean size of mouthful

DIGESTIVE MEAL 1		
Subject group	Mean grams/load	
Hyperphagic group	2.5	(S.D. 1.1, range 0.5-4.4, n=17)
Non-hyperphagic demented	2.0	(S.D. 0.8, range 0.9-3.7, n=13)
Normal elderly controls	2.2	(S.D. 0.5, range 1.0-2.9, n=14)

(iii) Cumulative ingestion rate - (kJ ingested each 5-minute interval)

The cumulative intake curves (figure 11.6 a-c) were almost linear for all three groups of subjects but there was some deceleration in the rate of intake towards the end of the meal i.e. more was eaten in the first half of the meal than the second half in each

of the three groups. There was no significant difference between any of the three groups in this reduction in intake in the second half of the meal.

The ingestion rate varied from individual to individual but for each of the normal controls the rate, throughout the meal, was virtually constant. However, people in the hyperphagic group who started off abnormally fast, eating more than 700 kJ in the first 5 minutes, did reduce their rate of intake during the course of the meal, (although chewing rates remained constant). The cumulative ingestion curves showed a similar pattern to the loading rate, demonstrating that the size of the piece of food ingested did not change markedly as the meal progressed (see figures 11.6 a-c).

Quadratic equations were fitted to the intake curves, using the methods of Kissileff and colleagues (1982). The degree to which the curves are fitted by a quadratic equation is measured by values for R^2 (the coefficient of determination). The R^2 values for the normal elderly were all 0.990 or more (mean 0.996, $n = 10$). The hyperphagic demented curves too fitted a quadratic (mean $R^2 = 0.994$, range 0.97 - 1.0, $n = 10$). The non-hyperphagic demented were more variable (mean $R^2 = 0.970$, range 0.91-1, $n = 11$).

The initial rates of eating (measured by the linear coefficient - b in the quadratic equation), in the hyperphagic group and the normal elderly were not significantly different from each other but both were significantly faster than the non-hyperphagic group (t-test; $t = 2.34$, $p = 0.034$ and $t = 4.81$, $p < 0.0005$ respectively) - see table 11.8.

Table 11.8 Quadratic equation coefficients

Group	Linear coefficient (b)	Quadratic function (c)	Coefficient of determination (R²)
Hyperphagic demented group (n = 10)	107.8	-0.57	0.994
Non-hyperphagic demented group (n = 11)	51.6	-0.02	0.970
Normal elderly group (n = 10)	145.9	-3.18	0.996

The quadratic function (c), which gives a measure of the inhibitory process, or deceleration, was significantly higher in the normal elderly than in either of the groups with dementia (t-test: normal elderly/hyperphagic group $t = 3.49$, $p = 0.006$; normal elderly/non-hyperphagic group $t = 2.74$, $p = 0.013$). The difference between the hyperphagic group and the non-hyperphagic group was not significant. The intercept (a) is assumed to be zero in these calculations. A positive intercept is an indication of the latency period before eating starts whereas a negative value indicates an initial acceleration in the eating rate. No reliable estimate can be made for the initial acceleration from these data because of the high variability of the latency period. Four of the non-hyperphagic controls appeared to have accelerating curves because of their long latency period.

Figure 11.6 a Cumulative intake curves - hyperphagic group

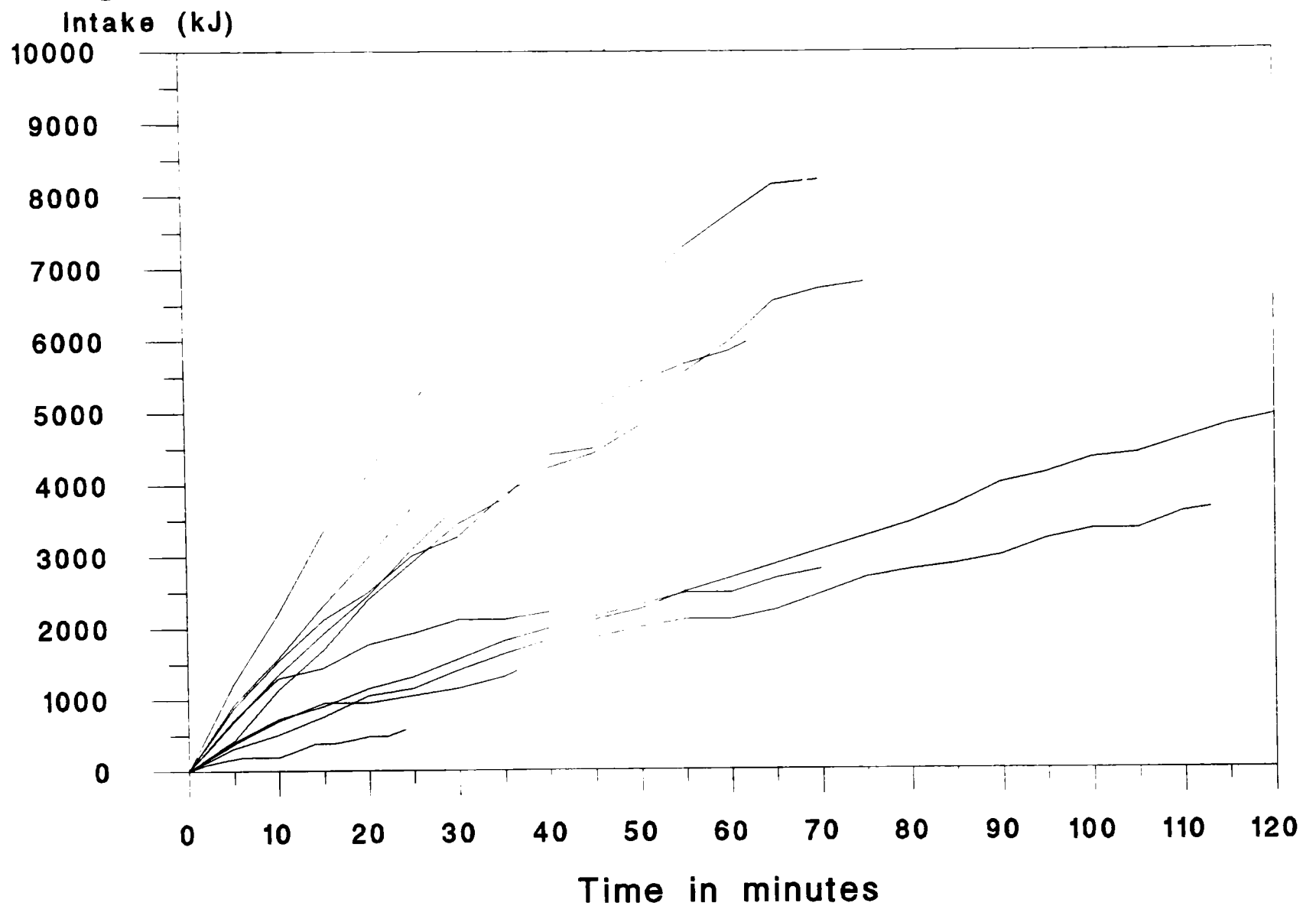


Figure 11.6 b

Cumulative intake curve
non-hyperphagic demented group

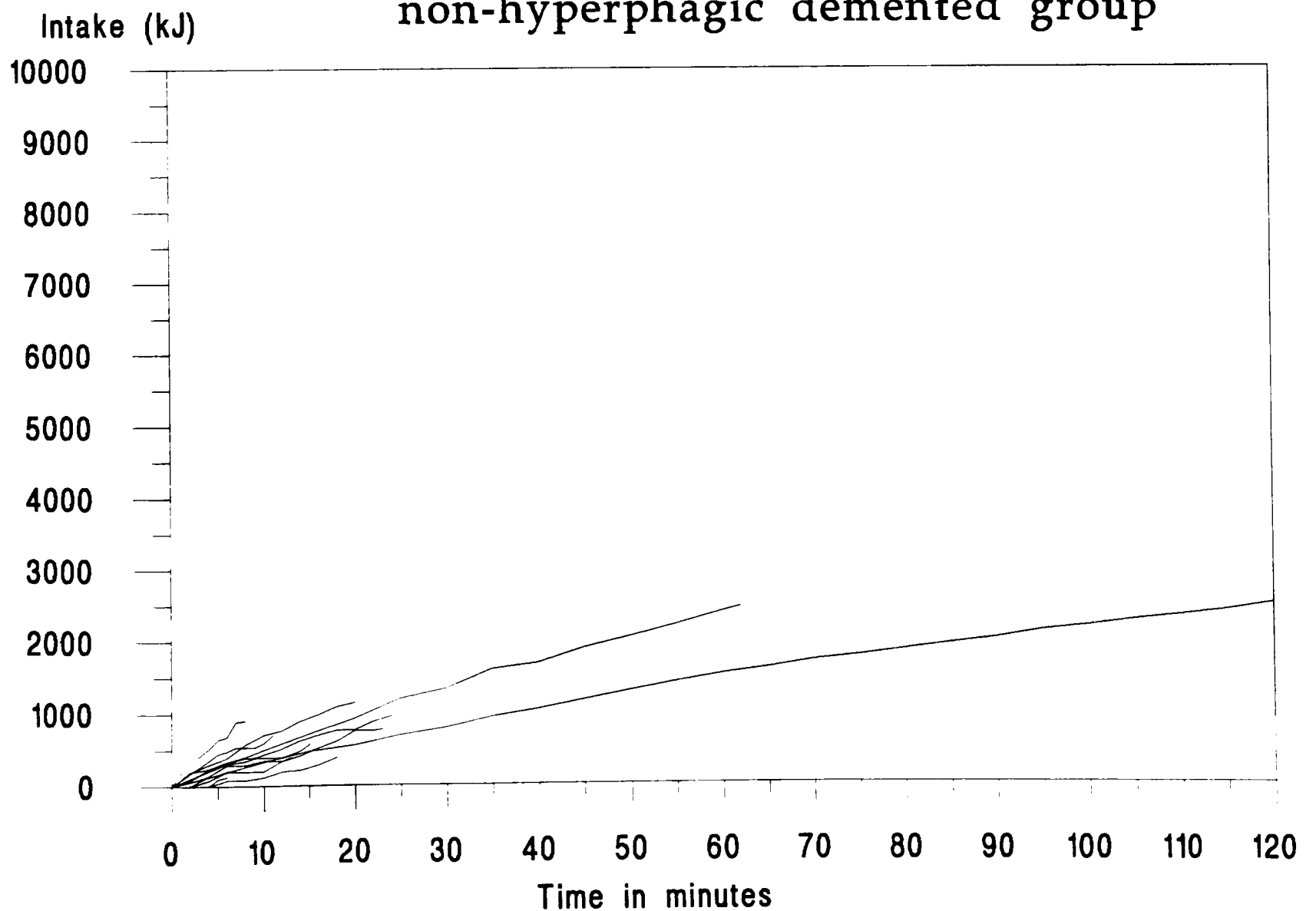
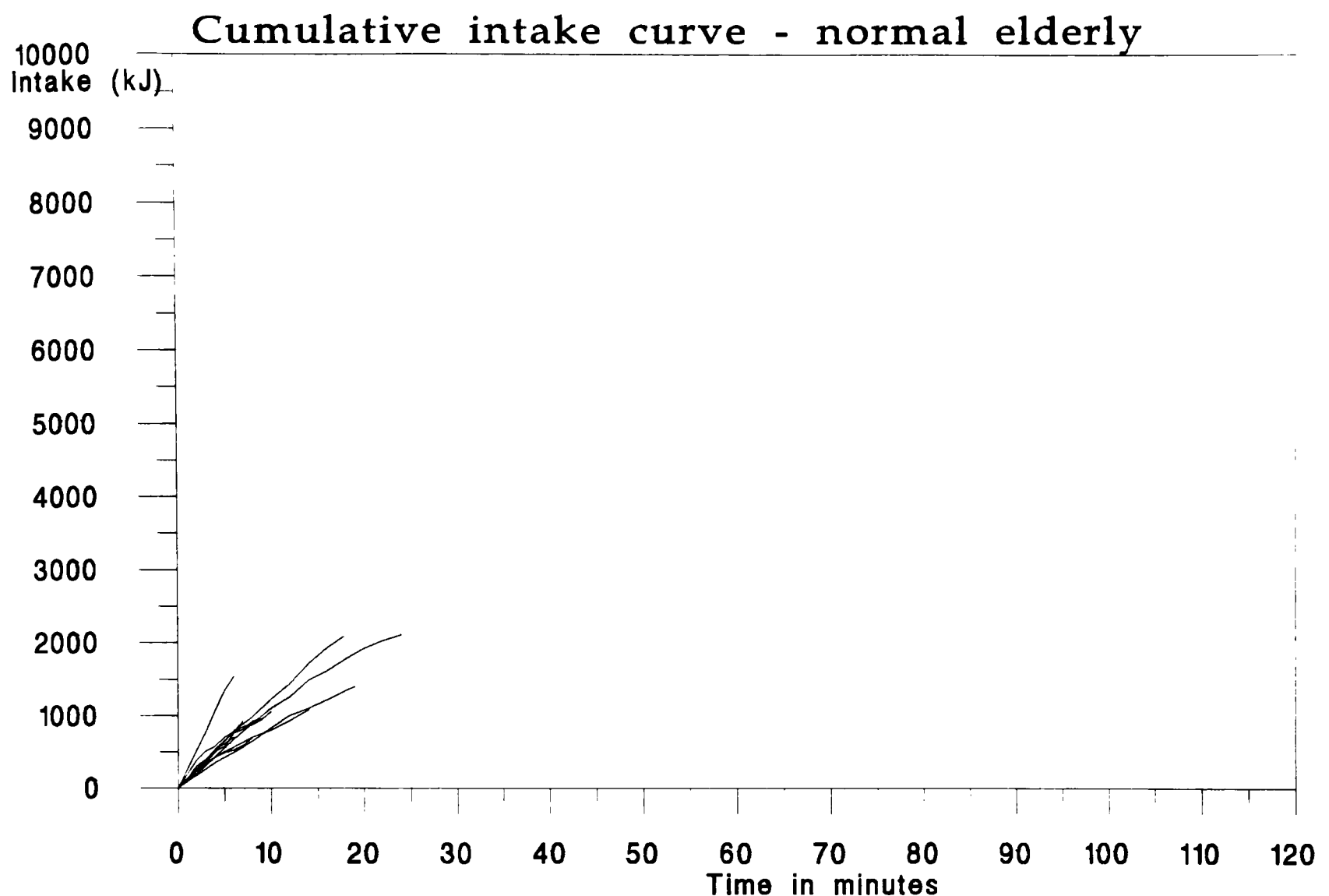


Figure 11.6 c



e) Analysis of eating behaviour

So far, any systematic changes in behaviour during the meal have been examined by seeing whether rates of eating behaviour (e.g. chewing rate, ingestion rate) have altered during the course of the meal. In this section, the question of changes during the meal will be examined both in terms of eating and non-eating behaviour. From the video-recordings, the time spent in various types of behaviour was examined. These types of behaviour were: loading, chewing, drinking, walking around and 'other' behaviour. 'Other' behaviour included time spent sitting but not eating or drinking (i.e. with no food or drink in the mouth and not loading food or drink.

During each half of the meal the percentage of the time spent in these activities was recorded for ten people in each of the three subject and control groups (see table 11.9

and figure 11.7 a-e). Intra-meal pauses, i.e. the time spent in 'other' behaviour, were found to increase in the second half of the meal in all three groups but the difference was not significant (table 11.9).

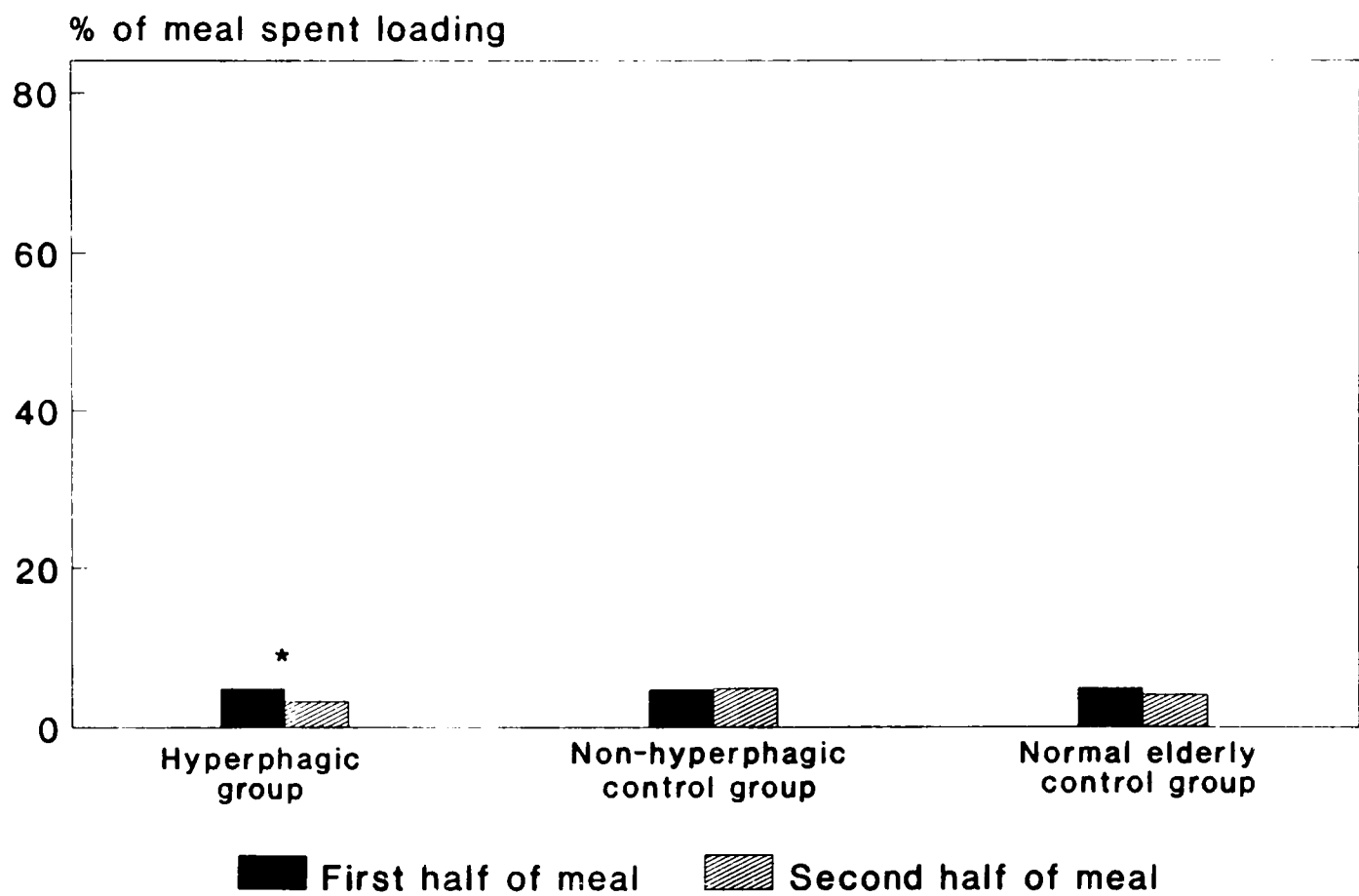
Table 11.9 Percentage of time spent in each activity in each half of the meal

Activity and group	First half of meal %	Second half of meal %	Results of t-test <i>t</i> - value and (probability)	
LOADING				
Hyperphagic demented group	4.91	3.28	2.73	(0.02)
Non-hyperphagic demented group	4.70	4.79	0.09	(0.93)
Normal elderly group	4.85	4.05	2.15	(0.06)
CHEWING				
Hyperphagic demented group	72.19	54.14	2.8	(0.02)
Non-hyperphagic demented group	62.54	62.03	0.06	(0.96)
Normal elderly group	83.36	82.75	0.23	(0.82)
DRINKING				
Hyperphagic demented group	3.69	5.04	0.68	(0.52)
Non-hyperphagic demented group	1.84	2.20	0.56	(0.59)
Normal elderly group	7.74	7.93	0.12	(0.91)
OTHER BEHAVIOUR				
Hyperphagic demented group	17.20	21.75	0.93	(0.37)
Non-hyperphagic demented group	30.84	31.41	0.06	(0.95)
Normal elderly group	4.13	6.31	0.84	(0.42)
WALKING				
Hyperphagic demented group	1.95	14.08	1.47	(0.18)
Non-hyperphagic demented group	0	0	-	
Normal elderly group	0	0	-	

Walking behaviour was not included in 'intra-meal pauses' as the only people who walked about during the meal were in the hyperphagic group and they were usually eating as they walked. They returned to the table periodically to collect more food, which explains why walking increases in the second half of the meal without affecting the overall ingestion rate. It also explains why the only significant differences between the two halves of the meal were in the hyperphagic group. In the second

half of the meal, the hyperphagic group were recorded as spending significantly less time loading and chewing food because, as subjects were walking, their loading and chewing behaviour was not recorded. However, when the figures for loading, chewing and walking were combined there was no significant difference between the two halves of the meal.

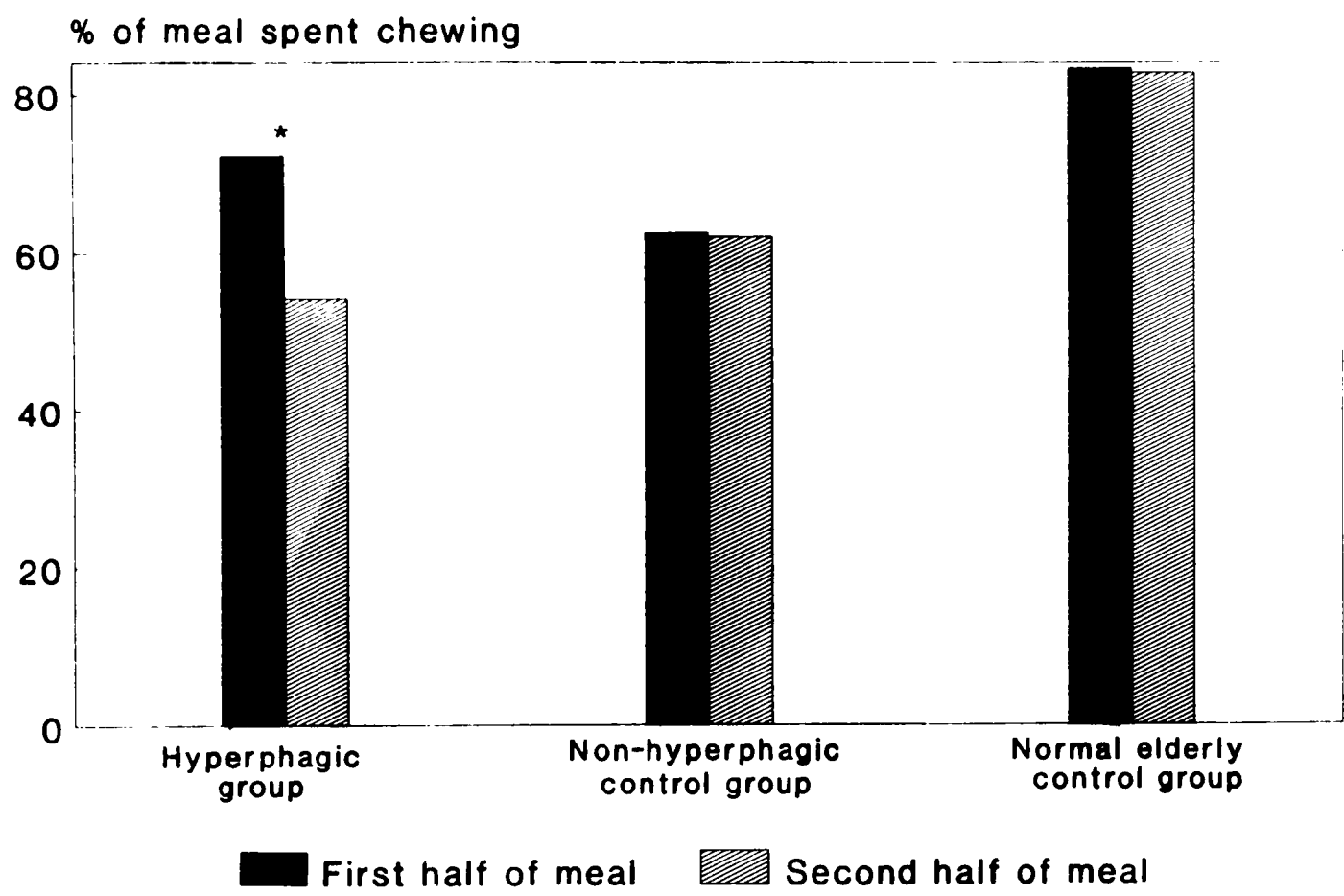
Figure 11.7 a **Loading time (% of meal)**
Time spent loading food into mouth



* denotes that difference is significant

Table 11.7 b

Chewing time (% of meal)
Time spent chewing food



* denotes that difference is significant

Table 11.7 c

Drinking time (% of meal)
Time spent drinking water

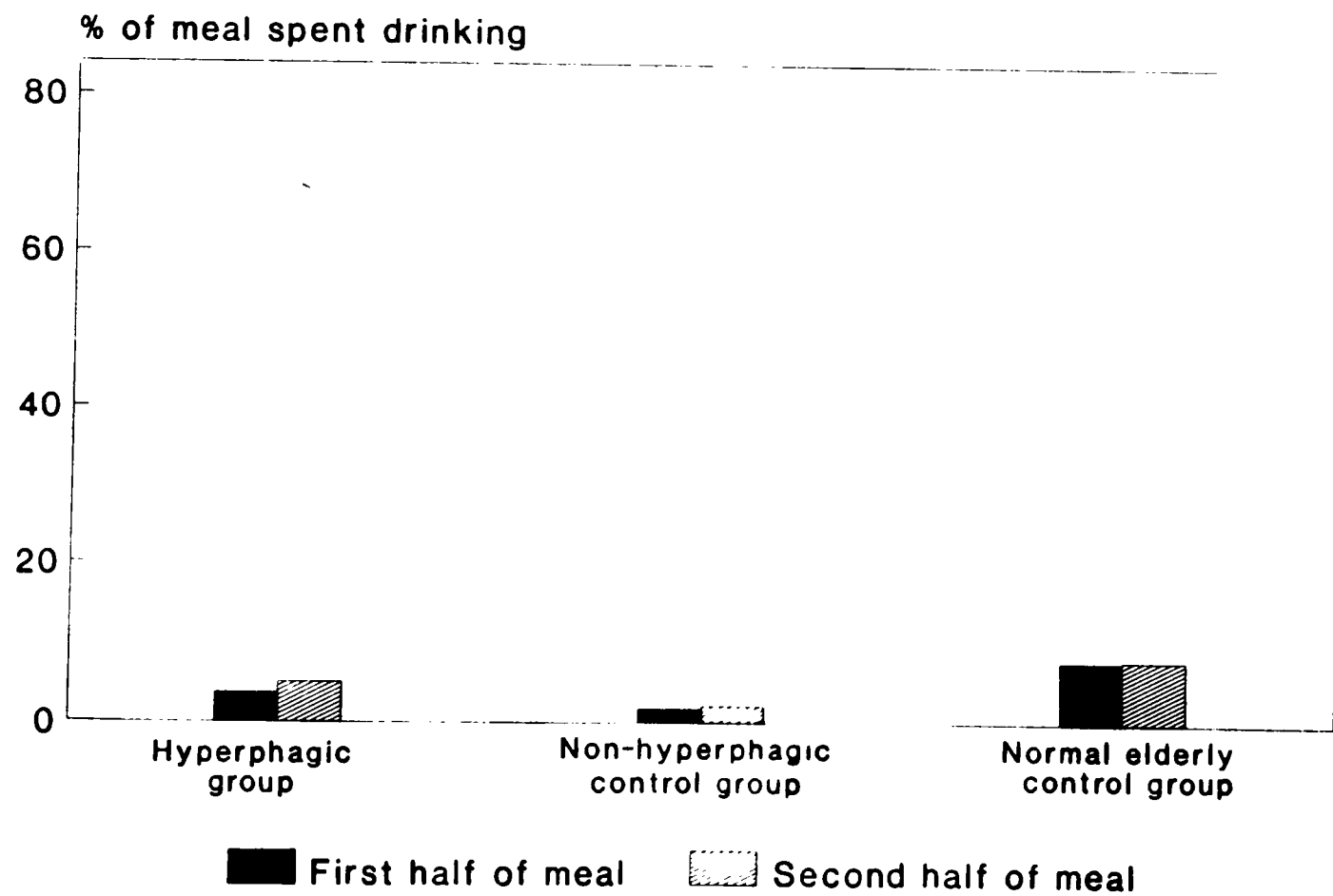


Table 11.7 d

Other behaviour (% of meal)

Latency plus intra-meal pauses

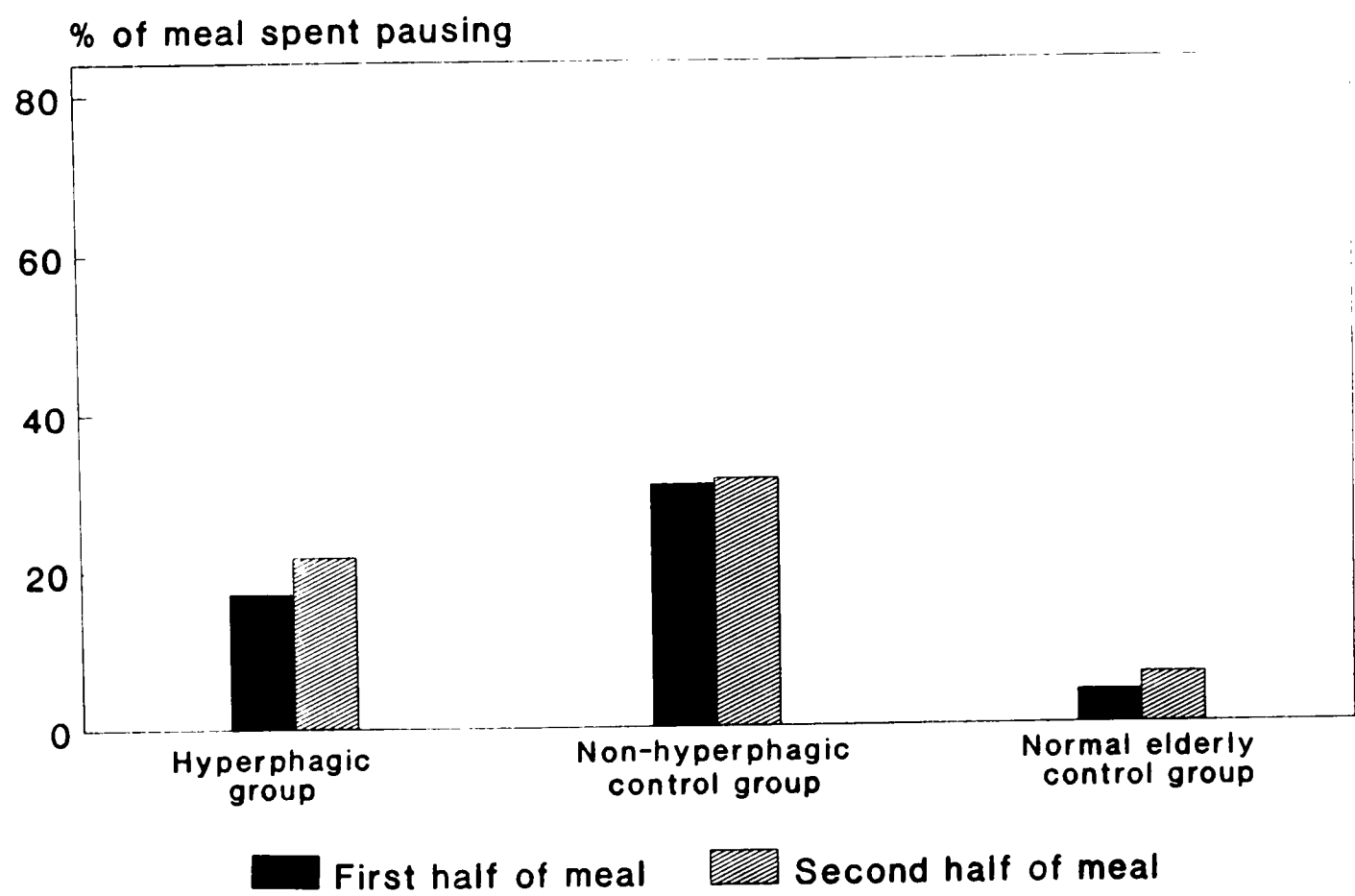
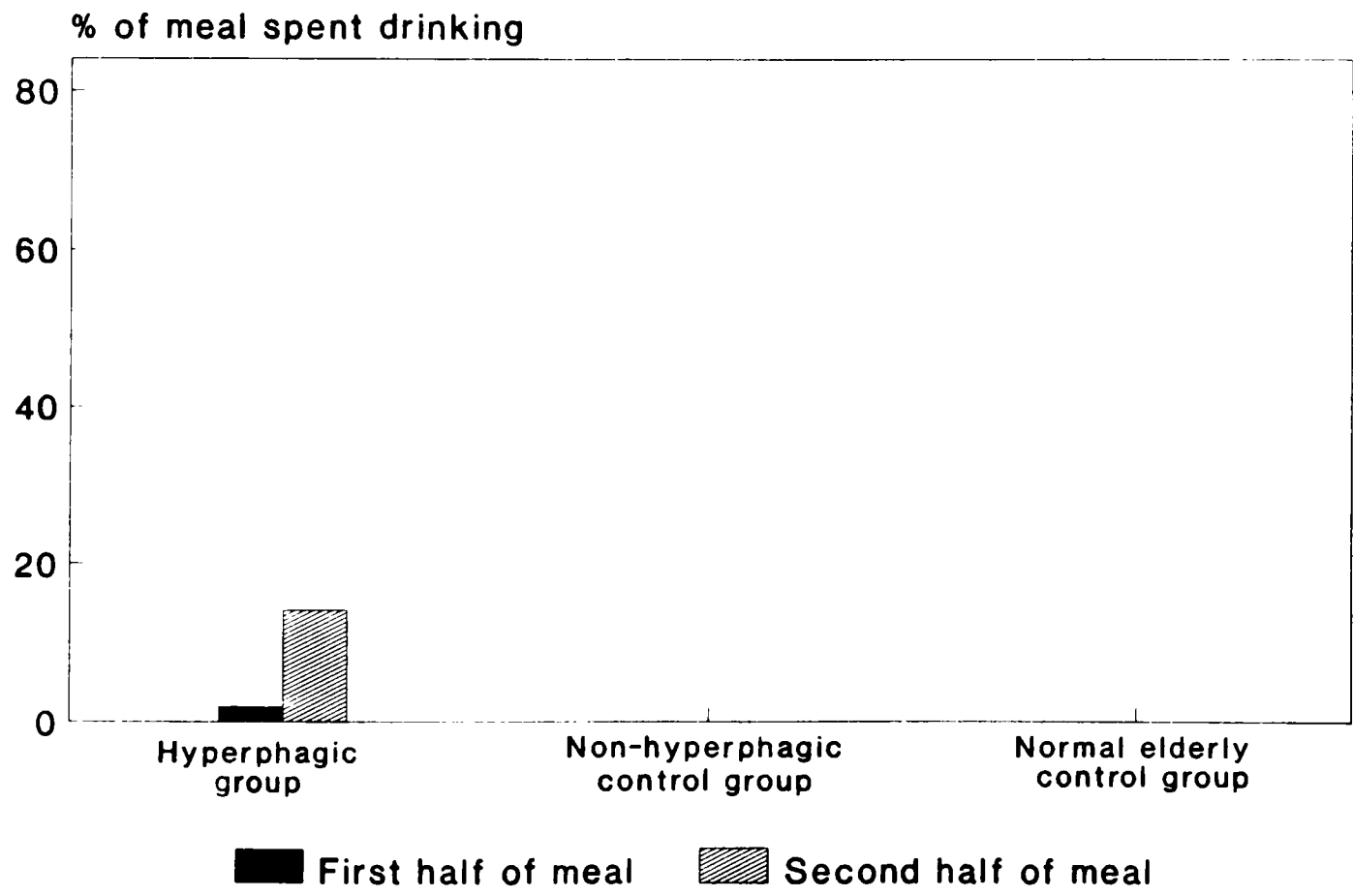


Table 11.7 e

Walking time (% of meal)

Time spent walking during course of meal



The analysis was repeated for each sixteenth of the meal and the results plotted (see figure 11.8 a-c). In the hyperphagic group more time was spent in drinking as the meal progressed. In three of the ten subjects, walking markedly increased towards the end of the meal (see figure 11.9 a-c for graphs showing time spent chewing and time spent walking for three individual subjects).

In the non-hyperphagic demented group, there was a greater proportion of ‘other’ behaviour than in the normal elderly. This included looking about, ‘fiddling’ with the biscuits (e.g. moving them round the plate, tapping them or crumbling them), talking, empty chewing movements. No-one walked during the course of the meal.

Figure 11.8 a Analysis of behaviour during meal
Hyperphagic demented subjects

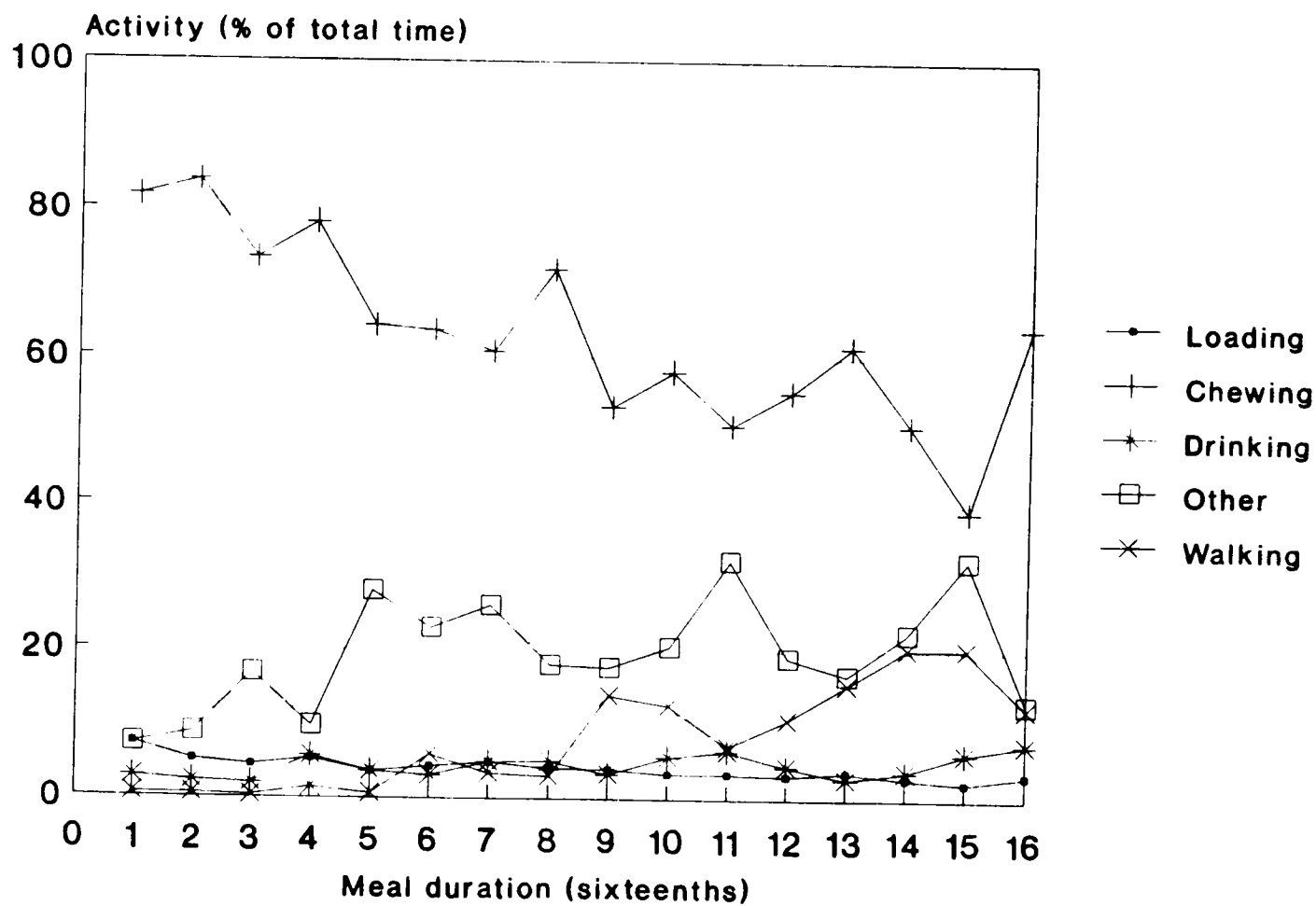


Figure 11.8 b Analysis of behaviour during meal
Non-hyperphagic demented controls

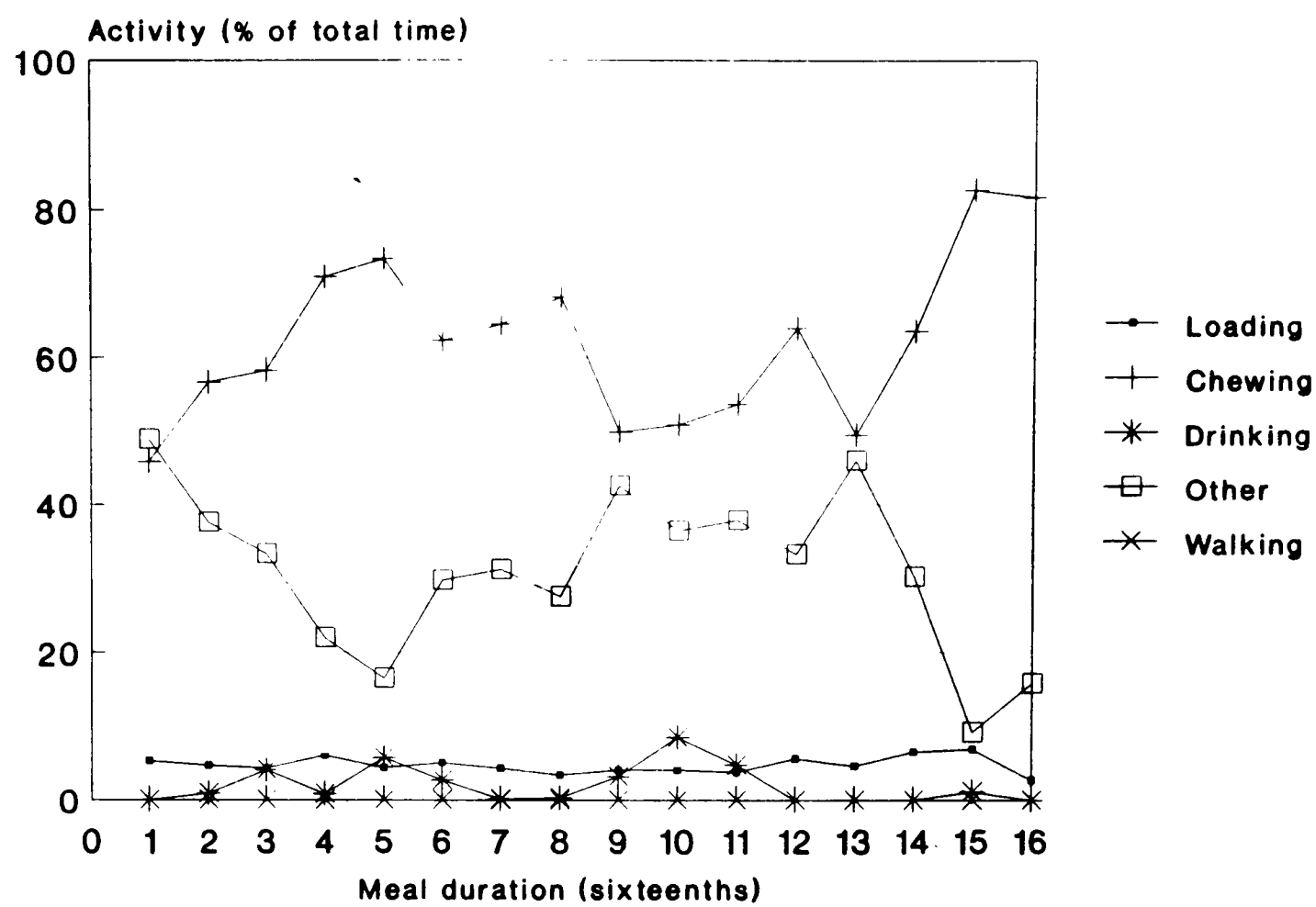
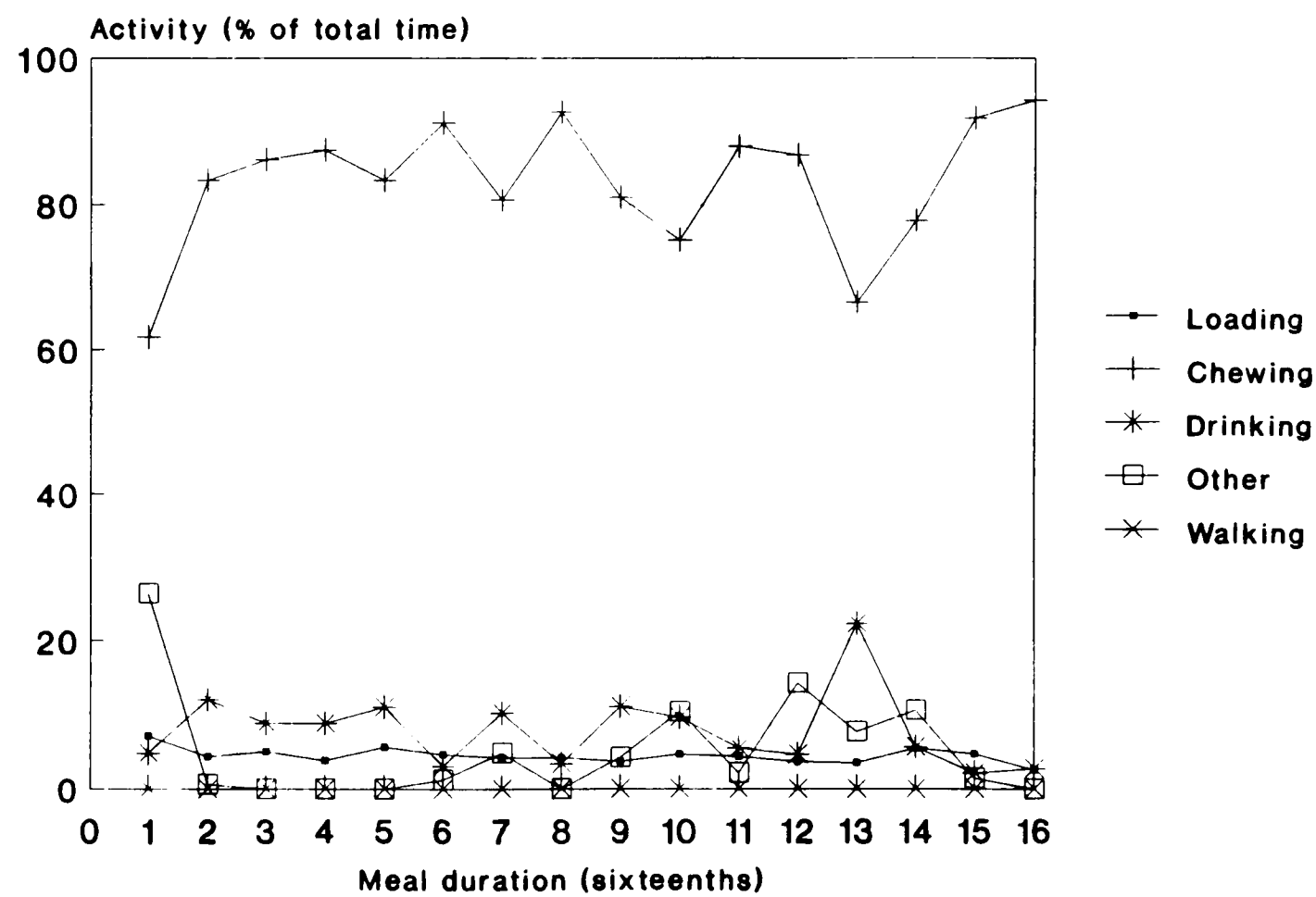


Figure 11.8 c Analysis of behaviour during meal
Normal elderly



The normal elderly were very uniform in their eating behaviour. They loaded food at regular intervals, sipped water intermittently throughout the meal and did not show much ‘other’ behaviour other than short intervals if they spoke or brief pauses between mouthfuls. No-one walked during the course of the meal.

As the Eating Behaviour Rating Scale (EBRS) has been used to assess the abnormality of eating in people with bulimia nervosa (see introduction to this chapter), the EBRS scores for both the first digestive biscuit and mixed meals were examined to see if the hyperphagic group had higher scores, which might indicate bulimic behaviour. The mean EBRS scores for the first biscuit and mixed meal respectively for the hyperphagic group were 3.7 (S.D. 3.4) and 7.3 (S.D. 6.8) and for then non-hyperphagic demented group 3.6 (S.D. 6.4) and 8.8 (S.D. 6.7). There was no significant difference between the two demented groups in the EBRS scores for either type of meal.

Figure 11.9 a Time spent chewing and walking (052)
Meal subdivided into 16ths

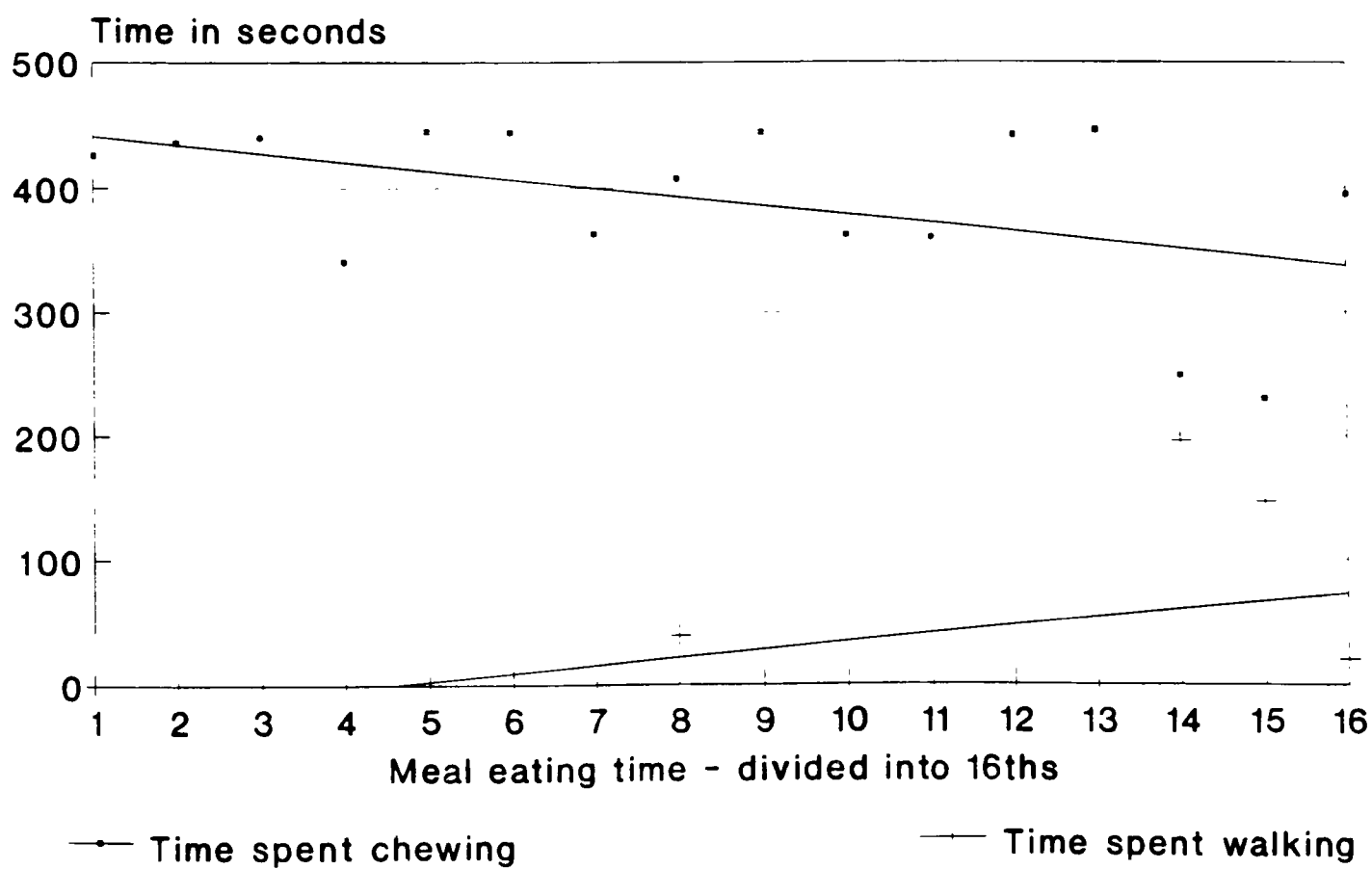


Figure 11.9 b Time spent chewing and walking (009)
Meal subdivided into 16ths

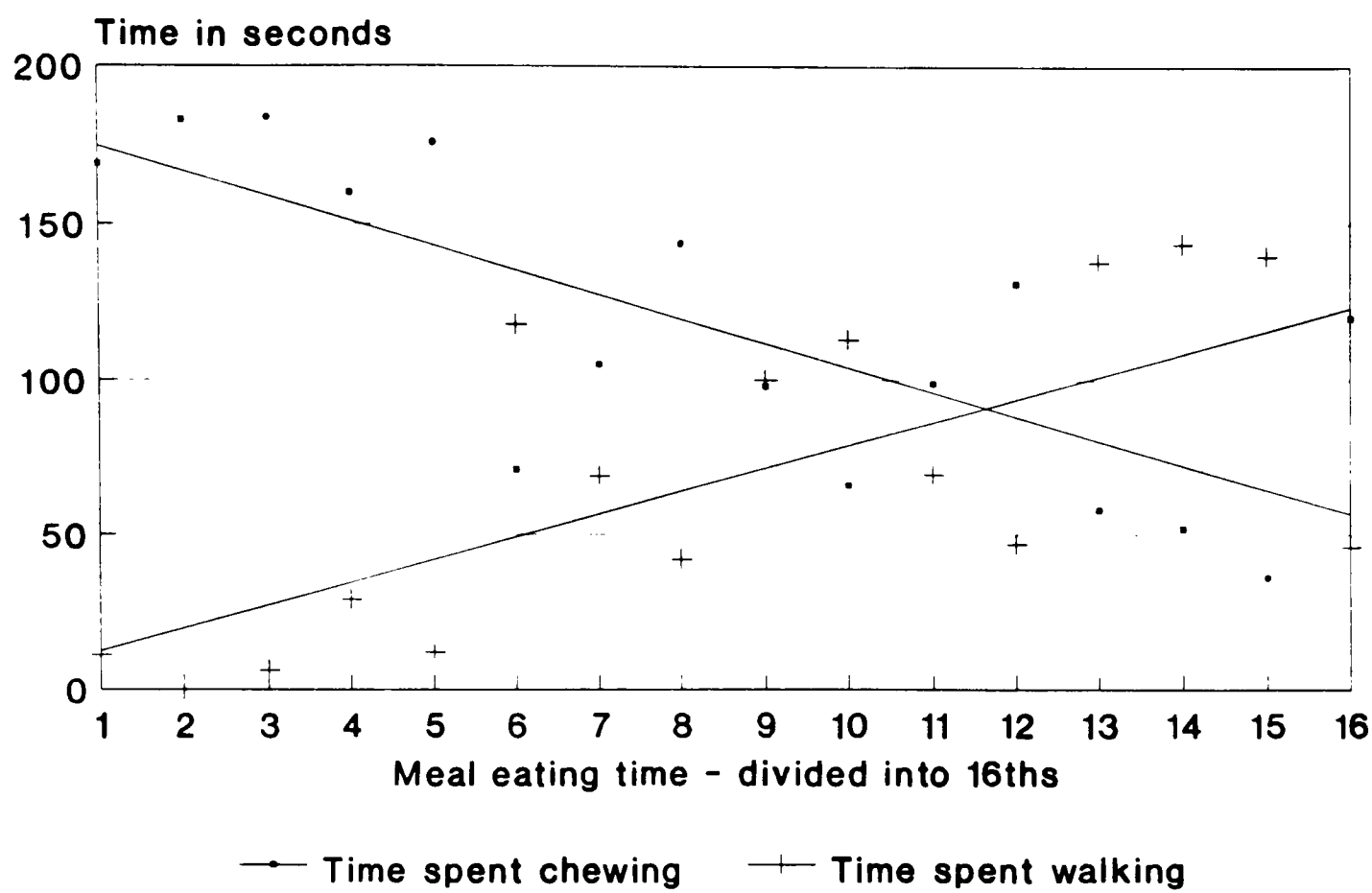
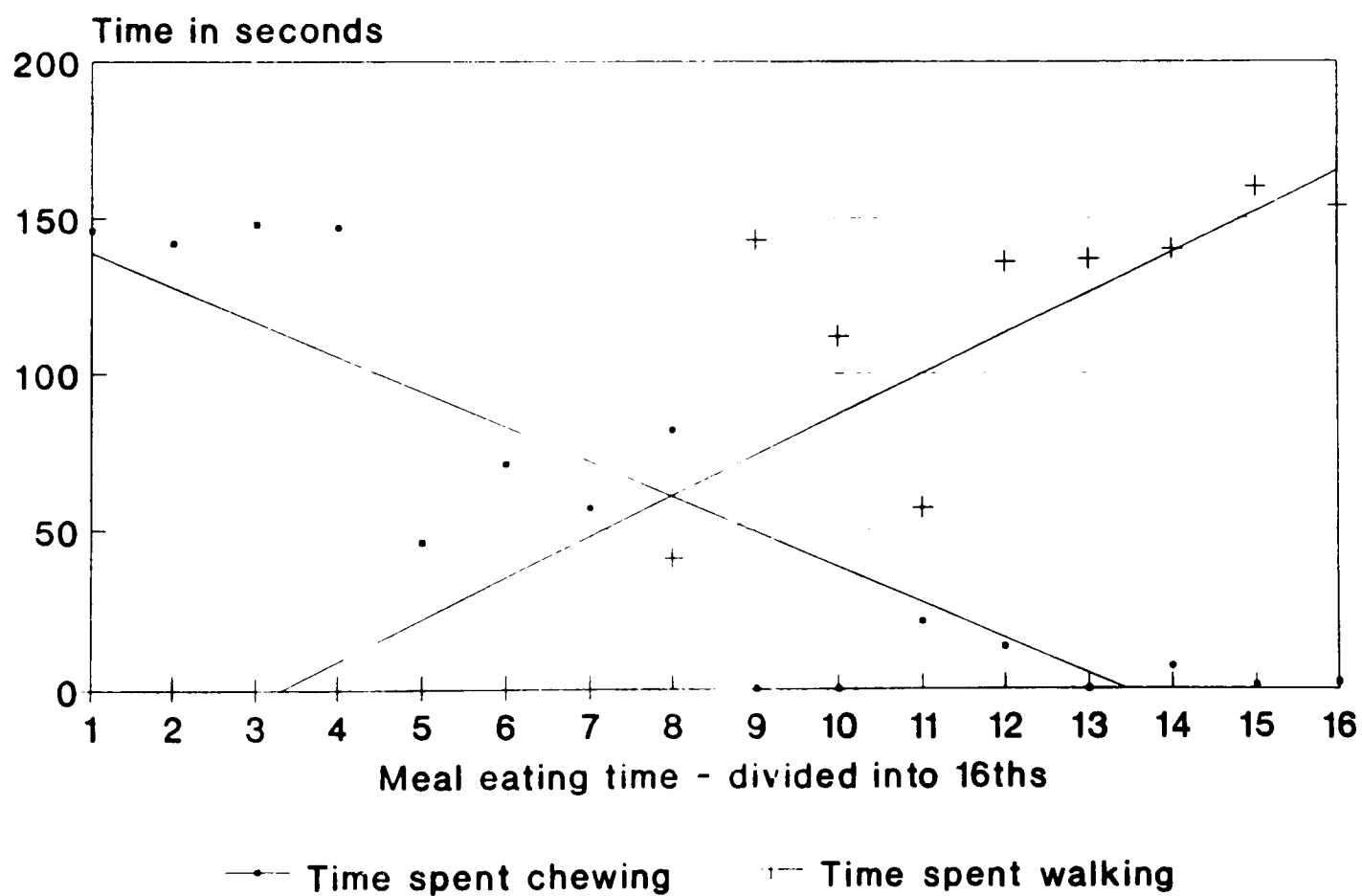


Figure 11.9 c Time spent chewing and walking (067)
Meal subdivided into 16ths



DISCUSSION

The inter-rater; intra-rater and test-retest reliability are good showing that measuring the microstructure of eating is likely to provide reliable evidence regarding the control of food intake. A comparison of the normal elderly with the non-hyperphagic demented group provides evidence of the effect of dementia on the control of eating. A comparison of the hyperphagic demented group with the non-hyperphagic demented group provides evidence of which abnormalities in control mechanisms may be related to the hyperphagia itself.

Control mechanisms and hyperphagia

The theories of control mechanisms suggest that two factors are of particular significance: hunger which controls the onset of the meal and provides an 'impetus' for eating and satiation which operates (increasingly) to bring the eating to an end. Cumulative intake curves demonstrate the interaction between positive and negative feedback during the course of the meal. Theoretically, the meal ends when the two are in balance.

a) Hunger

Latency is likely to provide a measure of hunger and, since traditional methods of measuring hunger (through self-report and visual analogue scales) have not proved a valid method in these moderate to severely demented groups, latency may be the only good measure of hunger. However, latency is also likely to be affected by cognitive factors such as the ability and speed in understanding the situation or the ability to concentrate on eating and not be distracted. Cognitive impairment appeared

to inhibit subjects from starting a meal, they tended to be distracted and often spent time looking round, moving the food or just sitting before eventually, and often after repeated invitations to eat, starting the meal. It may be these factors which lead to the greater variability in latency observed in the two demented groups. Although they varied, the demented subjects with hyperphagia were very different from the non-hyperphagic controls. The hyperphagic subjects often started to eat as soon as they could reach the table and the median time for them to start eating was very much less than for the non-hyperphagic group ($p = 0.007$). This strongly suggests that the drive to start eating (hunger) is much greater in the hyperphagic group than in the non-hyperphagic demented group.

The further effect of dementia on the microstructure of eating can be judged by comparing the non-hyperphagic demented controls with the normal elderly. Normal, elderly controls started to eat after a few seconds in the experimental setting whereas the non-hyperphagic group have a long latency period, as well as slower loading rates and low ingestion rate.

Despite the problems posed by dementia, the median latency rate of the hyperphagic group was lower than the normal group for both biscuit and mixed meals (although the difference was not significant). This short latency, together with the fact that several of the hyperphagic group took food before the table was prepared suggested that the hyperphagic group have increased hunger compared with non-hyperphagic demented subjects. It is difficult to come to any firm conclusion as to whether the hyperphagic group have a greater level of hunger than the normal elderly because

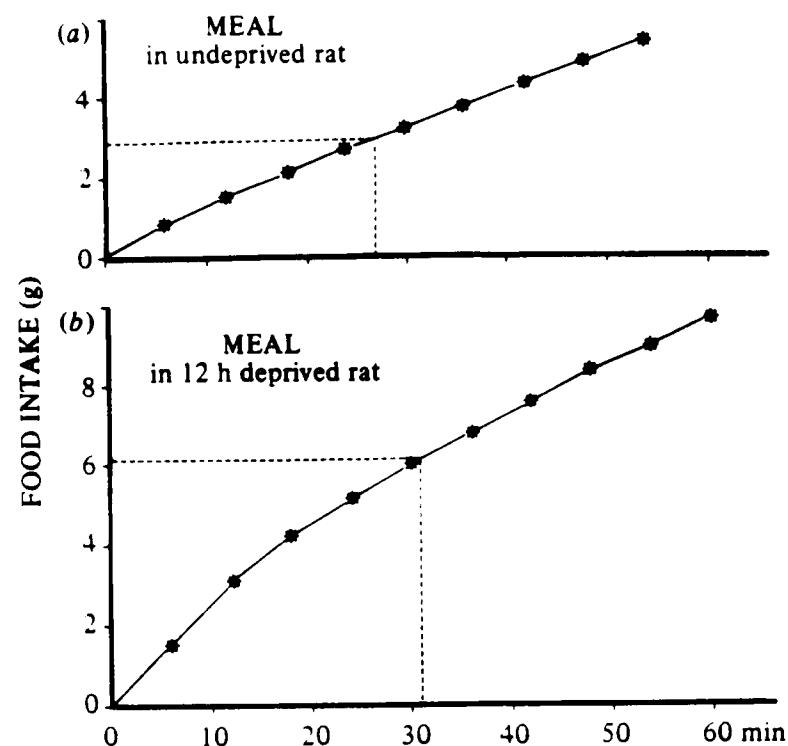
their cognitive impairment affects latency. However, the main effect of the dementia is to increase latency and the fact that median latency of people with hyperphagia is, if anything, less than the normal elderly, suggests that the level of hunger is probably greater amongst hyperphagic subjects than the normal elderly.

Although the hyperphagic group had a faster ingestion rate than the non-hyperphagic group, the mean was slower than the normal elderly which confirmed the absence of fast 'binge' eating although speed of intake could have been limited by slow reflexes and poor coordination. Only one hyperphagic person ate very fast and had to be restrained to prevent danger of choking.

Another indication of hunger could be the shape of the cumulative intake graphs (figure 11.6). Kissileff *et al.* (1982) found the cumulative food intake graph in young subjects was described by a decelerating quadratic function. Meyer *et al.* (1980) found a more linear curve in the elderly which was confirmed by the normal elderly control group in this study. Le Magnen (1985) describes how non-deprived rats, under *ad libitum* conditions, eat at a constant rate, after a short initial period of faster eating. After a period of food deprivation, the rats ate more rapidly during the first half of the meal (figure 11.10). The curves for non-deprived rats are similar in shape to the curves for the normal elderly. The curves for the non-hyperphagic demented group are irregular as they frequently stop and restart eating. The curve for some subjects in the hyperphagic demented group resembles that of the deprived rats. The rapid ingestion in the first half of the meal and the fact that the initial rate of eating (measured by the linear coefficient - b) is significantly higher in the hyperphagic than

in the non-hyperphagic group supports the hypothesis that hunger is driving the ingestion rate at the start of the meal. This provides evidence against the view that hyperphagia is simply a type of stereotyped behaviour. This issue will be considered in detail in Chapter 14.

Figure 11.10 Intake rates during (a) a long, nocturnal meal in undeprived rats and (b) during the first meal after 12 h of food deprivation (Le Magnen, 1985).



b) Satiation

The large quantity of food eaten by the hyperphagic group suggests, *prima facie*, that there is a disruption in the normal mechanism controlling termination of the meal (satiation or the negative feedback shown in figure 11.1). This either shows that there is a lack of negative feedback, which causes eating to slow down and stop or, conversely, there is an increase in the positive feedback mechanism. There is evidence from the quadratic function (c) that there was significantly less deceleration in the hyperphagic group than in the normal elderly. This strongly suggests that the lack of deceleration in the cumulative eating curve of the hyperphagic subjects, is due

to an absence of the negative feedback which is needed to bring about satiation. The hyperphagic group eat much more than the normal elderly therefore the absence of satiation is particularly marked. (The apparent lack of deceleration in the non-hyperphagic demented group compared with the normal elderly is likely to be a result of the prolonged latency period in the demented controls.) Positive feedback is difficult to research but an attempt has been made to explore the effect of palatability in the next chapter.

Although there is a major abnormality in satiation in hyperphagia, is there any satiating mechanism at all? This was investigated by looking at changes in the microstructure of eating, such as chewing and ingestion rate, and by looking for an increase in behaviour other than eating during the course of the meal.

Examining the microstructure of eating shows whether there is any evidence of slowing down after a large amount has been eaten i.e. that the amount eaten does have some effect, even if the meal does not end. In young, lean, normal people the pauses between food units increase significantly as the meal progresses (Bellisle & Le Magnen, 1981), therefore, more is eaten in the first half of a meal. Although there is a deceleration in food intake during the course of a meal in normal-weight adults and children (Kissileff *et al.*, 1982), obese adults and normal elderly seem to have a constant rate of ingestion, at least when taking liquid food (Meyer *et al.*, 1980).

The chewing rates remained almost constant in all three groups throughout the meal. In the normal elderly, there were some signs of satiation as loading rate and food

intake were significantly lower in the second half of the meal but, in the demented groups, the loading rate did not slow significantly, giving no clear evidence of satiation as the meal progressed other than the cessation of eating itself. The stability of ingestion rate and chewing rate for each individual confirms microstructure experiments done on normal lean humans, using recording devices (Bellisle & Le Magnen, 1980). The normal elderly controls, in the studies reported here, ate steadily with time spent chewing, drinking and other behaviour remaining constant for each individual throughout the meal.

Is there evidence (e.g. from increased rates of 'other' activity) in non-hyperphagic demented that they are increasingly distracted and, if so, how does this compare with the hyperphagic demented group? In all three groups, intra-meal pauses ('other' behaviour) were not significantly greater in the second half of the meal which again did not show evidence of satiation. The non-hyperphagic group showed more 'other' behaviour, than the other three groups but the pauses occurred during all stages of the meal. The pauses were the result of being easily distracted and frequent prompting was often necessary to find out if they had finished eating or whether they wanted more to eat.

In calculating the pause rate, walking was not included. The only people to walk during the course of the meal were in the hyperphagic group and they usually ate as they walked, which explains why, in the hyperphagic group, the time spent walking increased during the course of the meal (figure 11.7) but the cumulative intake curves (figures 11.6) did not decrease correspondingly.

In the hyperphagic group there appears to be a failure of the normal mechanism controlling satiation. If this mechanism is disrupted, in subjects who are hyperphagic, it is predicted that the rate of ingestion will remain constant throughout the meal until the person is physically incapable of eating more. Several people in this group had to be stopped because they seemed to have become physically uncomfortable.

Does this absence of any slowing in the rate of ingestion mean that there is no evidence of a satiation mechanism in the hyperphagic group? Apparently not, as shown by a subgroup of four people with hyperphagia who also tended to wander. For this group there was a conflict between the two types of behaviour. In order to eat in the standardised setting they needed to remain at the table but the 'drive' to hyperactivity pushed them towards moving about. After the initial rapid food intake they become increasingly active, leaving the table, often with food in their hand and returning to eat less frequently until, if they ceased to return within 5 minutes, the meal was stopped (see figure 11.9 and Appendix VII). This is interesting as it suggests there is a reduction in the 'eating drive' or an increase in the drive to walk. This could be thought of as evidence that the drive to eat decreases with the onset of satiation. Perhaps the probability, over a period of time, of switching from eating to walking and walking to eating depends on the ratio of these two 'drives'.

In the hyperphagic group there was some reduction in intake in the second half of the meal which is probably due to the rapid initial rate of eating in some subjects. Generally, throughout the meal, chewing, loading and food intake rates were relatively constant, if interruptions, such as walking, were not included. This showed

that people in the hyperphagic group did not fatigue appreciably, even after two hours, and slowing, indicating the onset of satiation, was not obvious. In the hyperphagic group this slowing, if it occurs, is only after very large amounts have been eaten. Slowing seemed to be the result of physical limitation rather than a response to physiological cues. There was no sign of increased eating in the second half of a meal as Meyer and colleagues (1980) noted in one hyperphagic person.

Some features of hyperphagia in dementia resemble BN or binge eating disorder i.e. eating more in a two-hour period than most people would normally eat, eating more rapidly than matched controls with dementia, eating until feeling uncomfortably full and the frequency of binge-eating over a period of time (if food is available). The fact that some people reported to be hyperphagic, especially those who were less impaired, did not overeat when observed, had a parallel with the embarrassment shown in binge eating disorder. The subjective criteria of lacking a sense of control and eating when not hungry is not verifiable reliably in severely demented people. The main distinction between hyperphagia in dementia and the other eating disorders is that there is no distress over excessive eating and no compensatory behaviours to prevent weight gain. Two women who were reported to overeat had occasionally vomited after a binge but there was no evidence of it being self-induced. One of them also abused laxatives at one stage but again there was no evidence for it being an attempt to control her weight.

Objective measurements of eating behaviour using the Eating Behaviour Rating Scale (EBRS Appendix III) gave a useful measure of the abnormality of eating behaviour.

As there was no significant difference between the EBRS scores of the hyperphagic and the non-hyperphagic groups, for either type of test meal, it indicates that the abnormal patterns of eating behaviour were probably due to dementia and it does not support the hypothesis that hyperphagia is a form of BN. There were no signs that the abnormalities in eating behaviour were due to the changes in attitude towards food intake and beliefs about body image seen in people with eating disorders such as anorexia and bulimia nervosa. The higher scores in people with dementia were the side-effects of impaired coordination and cognition.

In contrast to the demented subjects the people with bulimia nervosa chose low-energy foods, picked at their food and ate slowly, when they were observed in test meals.

There appears to be evidence for increased hunger in people with dementia who are hyperphagic. There is apparently a little evidence of a satiation mechanism in some people with hyperphagia, for example some people walk more or have more intra-meal pauses towards the end of the meal. However, the slowing only appears at a late stage in the meal and satiation is clearly impaired compared with people who eat normally. The microstructure of the meal can shed light on hunger and satiation but can say nothing about satiety. This issue will be examined in the next chapter.

Chapter 12 TO INVESTIGATE SATIETY IN AGEING, DEMENTIA AND HYPERPHAGIA

AIMS

To investigate the phenomenon of satiety in hyperphagia, through investigation of the effect of preload on subsequent intake.

To examine the effects of age and dementia on satiety.

INTRODUCTION

The research presented so far has investigated parameters within the meal. The massive food-intake of hyperphagic people suggests an abnormality in the normal mechanism of satiation (see previous chapters). The aim of the work reported in this chapter is to investigate the effect of preload on subsequent eating behaviour. On the basis of results with healthy young adults, Blundell (1991b), has proposed the concept of 'satiety'. He makes the distinction between satiation and satiety; satiation is the process that brings a period of eating to a close, whereas satiety is the inhibition of hunger and eating that arises as a consequence of food consumption (see definitions in Chapter 5).

Various mechanisms controlling satiety have been proposed (figure 5.1). Immediately after a meal (early satiety phase) cognitively derived feelings are important. The post-ingestive stage follows when sensory feedback from the stomach and intestine

give sensations of fullness. In the late stages the products of absorption bring about satiety (post-absorptive phase). Empirical data show that there is a tight physiological compensation for preload under normal circumstances (Rogers & Blundell, 1989a; 1989b). In rats, a carbohydrate preload delays the initiation of eating in proportion to the energy value of the preload and the rate of its metabolism (Booth, 1972). Booth also found that rats compensated by eating less after a preload of glucose, glycerol, alanine or lactate than they did after a preload of sodium chloride or urea. This was confirmed in humans by Herman and Mack (1975), who showed that, after a preload, lean young adults compensate by eating less at a subsequent meal. The use of preloads, also revealed a satiation effect which had not previously been known to exist in children with Prader-Willi syndrome (Zipf *et al.*, 1990). Disguised manipulation, giving apparently similar preloads with markedly different energy content (Hill *et al.*, 1987) shows that the good compensation which is observed is not due to cognitive factors.

An interesting question arising from the work so far reported in this thesis is, does the hyperphagic group retain this 'satiety' mechanism i.e. do hyperphagic subjects compensate for preload or is the satiety mechanism damaged? However, to answer this, two other questions are also raised. First, what is the effect of ageing on satiety? There are no data on the effect of preload on the elderly; previous work has been on young adults, dieters, the obese and people with eating disorders (Herman & Polivy, 1988). The second question is, what effect does dementia *per se* have on satiety? Therefore the aim of this series of studies was to see whether compensation for preload (i.e. satiety) operates in a) the normal elderly, b) in people with dementia

and c) in people with dementia who are hyperphagic. For comparison Peter Rogers and Nicky Elliman, at the Institute of Food Research, in Reading, repeated exactly the same experiments on groups of healthy young and middle-aged adults. The results of their studies will also be presented here in order to assess the effect of age.

ASSESSING SATIETY USING PRELOAD MEALS

Many experiments have shown that in normal young subjects there is a decrease in food intake following a preload meal. Kissileff *et al.* (1984) used rating scales to assess the effect of a preload on appetite and on the total intake of food at the subsequent test meal. They found that preloads which were more satiating reduced intake by decreasing the desire to eat (i.e. hunger) not by accelerating the onset of satiety, that is, preloads reduced the initial rate of eating and total intake but did not alter the duration of subsequent meals.

Unlike normal-weight young subjects, counter-regulation, after a preload meal, is found in dieters, the obese and also in people with bulimia nervosa (Hetherington & Rolls, 1991). Paradoxically, these groups of people were found to eat more at a test meal after having a high-energy preload. This is sometimes called a 'What-the-hell!' effect; having broken their self-imposed rules for eating, they temporarily give up their attempt to restrict food intake. This is difficult to demonstrate reliably in people with bulimia as their eating behaviour is very variable, swinging from restraint to binge-eating when they feel they have lost control.

METHOD

GENERAL PROCEDURE

In order to examine satiety in the subjects of this thesis, the first step was to design a preload experiment suitable for people with dementia.

1. Choice of preload

a) Comparability of preloads

Two preloads were required which were indistinguishable in volume, taste and appearance but which had different energy values and therefore different energy densities.

b) Suitability of preloads

To allow a proper comparison, the same method needed to be suitable for the normal elderly and the two groups with dementia. It was difficult to select a preload suitable for people with severe dementia. A variety of preloads were considered, including biscuits, sandwiches and drinks. At first drinks were thought to be too prone to spillage but it was more difficult to encourage people in the demented non-hyperphagic group to finish a set amount of solid food. By careful supervision, and by helping when necessary, it proved safe and relatively easy to encourage those with severe dementia to finish preload drinks in a reasonable time. Although some of the non-hyperphagic demented took up to half an hour to finish the preload completely, most of this group and everyone in the other two groups finished in five minutes.

Two preload milkshakes, developed by Rogers, were used. One was low-energy (660 kJ) and the other high-energy (1870 kJ). Their composition is given in table 12.1.

A number of precautions were taken to ensure their suitability.

Table 12.1 Contents of preload drinks

LOW-ENERGY PRELOAD - 660 kJ (160 kilocalories) 200 g banana or strawberry flavoured milk 10 g double cream	
HIGH-ENERGY PRELOAD - 1870 kJ (450 kilocalories). 134 g banana or strawberry flavoured milk 46 g double cream 42 g maltodextrin	

Energy from	Low-energy preload		High-energy preload	
	Total (kJ)	%	Total (kJ)	%
Protein	118	17.8	91	4.9
Fat	280	42.4	896	47.9
Carbohydrate	262	39.8	883	47.2
Total	660	100.0	1870	100.0

(i) Apparently identical characteristics

A fruit-flavoured milkshake was used as it was easy to manipulate the energy density without substantially altering the appearance, texture or taste. Addition of double cream and maltodextrin increased both fat and carbohydrate content without altering sweetness, and hence palatability, which might stimulate subsequent food intake. This was important as the test meal is given one hour later, which is within the period where previous intake of sweet food is known to have a stimulating effect on appetite (Rogers & Blundell, 1989a). Sweetness and creaminess give cues to energy value (Booth *et al.*, 1989), therefore as well as keeping sweetness constant, a little cream was added to the low-energy milkshake to try to keep the creamy texture similar. The milk-shakes were virtually identical in volume, flavour and appearance and, when given a week apart, the two drinks were apparently indistinguishable.

(ii) Balance of macronutrients

A preload with a balanced macronutrient content (i.e. with a proportion of each of the three macronutrients) was chosen because over-representation of one of the macronutrients in the preload might lead to a compensatory intake of the other macronutrients at the subsequent test meal (Wurtman, 1983).

(iii) Avoiding sensory specific satiety

The preload differed from food given at the test meal as presenting a similar food as the last meal is likely to decrease the intake of that food, as a result of sensory-specific satiety (Rolls *et al.*, 1988). This suppression persists even after an hour (Hetherington *et al.*, 1989).

(iv) Proportion of macronutrients

As protein appears to have a greater satiating capacity than carbohydrate (Hill & Blundell, 1986), extra protein could have been added to increase the satiating capacity of the high-energy preload. However, the protein content of the two preloads was kept virtually constant to avoid a possible change in the production of neurotransmitters, such as 5-HT or dopamine, which might possibly have an effect on appetite or influence the ratio of macronutrients chosen (Leibowitz, 1990). Increasing the proportion of carbohydrate might stimulate insulin production, and therefore indirectly alter brain 5-HT production but this was unavoidable as too high a proportion of fat is not desirable owing to its weak inhibition on satiation (meal size) and satiety (post-meal inhibition). In addition, elderly people might have found a very high-fat preload unpleasant. Even with this level of cream, two elderly people

had to be excluded from the experiment as they found the high-energy milkshake too rich and were unable to finish it.

2. Time interval between preload and meal

On two occasions, at least one week apart, a preload was given one hour before the normal time of the midday meal (although breakfast and mid-morning snack were eaten as usual). The test meal was given an hour after the preload. This interval should give enough time for the post-ingestive and possibly the early post-absorptive mechanisms to operate but, based on evidence from previous studies, not long enough for the preload to lose its effect on satiety.

The young and middle-aged groups, on a third occasion, were given 200 ml of water as a zero energy preload. The order, for the three preloads, was balanced. As the meals for the elderly subjects, and those with dementia, had to be given one person at a time, in their own home, the water preload was not used, as an extra meal would have been an additional imposition on controls and carers. All but one subject had already had a mixed meal without an initial preload, as part of the experiments reported in earlier chapters, although this had been some weeks previously.

3. The test meal

An hour after the start of the preload meal, the standard, mixed test-meal was given (see Chapter 9 for details). At least a week later the alternative preload meal was given followed an hour later by the standard mixed meal. The two preload conditions were given at least a week apart to prevent people noticing any difference between

the preloads.

4. Precautions

For normal subjects, the order of foods on the table was rotated for each meal and for each successive individual, if the first test meal had been arrangement A, the next meal would be arrangement B and the third C (see Chapter 9). This, and the time interval of at least a week, was to avoid controls trying consciously to repeat their choice of food made at the previous test meal.

The reason for this precaution was that people remember the satiating effect that a certain food has and the next time it is eaten they will assume it will have a similar satiating effect afterwards. Satiety is thought to be a conditioned reflex (Booth, 1977), hence the disguised manipulation. Although conditioning may not occur after one trial, a conscious effort might be made to make the same choices as before. The full post-absorptive effect is likely to take longer than an hour so, as the preloads appear identical, the normal subjects might remember the physiological effect (satiating efficiency) that the preload had on the previous occasion and may adjust their food intake accordingly. To eliminate any order effect the sequence of the preloads was balanced so that half the people in each group had the low preload first and half had the high preload first.

THE EFFECT OF AGEING

Most preload work has been done with young subjects and previously there had not been a study to investigate whether elderly people compensate for food already eaten.

Young controls

To test the validity of the method, a group of young people were given the three preload and test meals to see if the preload altered subsequent intake. The tests on the younger groups were carried out by Rogers and Elliman at the Institute of Food Research in Reading. The method used and the meals given were identical to those used in my study with elderly and demented groups, except that in Reading the meals were given simultaneously to a group of subjects, in individual cubicles, in a food laboratory and they were not videoed. In Reading, 10 subjects aged 21-30 were tested, and, in addition, 3 more in this age group were tested in Oxford (one of the Oxford group did not have the water preload 'meal').

Middle-aged controls

Six subjects aged 40-47 were tested in Reading.

Normal elderly controls

The normal elderly (as well as the non-hyperphagic demented and hyperphagic subjects) were a sub-set of people who took part in the studies reported in earlier chapters of this thesis. Data for the mixed meal intake, without preload, were available for nine of the ten normal elderly (although usually this was several months before the preload meals). Two milkshake preloads followed by mixed meals were given to ten normal older controls matched by age and sex with ten of the hyperphagic, demented subjects.

THE EFFECT OF DEMENTIA

To see whether dementia made a difference to the ability to regulate food intake after a preload, eight matched non-hyperphagic controls were tested (see table 12.2). In four cases the preload meals were given several months after the initial mixed meal. For the two dementia groups, mixed food meals were given in the same configuration each time to prevent any change in food intake being caused by a position effect (see Chapter 10).

THE EFFECT OF HYPERPHAGIA

The hyperphagic group were given the two preload meals either a week before or a week after one of the repeat mixed meal without preload.

TABLE 12.2 Description of test groups

Group	Mean age	Sex ratio	Total no.
Young	24.9	5F:7M	12
Middle aged	44.2	3F:3M	6
Normal elderly	74.5	6F:4M	10
Non-hyperphagic demented	76.3	5F:3M	8
Hyperphagic demented	75.9	9F:4M	13

If there is compensation for a preload, total intake should decrease in proportion to the size of the preload. In people with hyperphagia the endpoint of the meal sometimes seemed arbitrary, so the cumulative intake in the first quarter hour, half hour and hour were calculated to see if the preloads had any effect on the early part of the meal. Kissileff *et al.* (1984) found that preloads which were more satiating reduced intake by decreasing the initial rate of eating and total intake but did not alter the duration of subsequent meals.

RESULTS

The mean total consumption at test meals for each of the subject groups are given in tables 12.3 (test meal only) and 12.4 (preload plus test meal). These data, for people who received all three preload conditions, are given as histograms in figure 12.1.

Table 12.3 Total mean consumption at test meal (excluding preload)

Group	No preload (0 kJ)	Low preload (660 kJ)	High preload (1870 kJ)
Young (n=12)	4277	3567	2988
Middle aged (n=6)	3182	3165	2831
Normal elderly (n=9)	1671*	1775	1431
Non-hyperphagic demented (n=8)	2273*	972	1527
Hyperphagic demented (n=13)	4105	5065	4402

* denotes that the majority of meals in this group were not eaten within the same month as the preload meals, therefore eating may have changed in the meantime.

Table 12.4 Total mean consumption of preload plus test meal

Group	No preload (0 kJ)	Low preload (660 kJ)	High preload (1870 kJ)
Young (n=12)	4277	4228	4858
Middle aged (n=6)	3182	3826	4701
Normal over 50 (n=9)	1671*	2436	3301
Non-hyperphagic demented (n=8)	2273*	1632	3397
Hyperphagic demented (n=13)	4105	5725	6272

The effect of age on total intake

There was a significant effect of age on total intake during the test meals. An analysis of variance of between-subjects effect showed a significant effect of age on food intake (ANOVA: $F = 7.06$, $df = 2,24$, $p = 0.004$). The younger age group

ate more than the middle-aged group in each of the three preload conditions. Both the younger group and middle-aged group ate significantly more than the elderly normal controls (t-test, $p < 0.05$ in each case). In each of the three preload conditions the hyperphagic group ate significantly more than the both the normal elderly and non-hyperphagic demented groups (t-test: $p < 0.05$ in each case) see tables 12.3 and 12.4.

COMPENSATION FOR PRELOAD (see figure 12.1)

The first step is to see if there is any compensation for preload, i.e. is there a significant reduction in food intake during a test meal following a preload? If there is compensation the second step is to estimate the efficiency of the compensation.

a) The effect of preloads on test-meal intake

In this experiment the baseline is taken as the low-energy condition for two reasons. First in the water preload condition subjects obviously are aware that the energy content differs from the milkshake preloads, therefore there is likely to be a cognitive element in the subsequent level of food intake and the second reason is that in the normal elderly and non-hyperphagic groups the zero-energy condition was in some cases many months previously, therefore increased age, change in season or state of health might influence the results.

After the high-energy preload, the young ate significantly less food than after the low-energy preload (paired t-test: young group $t = 5.27$, $df = 11$, $p < 0.0005$). The normal middle-aged group, the normal elderly and the hyperphagic demented group

also ate less at the test meal following the high-energy preload, but the difference in intake after the high and low preload conditions was not significant. In the case of the non-hyperphagic demented, the intake at the mixed meals following the preloads was very variable and, overall, there was no effect of preload on subsequent intake.

b) Accuracy of compensation for preload

The precision of compensation for preload can be examined by comparing total intake i.e. preload and test meal. For the young and middle-aged, when the zero-energy preload was concurrent with the other preload conditions, the food intake after a non-nutritive preload can be used as a baseline level. If there is no compensation the intake of the mixed meal would be expected to be the same regardless of preload. If there is perfect compensation, the total intake of preload and test meal would be expected to be constant and equal to the baseline value and, if this is the case the 'satiating efficiency' of the preload = 1.

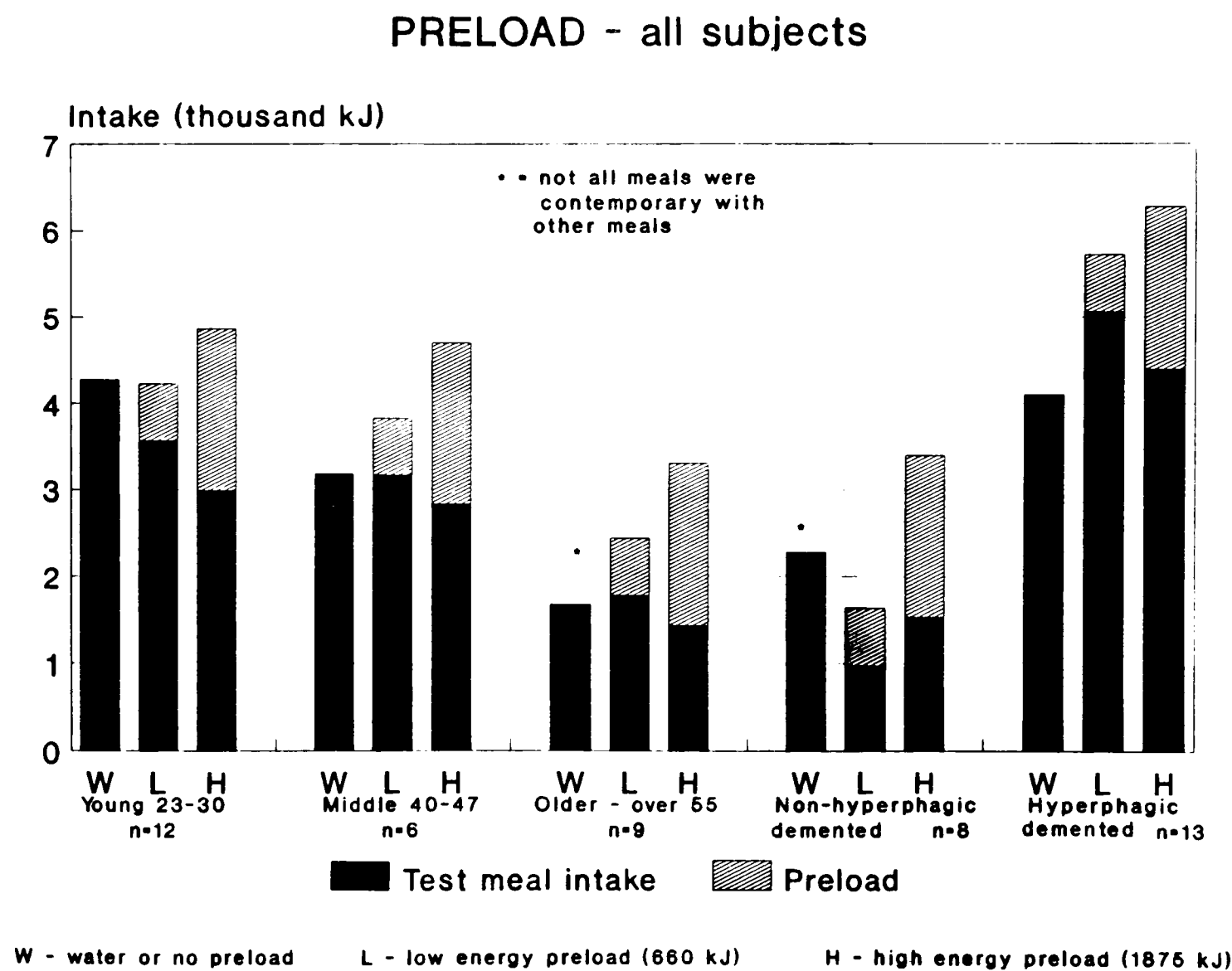
Young group

The young compensated almost perfectly between the water and low-energy preload meals i.e. the total energy value of the low-energy preload drink and the subsequent mixed meals was approximately equal to that of the mixed meal which followed the water preload. The total energy value of the high-energy preload and the following meal was significantly greater than the mixed meal with water preload (paired t-test: $t = 2.86$, $df = 11$, $p = 0.015$). There was clear compensation for the preload, as the intake after the low energy preload was significantly more than after the high energy preload ($t = 5.27$, $p < 0.0005$).

Middle-aged group

Slight compensation occurred after the high-energy preload when compared with the baseline but the difference was not significant (paired t-test: $t = 2.01$, $df = 5$, $p = 0.101$). The energy intake after the low-energy preload did not differ from the baseline value i.e. after the water preload, and there was no significant difference in intake after the low- and high-energy preloads. This finding that the middle-aged group shows less compensation than a young group, confirmed a previous, unpublished study carried out by Rogers (personal communication).

Figure 12.1



Normal elderly

The results are summarised in table 12.5. Disregarding ‘no preload’ meals which were not concurrent with the other two, there was compensation but the reduction in test-meal size was not significant at the $p \leq 0.05$ level. Although the differences were small, 8 of the 10 who had high and low preload ate less after the high preload meal.

Table 12.5 Mixed meal intake - Normal elderly n = 10

Preload condition	Mean kJ	S.D.	Minimum	Maximum
Low preload (660)	1884	726.0	1010	3124
High preload (1870)	1606	685.7	858	3172

For the three age groups above, an analysis of variance of within-subject effect showed a significant relationship between age and preload condition (ANOVA: $F = 6.90$, $df = 4,48$, $p < 0.0005$).

Non-hyperphagic demented

The results, summarised in table 12.6, were very variable between individuals and between preload condition for each individual. There was no significant difference between the test meal results after the high and low-energy preloads, the mean after the high-energy preload was higher than following the low-energy preload.

Table 12.6 Mixed meal intake - Non-hyperphagic demented n = 8

Preload condition	Mean kJ	S.D.	Minimum	Maximum
Low preload (660)	972	649.4	178	1789
High preload (1870)	1527	1609.1	251	5222

Hyperphagic demented

The results, summarised in table 12.7, show that the total quantity of food eaten was very variable and the differences between the preload conditions were not significant (paired t-test for high and low preload conditions $t = 1.17$, $df = 12$, $p = 0.265$).

Table 12.7 Mixed meal intake - Hyperphagic demented n = 13

Preload condition	Mean kJ	S.D.	Minimum	Maximum
Water preload	4105	2345.6	1472	9359
Low preload (660)	5065	3174.4	999	10728
High preload (1870)	4402	2601.0	207	8751

c) Satiating efficiency

Where there was a difference in intake following preload (i.e. in the three normal, non-demented subject groups), the ‘satiating efficiency factor’ was calculated (c in table 12.8); this was based on work by Kissileff (1984). In this experiment the most reliable method of measuring satiating efficiency (c) was taken as a/b , where (a) was the energy intake at the test meals following the low-energy preloads minus the energy intake at the test meal following the high-energy preloads (i.e. the second column of figures minus the third column in table 12.3) divided by (b) the difference in energy between the high-energy and the low-energy preloads (i.e. $1870 - 660 = 1210$ kJ).

Table 12.8 Satiating efficiency (comparison of low- and high-energy preloads)

Group	(a) Difference in test meal intake (kJ)	(b) Difference in preload intake (kJ)	(c) Satiating efficiency
Young (n=12)	579	1210	0.48
Middle aged (n=6)	334	1210	0.28
Normal over 50 (n=10)	278	1210	0.23

Satiating efficiency of the preload decreases with age but an analysis of variance did not show a significant effect of age group on satiating efficiency (ANOVA: $F = 1.62$ [2,25], $p = 0.219$)

d) Eating rate

The rate of eating was examined by measuring energy consumption per unit time over the whole length of the meal. The effect of preload on this rate was examined. Meal time was not recorded in the two younger normal groups but for each of the three elderly subject groups the differences in rate, following high preload and low preload conditions, was examined (see table 12.9). A paired t-test was used to determine whether any of these differences was significant. The only significant result was that the normal elderly ate more slowly after the high preload than after the low preload ($t = 4.05$, $p = 0.003$).

Table 12.9 Eating rate (kJ eaten per minute)

Group	Low preload	High preload
Normal over 50 (n=10)	118.5	104.7
Non-hyperphagic demented (n=8)	30.6	35.9
Hyperphagic demented (n=13)	70.0	62.6

As the hyperphagic group ate for such a long time, it was possible that the effect of preload might not affect the overall eating rate but there might be a difference at the beginning of the meal. To check whether the type of preload affected eating rate during the first hour of the meal, cumulative intake curves were plotted against time for each preload condition both for mass of food eaten (figure 12.2) and for energy

intake (figure 12.3). The three curves were similar in each figure, showing no clear effect of preload on eating rate.

ASSESSING HUNGER AND FULLNESS SUBJECTIVELY

AIM

To assess subjective feelings of hunger, fullness and desire to eat using visual analogue scales in order to see whether there is any change after a preload.

INTRODUCTION

Hunger is the urge to eat, cued by the internal stimuli resulting from food deprivation. In many preload experiments the effect of preload on hunger and fullness is investigated using visual analogue scales (Rogers & Blundell, 1990).

Assessing hunger in people with dementia is likely to be very difficult because of the cognitive impairment. The purpose of the experiments described in this section was to use visual analogue scales to examine the time course of hunger following the different preloads and to try to develop a method for rating internal stimuli in the subjects with dementia.

Lists of food have been used by Hill and Blundell (1986) to assess hunger. This method had been successfully adapted, using pictures, to assess hunger in children with Prader-Willi syndrome (Holland, *et al.*, 1993). When the children were asked if they felt like eating the food shown in the picture, they said 'yes' to a greater number of pictures before the meal than after.

Figure 12.2

Hyperphagic demented
Intake during first hour - mass

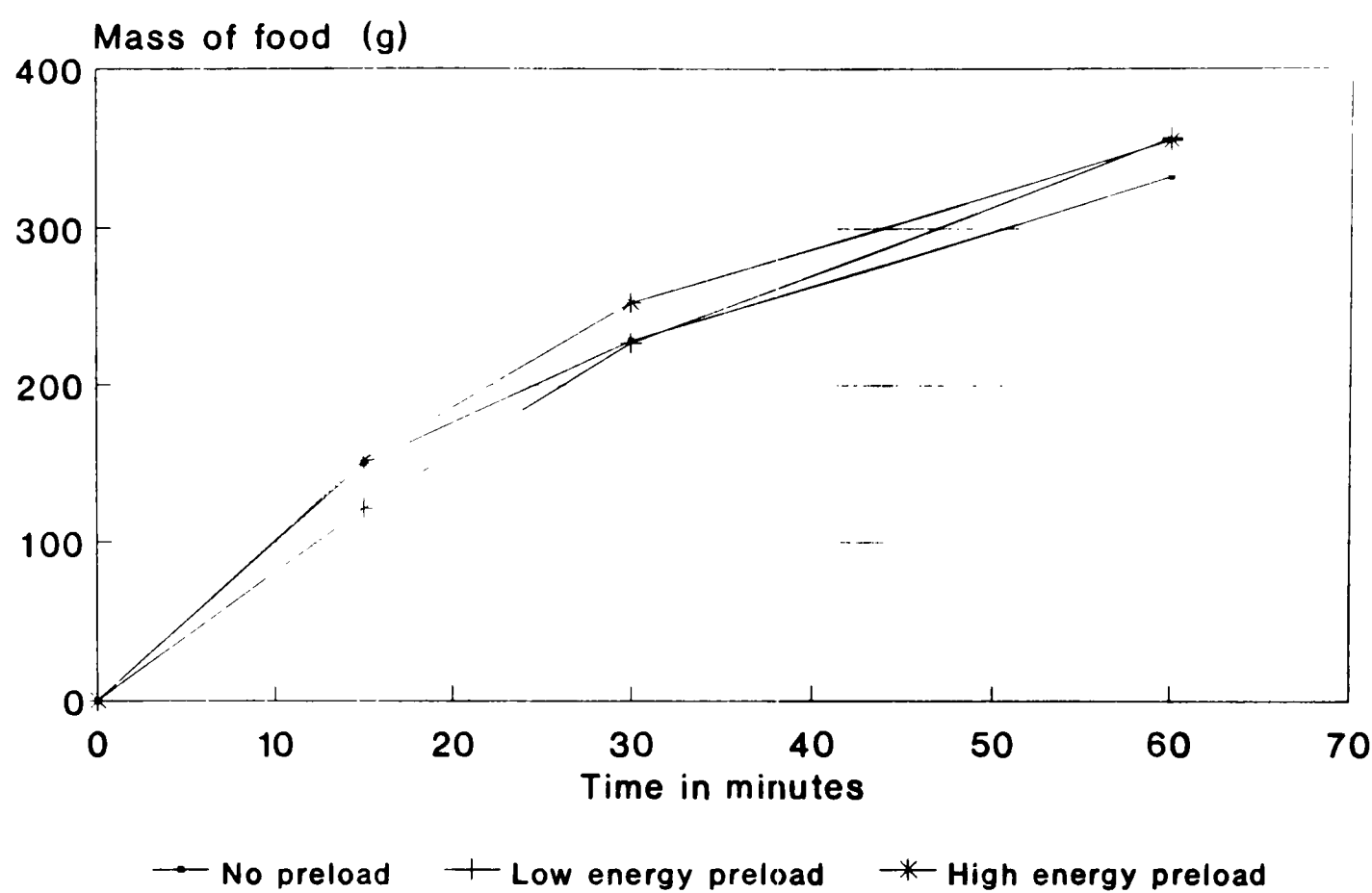
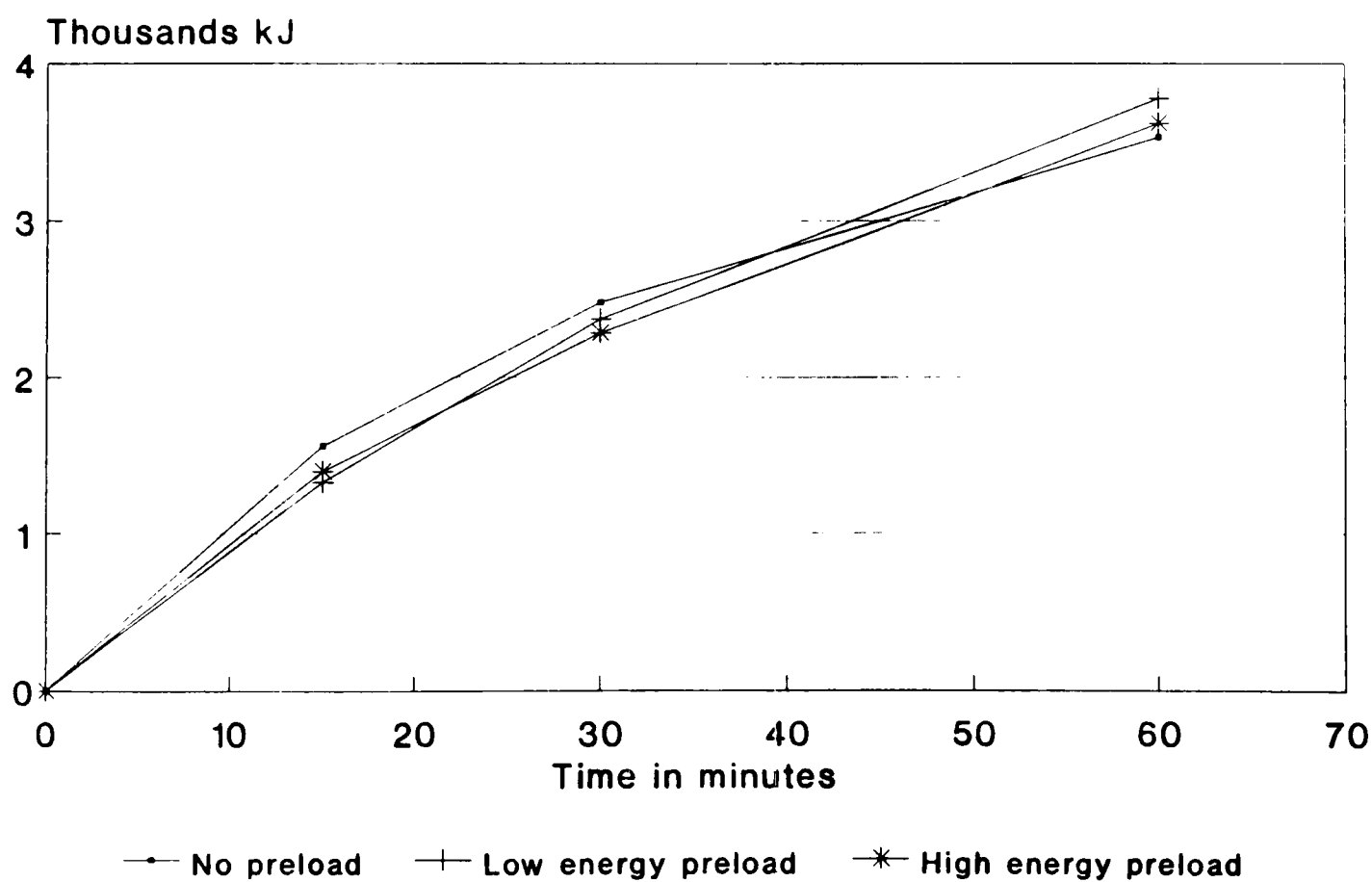


Figure 12.3

Hyperphagic demented
Energy intake during first hour (kJ)



METHOD

1. Normal subjects

Visual analogue scale (VAS)

The normal controls were asked to fill in visual analogue scales (see Appendix IV). They were asked to assess how hungry they felt, how strongly they wished to eat, how full they felt, and how much they thought they could eat. The 100 mm scales were numbered every 10 mm and anchored each end by extremes e.g. I am not at all hungry (0) at one end and I am extremely hungry at the other (100). They were asked to circle the number that indicated most how they felt at that moment. They were also asked to complete the same scales before and after the preload, half an hour after the preload and before and after the mixed meal. They were asked how much they liked the preload to see if there was a difference in perceived palatability between the high and low-energy preloads.

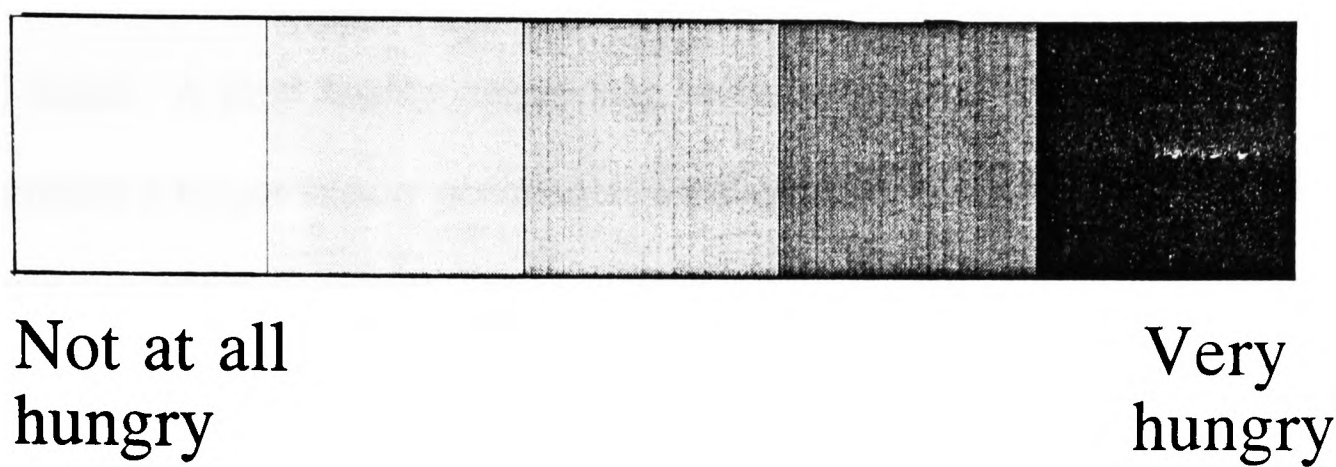
2. Subjects with dementia

As the standard visual analogue scales were not suitable for use with the subjects with dementia alternative measures were tried: a simplified VAS was devised and also a method used on children with learning difficulties was used.

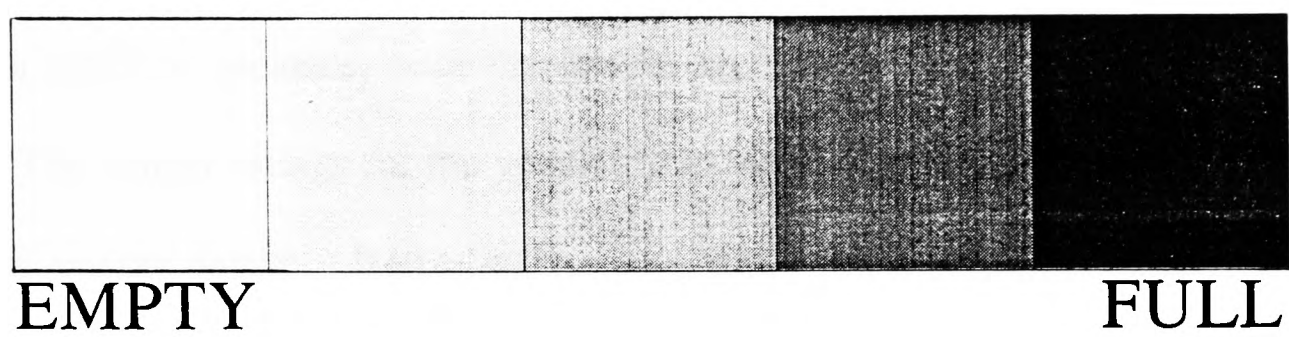
(i) Simplified visual analogue scale

A simplified scale was devised to assess hunger and fullness (figure 12.4) and used as in the method above but asking for a verbal response.

Figure 12.4 How hungry are you now?



How full are you now?



(ii) Pictures of food

As most people with hyperphagia were unable to read or to understand verbal instructions, the picture method was tried. In a pilot study, ten subjects with hyperphagia were shown 13 large, clear, glossy, coloured photos of a range of easily recognisable sweet and savoury foods e.g. banana, chocolate bar, chips. The pictures were shown slowly, one at a time, and subjects were asked whether they felt like eating that food at that moment. They were asked before the meal, during and after the meal. Some were also asked what the foods were to see if they recognised them.

(iii) Latency

For the three elderly groups, latency was recorded at the beginning of each of the preload meals. A short latency period may be an indicator of hunger (see Chapter 11), therefore a longer latency period after a preload might indicate that the preload was having an effect on satiety.

RESULTS

1 Normal subjects

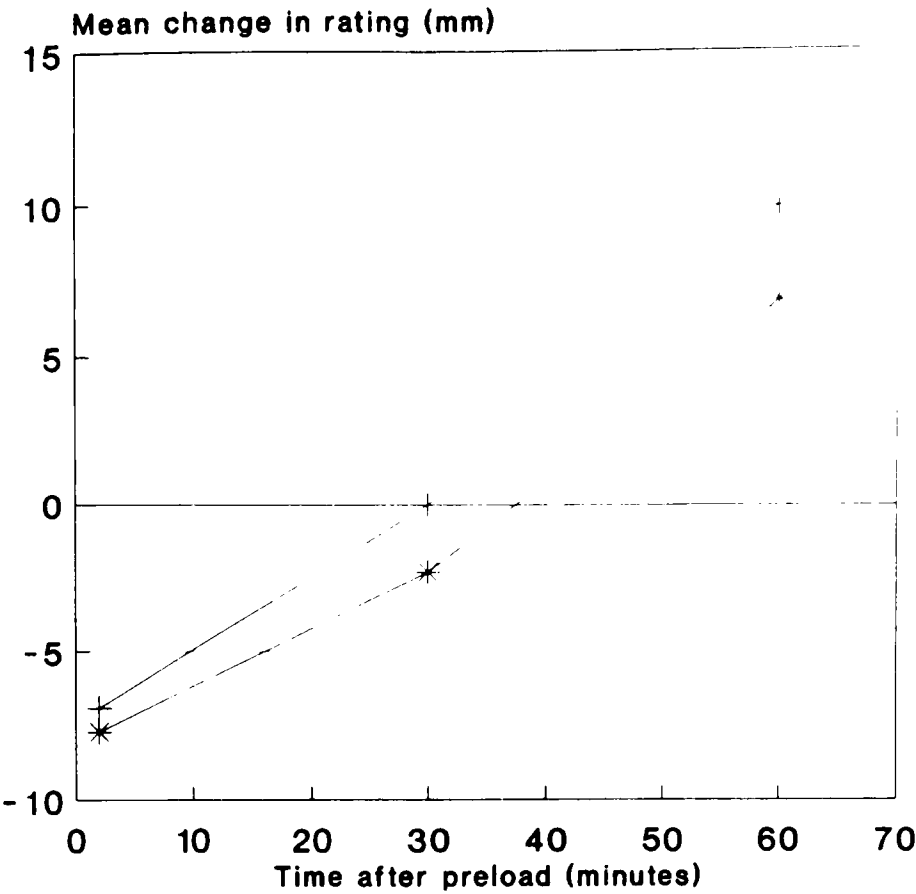
(i) Hunger

All three groups (young, middle-aged and elderly) felt less hungry directly after both the high and low preloads, with the middle-aged being the most affected (figure 12.5). The hunger ratings for the young group were clear and consistent with their test-meal energy intake. Interestingly, there was no difference in hunger ratings between the low and the high preloads immediately after each preload but the young group were less hungry following the high preload after 30 and 60 minutes. Water reduced hunger less than the milkshakes immediately afterwards. After half an hour the young group were back to the baseline after the low preload and after an hour most hunger ratings were higher than before the preload. The difference between the preloads did not affect the hunger ratings of the elderly. Young and old groups felt slightly less hungry after the high preload than after the low one. There was no significant within-subject effect with age by the time after preload or by preload condition but there a significant effect of time on hunger ratings (ANOVA: $F[2,52] = 32.7, p < 0.0005$) i.e. hunger ratings changed over time, decreasing immediately after the preload and increasing during the course of the next hour.

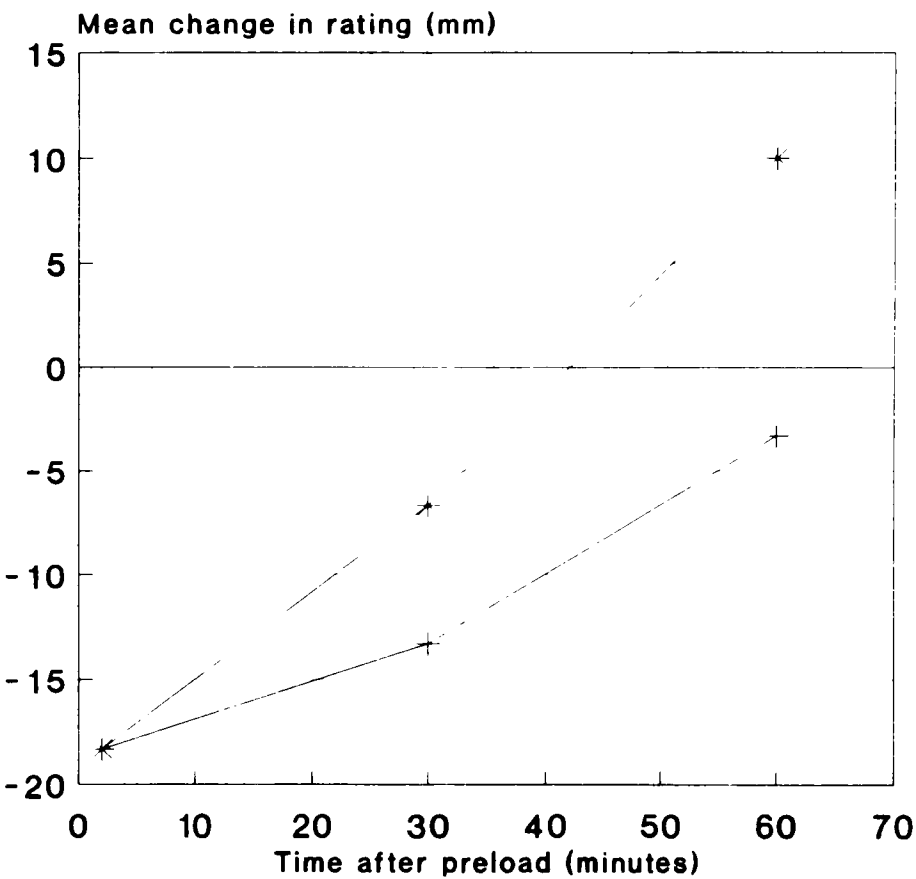
Figure 12.5
SUBJECTIVE
RATINGS
OF HUNGER

Young group

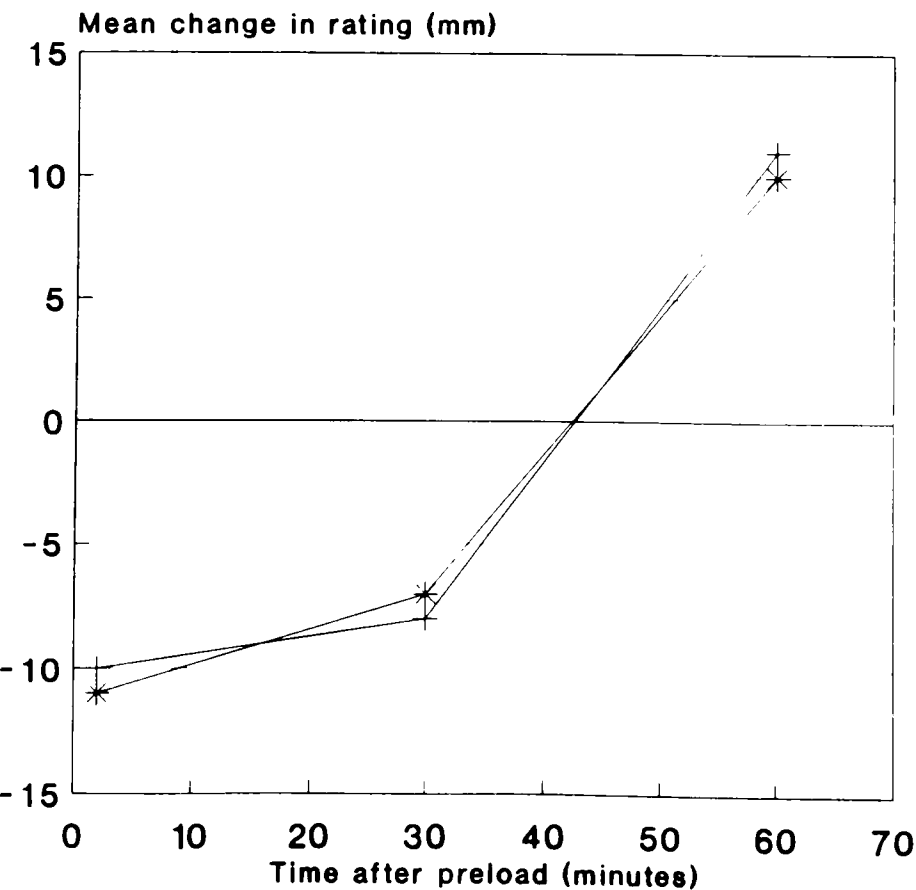
- + Low preload
- * High preload



Middle-aged
group



Elderly group



(ii) Fullness

All three groups felt fuller immediately after the high preload than after the low preload (figure 12.6). The feeling of fullness decreased in the young and middle-aged groups after 30 minutes but the elderly group still felt full an hour later after both preloads. The greater effect of the higher preload on fullness was still apparent in the young group after an hour. There was no significant within-subject effect with age by time or condition but there a significant effect of time on fullness ratings (ANOVA: $F[2,52] = 8.1, p = 0.001$).

(iii) How much subjects thought they could eat

After the preloads the amount people thought they could eat decreased, but returned to the baseline before the test meal (figure 12.7). There was no significant effect of age by condition or time.

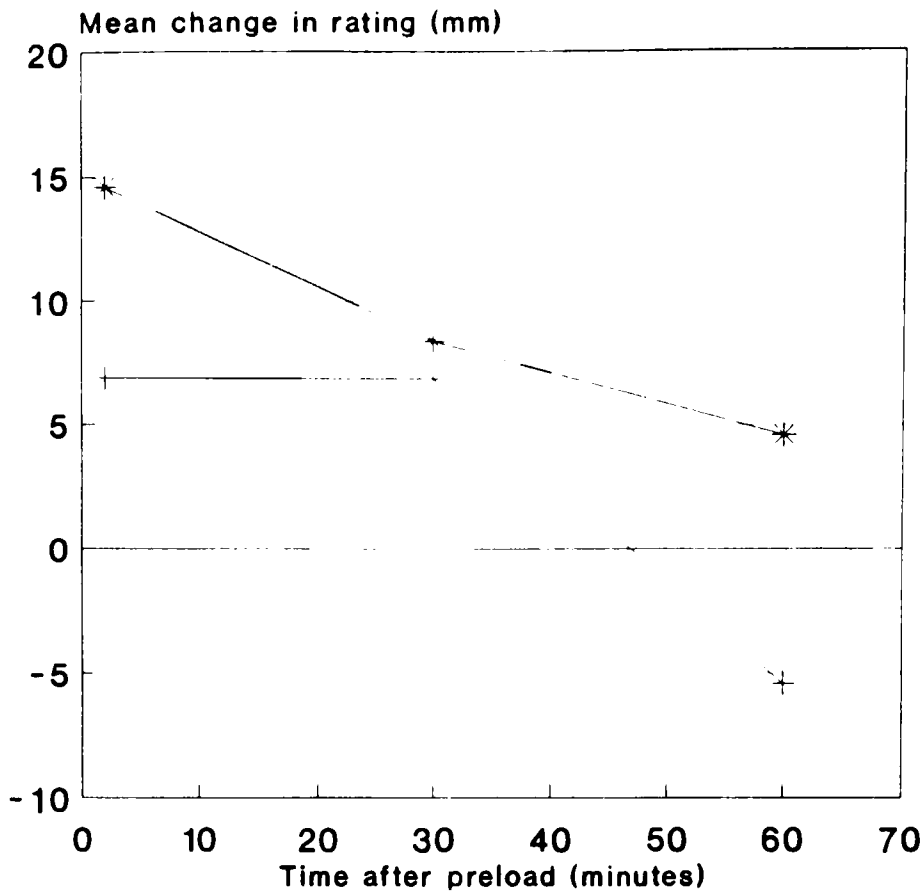
iv) Liking rating for preload drinks

Most subjects did not notice that the two preload drinks were different although some of the younger people (under 50), who were not formally asked, commented that they disliked the richness when given the high-energy drink. Most elderly (over 65) gave the drinks a high 'liking' rating in a standard 100 mm VAS (see Appendix IV) and there was no significant difference in the liking rating between the high and low preload milkshakes (mean rating low preload - 75 mm, range 40 - 100 mm; high preload - 76 mm, range 40 - 100 mm).

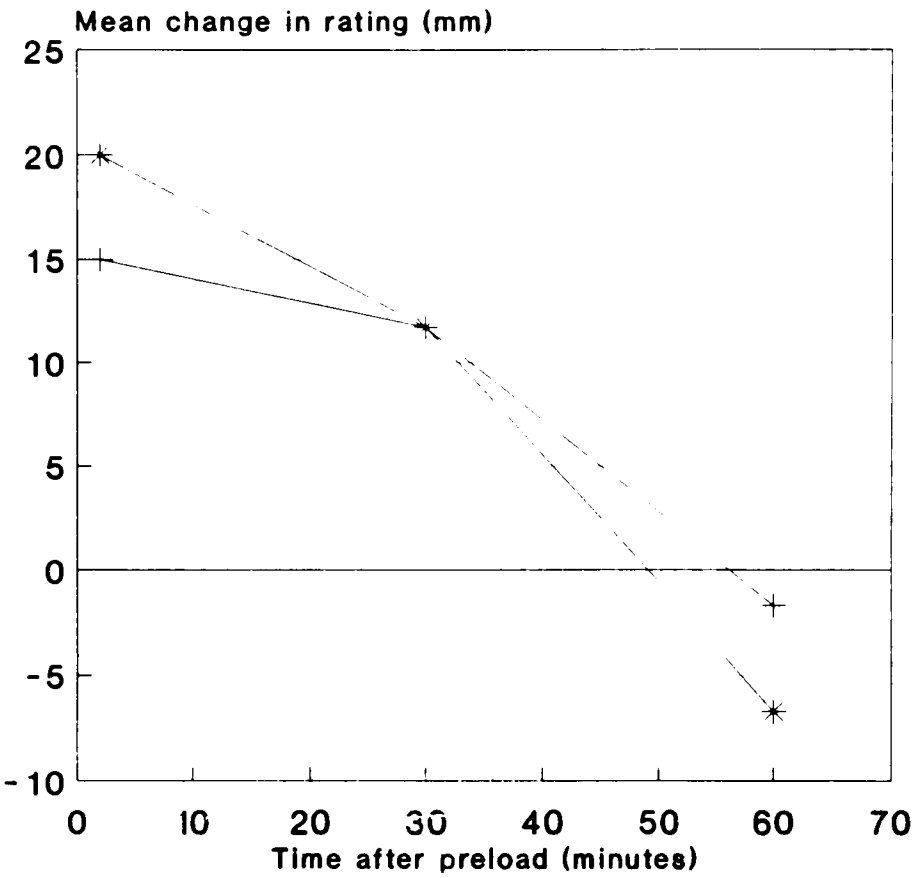
Figure 12.6
SUBJECTIVE
RATINGS
OF FULLNESS

Young group

- + Low preload
- * High preload



Middle-aged
group



Elderly group

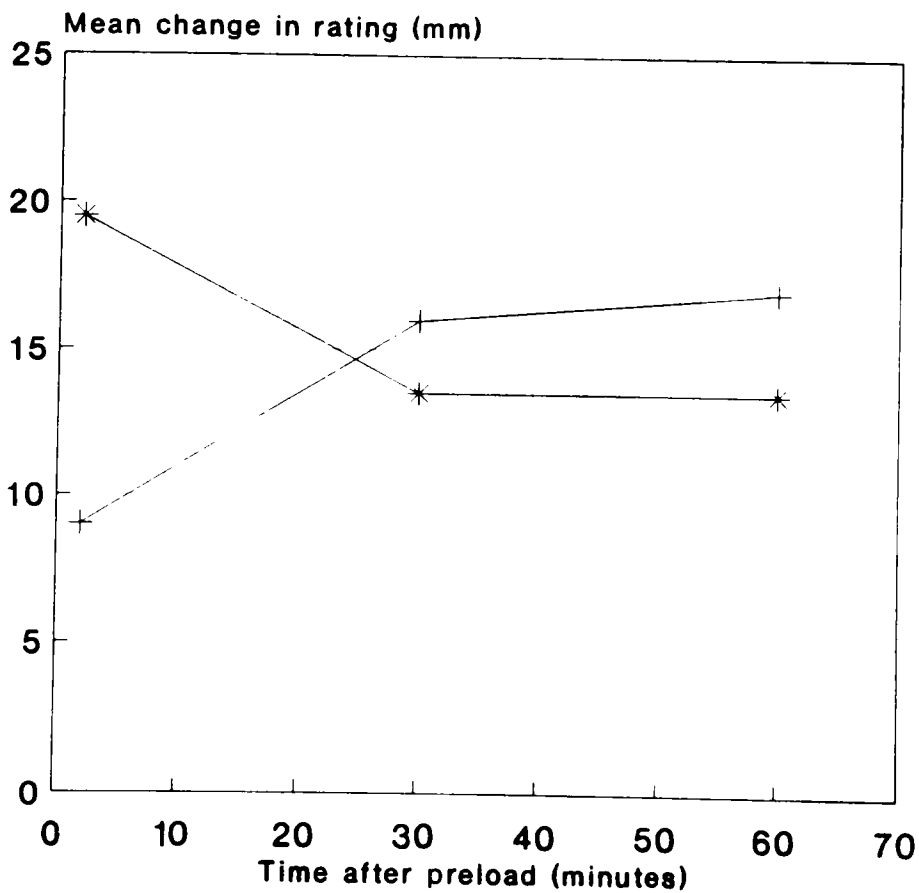
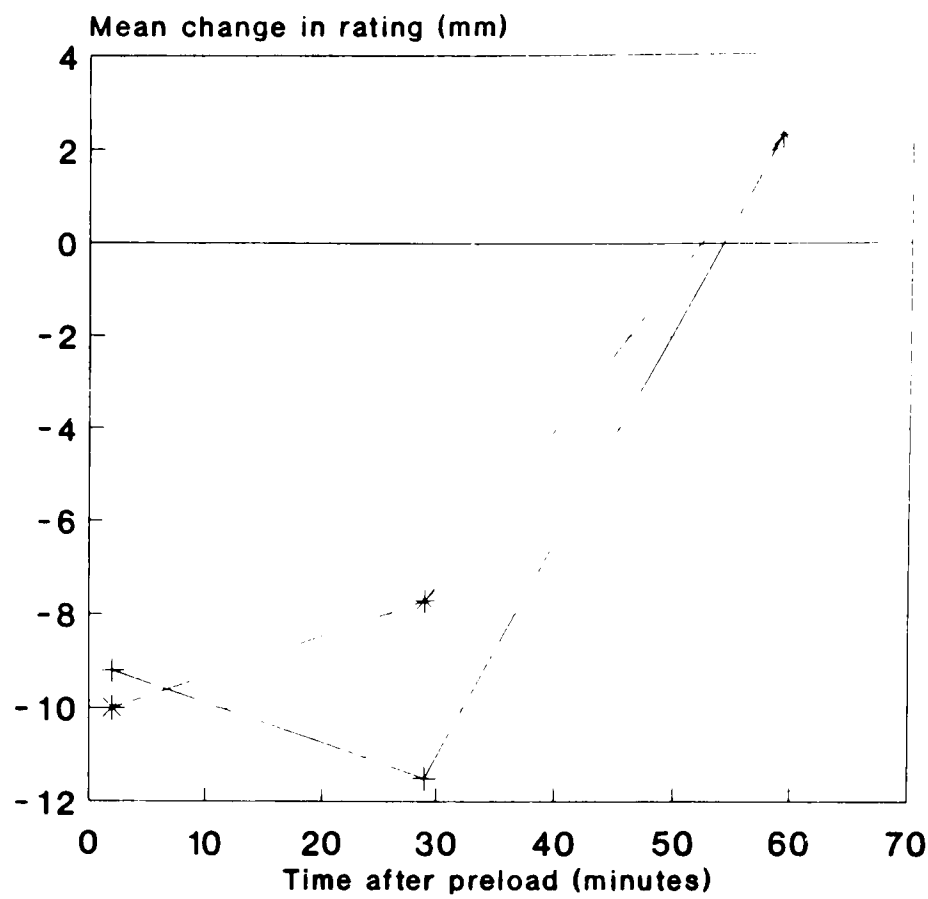


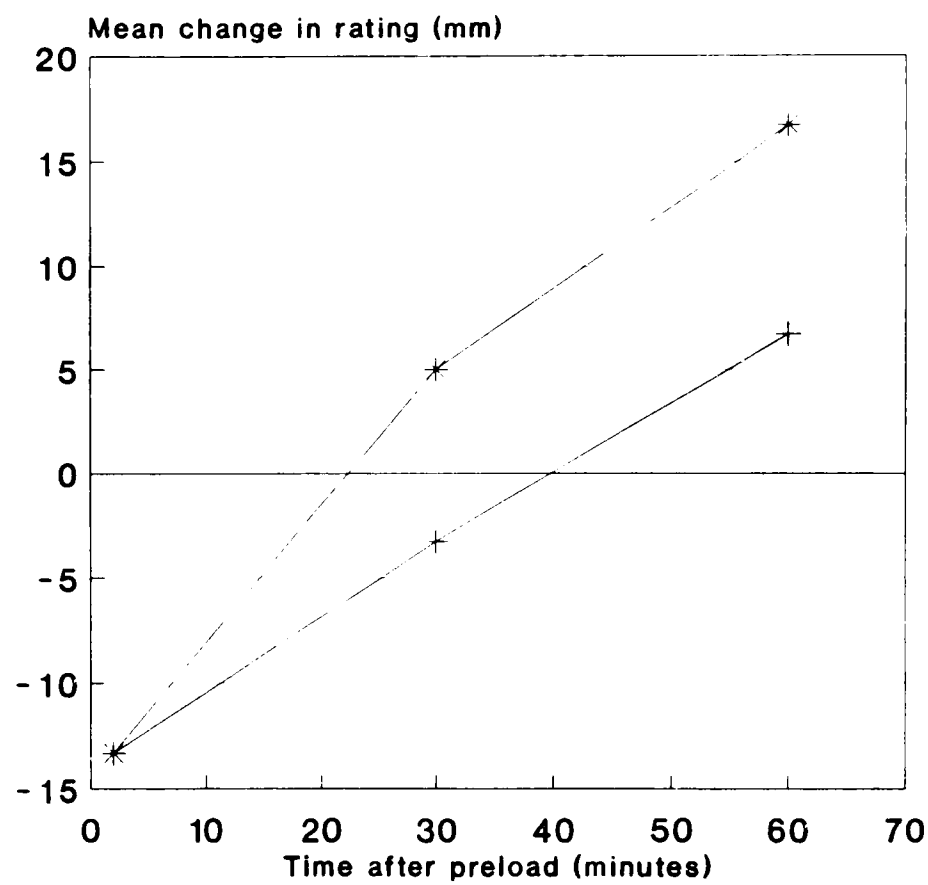
Figure 12.7
SUBJECTIVE
RATINGS
‘COULD EAT’

Young group

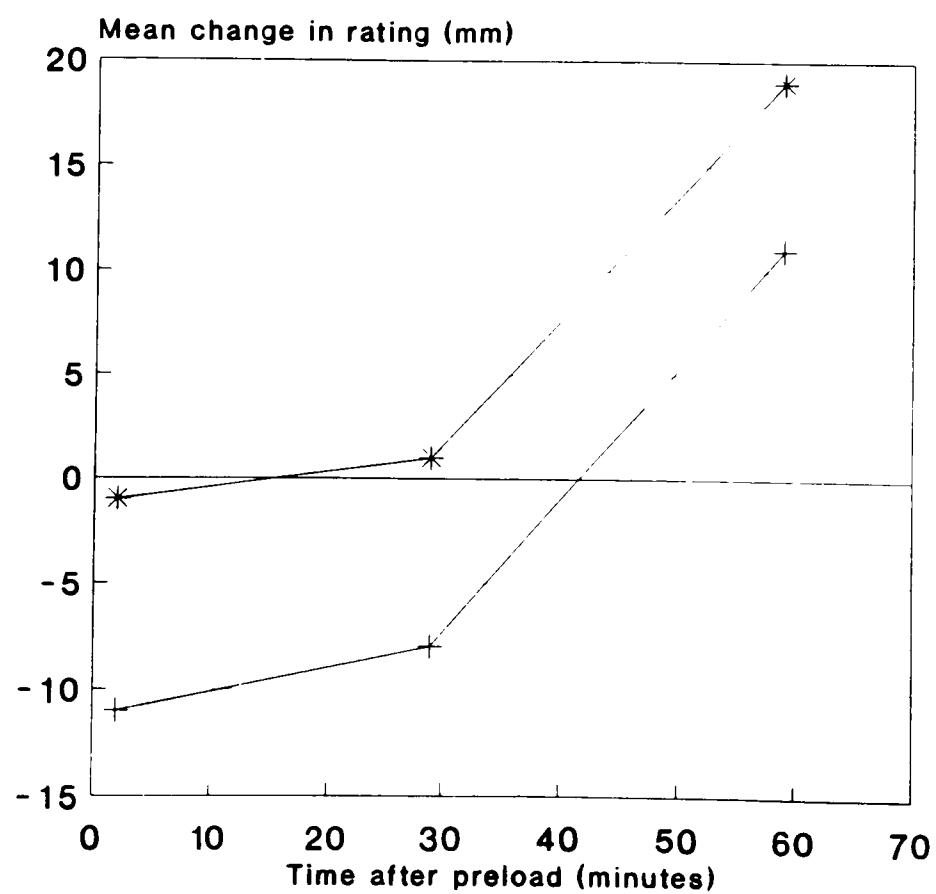
- + Low preload
- * High preload



Middle-aged
group



Elderly group



2. Subjects with dementia

(i) Visual analogue scales

The VAS, used to assess hunger and fullness in the normal group, was tested on one of the least impaired controls with dementia but she was unable to understand it. In the two demented groups even the simplified VAS was found to be too difficult to understand.

(ii) Food pictures

When the pictures of food were shown, most subjects with dementia were unable to recognise the foods. Even those who were less demented did not give answers which were consistent or reliable. It seems that the degree of cognitive impairment, in these demented subjects, was greater than the Prader-Willi Syndrome children, for whom the food pictures were developed (Holland *et al.*, 1993).

(iii) Latency

Table 12.10 Latency (Median in seconds)

Group	No preload	Low preload	High preload
Normal over 50 (n=9)	22.0*	18.0	17.0
Non-hyperphagic demented (n=8)	176.0*	57.0	83.0
Hyperphagic demented (n=13)	9.0	45.0	4.0

* denotes that the majority of meals in this group were not eaten within the same month as the preload meals, therefore eating may have changed in the meantime.

There was no clear effect of preload on latency which might have reflected a change in hunger (see table 12.10). As in the previous test meals, the normal elderly started after a relatively uniform period of time, for each of the meals, ranging from 4 - 74

seconds. The non-hyperphagic demented controls were very variable and often needed encouragement to start. Some started at once while others took up to 23 minutes before they started to eat. Some of the hyperphagic demented group were slow to start but many took food the second it was presented regardless of the type of preload.

DISCUSSION

The purpose of this set of experiments was to see whether preloads of different energy values affected the amount eaten and eating rate. The method involved giving different preload milkshakes, which were designed to have similar taste, texture and volume to prevent the difference in energy density from being noticed. In a third condition a zero-energy preload was given which was either 200 ml water or no preload at all. In this way the energy content of the milkshakes was disguised so that any compensation was likely to be 'physiological' rather than 'cognitive'. The implications of the results are considered under three headings: the effect of ageing, the effect of dementia and the effect of hyperphagia.

1. Effect of ageing

The young age group compensated well for the preload. There was some apparent compensation in the middle-aged group but the difference was not significant. The normal elderly controls did eat less after a high-energy preload than after a low-energy preload but the degree of compensation was less than in the two younger groups. This lack of significance might be due to small numbers (type II error). Larger sample sizes are needed to confirm the significance of these findings.

The young apparently have tight physiological control over food intake. Compensation becomes weaker with age, presumably as the mechanisms governing satiety become less effective. The decreasing ability to compensate as people age may be because they are less sensitive to physiological cues governing sensations of hunger and satiety. For older people the memory of what they have eaten may be

more important than bodily sensations. They may become more inflexible in their routine and the amount eaten might be determined by habit and influenced by environmental cues such as time of day. These learned responses may be stronger in the elderly and, even given the same physiological control, they might act to keep test meals relatively constant whatever the preload. In support of this, other work has found that subjects who did not compensate had more regular meal patterns whereas subjects who compensate had a more flexible schedule (Spiegel, 1973).

2. Effect of dementia

According to Blundell's theories of satiety, the early period of satiety is governed by cognitive processes (figure 5.1). In people with dementia, memory for recent events is usually affected early in the course of the disease. Most of the subjects in this study with dementia were severely impaired (mean MMSE 3.7). It is unlikely that they would have any recollection of the preload meal, consumed an hour earlier, which might influence subsequent meal size. Perhaps, in retrospect, this should have been tested directly. Certainly it is most unlikely that the subjects with dementia would be able to remember the satiating efficiency of the preload consumed a week previously. Without a memory for recent events, subjects would not remember what they had already eaten, therefore better compensation might be expected if they made no conscious compensation for the preload. Intake would then be the result of physiological control mechanisms but the wide variation in test meal size shows no correlation between preload and subsequent test meal intake.

In the normal elderly there is a near-significant reduction in intake after a high preload than after a low-energy preload ($p = 0.071$) and there is a significant effect of preload on eating rate. In dementia there is no evidence at all for compensation. Indeed, in the non-hyperphagic demented, the group mean shows a (non-significant) increase in meal size after the high preload compared with the low preload. This lack of compensation is true of both demented groups and thus, (unlike satiation and hunger) satiety does not seem to be a mechanism which differs in hyperphagia from non-hyperphagia.

The wide range of the results may be explained by 'loosening' of physiological control, if so is this another example of dementia being an exaggeration of ageing? The breakdown of homeostatic mechanisms is reflected in other behaviour changes, for example in sleep studies the normal changes of sleep pattern, which occur in ageing, are found in a more extreme form in dementia (Prinz & Vitiello, 1993).

With no cognitive and no physiological control the ending of the meal may be random; higher intakes than expected could be the result of forgetting the preload, of having no awareness of future requirements or of losing socially acceptable restraint which governs the normal endpoint of a meal. Lower intake than anticipated occurred if the meal ended prematurely for example if the people forgot they were eating and were distracted, wandered away from the table or fell asleep.

3. Effect of hyperphagia

There is no evidence that satiety is affected by a preload in the people in the hyperphagic group. There seemed to be no subsequent effect of the preload in reducing the amount of food consumed. Conversely there was no indication of the counter-regulation seen in people with bulimia but this would not be expected if they cannot remember the preload.

This lack of evidence of satiety may be a false negative result as :

a) The hyperphagia group may no longer be at the peak of the hyperphagic stage. The preload meals were given several months after the initial meals used to classify hyperphagic behaviour. This probably explains why the mean total consumption was lower than might be expected as some of the subjects were showing less hyperphagic behaviour by the time the preload meals were given. However, although intake was erratic all 13 exceeded the stringent threshold of 3337 kJ during at least one of the three preload/mixed meal conditions. Not all meals ran their full course. Three people in the group were stopped because they seemed to be uncomfortably full or because they were still eating after two hours.

The preload experiments should ideally have been carried out at the time of the initial test meals but this was not feasible as the number of meals was limited by time, as only one meal could be given each day, and it was also undesirable to allow subjects to eat excessively too frequently.

b) The preloads may not have been sufficiently different in energy value to show a difference in the hyperphagic group but a larger preload would not have been tolerated by the other two elderly groups.

c) The time interval of one hour between preload and test meal may not have been ideal for this group. If the interval had been longer or shorter it might have had an effect; Blundell's analysis (see figure 5.1) suggests that different mechanisms operate at different times.

If, in dementia, there is no memory of the effect which each of the foods previously had on the body, the physiological effect of the volume of food in the stomach may be more important in ending the meal than in cognitively estimating the satiating power of food. The rate of eating may only reflect the rate at which a set volume of food can be adequately chewed and swallowed. Judging from the prolonged period of eating, subjects with hyperphagia have an abnormal response to, or absence of, internal cues governing satiation and satiety.

Assessing hunger and fullness

Visual analogue scales showed that difference in energy level of preloads had an effect on fullness and hunger in the normal young but in the middle-aged and elderly the results were not significantly different after high and low preloads. The lack of difference in hunger ratings between low and high preloads, immediately after each preload, suggests that the different appetite effects of these treatments is due to energy difference rather than a sensory difference. The reason why the reduction in hunger

immediately after water is less than after the milkshakes is presumably because of expectancy effects cued by the sensory differences. The middle-aged group was small and the anomalous results (greater hunger after the high-energy preload can be accounted for by the unusually low baseline of hunger in the high preload condition). The lack of difference in the hunger ratings after different preloads in the elderly may account for the absence of compensation at the following test meal. This shows that subjective sensations, depending on the preload, vary in younger but not older people. The difference in energy content of the disguised preloads did not have an effect on the feelings of hunger and fullness in the middle-aged and elderly showing that they were less affected by internal satiety cues.

Putting this together with data on 'compensation' of food intake, a reasonable hypothesis is that hunger and satiety mechanisms, in the young, are more powerful or affected more by intake. The direct methods of assessing feelings of hunger or fullness were unsatisfactory in dementia, even with people who were only moderately demented. Indirect methods such as latency period showed no clear effect of preload.

Chapter 13 PALATABILITY AND FOOD INTAKE

AIM

To examine the effect of palatability on the quantity of food eaten.

INTRODUCTION

1. Palatability and food intake

Palatability is a key variable affecting overall food intake. There is the question, therefore, of whether palatability is abnormal in hyperphagic people. Palatability is a hypothetical construct which is used to define the hedonic qualities of food including taste, smell, flavour and texture (Rogers, 1990b). It is influenced by innate factors which can be modified by learning. Rogers' model of food intake (figure 11.1), based on previous experimental evidence, proposes that the cumulative intake curve for food eaten during a meal is a combination of its stimulatory (or positive feedback) effect and inhibitory (or negative feedback) effect on the body. Palatability affects the degree of positive feedback. Experimentally, for example, by using an opioid antagonist, palatability of food can be reduced without affecting feelings of hunger (assessed subjectively by visual analogue scales) and, conversely, hunger can be reduced without affecting palatability (Rogers, 1990b). It is expected that with higher palatability there would be a higher cumulative intake of food as there would be a higher positive feedback from oral stimuli (Rogers, 1994) primarily because termination of a meal is when negative and positive feedback exactly balance.

Hyperphagia itself could be explained on this model, either through damage to the negative feedback system (which is basically what has been considered earlier in experiments investigating satiation) or by abnormality in perceiving palatability (essentially hyperphagia would result from very high palatability). The issue which will be examined in this chapter, is not whether hyperphagia can be caused by very high palatability but rather whether any effect of palatability on intake can be detected, as the model implies. Does reducing palatability in hyperphagia reduce overall food intake, as would be predicted if this model applies to people with hyperphagia?

2. Abnormal palatability in dementia

There are reasons for thinking that the perception of palatability may be blunted in dementia. Both olfaction and taste, which are both likely to underpin normal palatability, have been shown to be abnormal in dementia.

a) Olfaction in dementia

In mild dementia, olfactory detection thresholds are similar to age-matched normal controls (Koss *et al.*, 1988). In later stages of dementia, especially in Alzheimer's disease, subjects perform significantly worse than controls in olfactory tests (Knupfer & Spiegel, 1986; Serby, 1986; Doty *et al.*, 1987). This may account for the lack of discrimination in the choice of food and even coprophagia (Ghaziuddin & McDonald, 1985). Many people with dementia are reported to eat anything they are given, including things they used to dislike. It could also explain why some people with hyperphagia eat or drink substances which would appear to be noxious such as soap,

faeces or shampoo. Some reports consider that olfactory dysfunction could be regarded as a marker or even a predictor of dementia of the Alzheimer's type (Peabody & Tinklenberg, 1985; Perl *et al.*, 1992).

b) Taste in old age and dementia

Unlike the sense of smell, taste is reported to be well-preserved in the normal elderly (Stevens *et al.*, 1984; Weiffenbach *et al.*, 1990) and in early AD (Koss *et al.*, 1988). With increasing age, there is a decline in the sensitivity of sense cells and taste thresholds rise but there is no evidence of serious loss with age (Bartoshuk *et al.*, 1986). Higher concentrations of sugar and salt were rated as more pleasant in the elderly than in the young but the reasons may be cultural, contextual or sensory. It may be because, to the elderly, they taste less strong or because, in foods, they compensate for reduced olfactory stimulation (Murphy & Withee, 1986). Busse (1980) reported that cells detecting sweet and salt deteriorated first, therefore foods tended to taste sour or bitter.

In Murphy's review (1992) she found bitter to be the taste quality most affected by age and sweet the least. Elderly men were less sensitive to the bitter taste of caffeine than elderly women or young men (Booth *et al.*, 1989). Detection thresholds for quinine HCl were not found to be higher in patients with dementia (not just AD patients) than in age-matched controls but were higher than the thresholds in young subjects (Schiffman *et al.*, 1990). De Ajuriaguerra *et al.* (1976) found that some people with dementia ate very bitter or very salty food without reacting to the taste. Others might reject one taste, for example saltiness, but eat bitter food without

complaining. This lack of sensitivity to unpleasant tastes might explain the pica found in hyperphagia.

c) Pica in dementia

Pica has been reported frequently in people with dementia (see Chapter 7). Unsuitable food may be eaten, such as pet food or scraps from waste bins, or substances which resemble food such as soap or leaves. It can be any object which can be put in the mouth and some potentially dangerous things have been eaten, reports from carers include shampoo, pot scourers, pot plants, soil, a live frog and the ward budgie.

The high incidence of pica may mean that subjects with dementia who are reported to be hyperphagic are:

- (i) not able to discriminate between food types and therefore could not choose palatable food when given the choice;
- (ii) desperately hungry and in the absence of palatable food will eat anything. In rats for example, after food deprivation a higher concentration of quinine needs to be added to food before eating is inhibited;
- (iii) different from non-hyperphagic, dementia-matched controls in their ability to discriminate between foods.

Could changes in perception of palatability cause hyperphagia?

The experimental work, cited above, implies that food would need to have enhanced palatability to cause hyperphagia. However, there is evidence to suggest that lack of a sense of taste or smell could decrease the satiating efficiency of food. For example, two people who suddenly lost their sense of smell (personal communications) both said they had to learn how much food to eat as they found eating was no longer satisfying and both had tended to gain weight at first. This sensory loss may result in passive hyperphagia as eating continues, at the same rate, for a longer time than normal (as opposed to active hyperphagia where food is actively sought). Detailed studies showed that increase and decrease in weight, after loss of smell or taste, was very variable but patients with anosmia tended to put on weight, 13% gaining more than 10% of their pre-disorder weight. When loss of smell is the result of trauma this gain can be rapid; over 6 kg within 2 weeks of the onset. These patients increase their intake of foods rich in fat, sugar and salt (Mattes & Cowart, 1994).

In this chapter the focus is on the more general question: is there evidence of any difference in the effect of palatability on eating behaviour in hyperphagics compared with non-hyperphagics, rather than whether food is more palatable in hyperphagia. How can palatability of foods be assessed in people with dementia other than by measuring total intake? Experiments with normal subjects usually rely on the subject's own report. This is not possible with people with dementia but alternative methods are to analyse:

a) Microstructure of eating

Palatability affects the microstructure of eating (see Chapter 11). When less palatable foods are eaten chewing rate is slower, chewing time per food unit is longer and the pauses between food items increase therefore eating rate is lower (Bellisle & Le Magnen, 1981; Le Magnen, 1987; Bellisle, 1989). Less palatable foods should result in a lower intake and shorter mealtimes.

b) Facial expression

The role of palatability in hyperphagia could be investigated by studying facial expression in response to foods of different palatability. It is known that there is an innate aversion to bitter substances in babies and the sensation of bitterness causes recognisable facial changes (Steiner, 1979; Ganchrow *et al.*, 1983). In babies the response to bitter stimulation is an arch-like mouth opening or depressed mouth angles, expressive of disgust. The response is quicker, more dramatic and violent than responses to sweet or sour tastes. A similar sudden and intense ‘gustofacial reflex’ is triggered in adults regardless of age, cultural, educational or ethnic background. The aversion reaction to bitter taste may be accompanied by retching, head turning or shaking. This reaction was seen in normal elderly and to a lesser extent in people with dementia (Perl *et al.*, 1992).

Is food intake affected by palatability?

The feedback model (figure 11.1) suggests that the issue of palatability is worth investigating. The purpose of the research presented here was to find a way of decreasing the palatability of a standardised food; to show that subjects are able to re-

identify the unpalatable food and to examine whether food intake is lower for the less palatable food. Although the method used to test this failed, it did raise some interesting experimental issues.

Is there evidence that people with dementia (i) with hyperphagia and (ii) with normal food intake (matched for level of dementia) have food preferences? Evidence from the mixed test meals, when foods of relatively similar palatability were provided, suggested that 14 out of 18 people with hyperphagia showed some ability to discriminate between foods, although this was analysed on the basis of macronutrient choice rather than palatability (see Chapter 10). The other four people chose food by its position on the table.

It was not possible to use standard methods of assessing palatability, e.g. visual analogue scales, with these moderately or severely demented subjects (see Chapter 12). These subjects could not report verbally to identify tastes or rate the intensity or pleasantness of a taste. The only practical way seemed to be avoidance methods, as used in animal work, where animals quickly learn to avoid noxious foods when they are presented with a choice.

DEVELOPING A SUITABLE METHOD

Development of suitable foods

Most unpalatable substances are harmful. Of the possible unpleasant-tasting substances, quinine was chosen for these studies as the most suitable as it is frequently prescribed for the elderly, in far higher doses, to treat cramp. Caffeine

was rejected because of the danger of cardiac arrhythmias and urea was not thought suitable, as carers, who need to give consent, would probably find the idea undesirable.

To test food choice, quinine needed to be combined in an easily recognised and normally-palatable solid food. Ways of incorporating quinine in bland foods were tried. When mixed with cream cheese on a cracker, it was suitably unpalatable but was too messy. A non-sweet coating on plain biscuits was attempted using maltodextrin but it did not set to form an 'icing'. Combinations of icing sugar and maltodextrin also failed to set satisfactorily. With icing sugar alone, the quinine mixture set normally and seemed sufficiently unpalatable. There was the disadvantage of sweetness masking the bitterness to some extent. However, experimental evidence (Lawless, 1979; 1987) suggests that the tongue adapts to sweetness. Therefore, when a quinine biscuit is eaten after eating a sweet biscuit, the perceived bitterness of the quinine should be equivalent to the quinine without the sweetness. Using a biscuit, rather than drops of a solution or an impregnated strip of filter paper, meant that the whole mouth was stimulated, exposing a larger number of receptors and, in addition, this would overcome any localised taste losses (Bartoshuk, 1989).

Control biscuits

Small, low-sugar digestive biscuits were used (average mass 9.1 g per biscuit, energy 190 kJ). Icing mixture was made with 8 g water to 50 g icing sugar and two drops of pink or yellow food colouring delivered from a 1 ml syringe barrel.

Quinine biscuits

Icing mixture was made as above but with a solution of food grade quinine hydrochloride (formula weight 360.9) instead of water. For the pilot work a series of biscuits were prepared with a range of quinine concentrations. A 0.04 M solution, made using de-ionised water, gave a coating which tasted very unpleasant to a group of normal young and middle-aged people. This was much higher than the detection threshold of 5.6×10^{-9} - 1.8×10^{-4} M, found in taste tests on people up to 87 years old (Coward, 1989), when a solution of quinine sulphate was used on its own. Wet icing was made by adding 8 ml 0.04 M quinine hydrochloride solution to 50 g icing sugar. Colouring was added as above but using the contrasting colour to the control.

This concentration gave 10 mg of quinine hydrochloride when 5 g of the wet icing mixture was spread on one biscuit. This is equivalent to the quantity of quinine found in a small glass of bitter lemon. Approval from the local clinical research committee was given for a maximum of ten such biscuits to be eaten at a meal.

Each low-sugar digestive biscuit was coated evenly on the upper surface with 5 g of one of the above mixtures. Before it set, it was decorated with a few coloured sugar strands on the pink biscuits and a few chocolate strands on the yellow biscuits. This was designed to make each type of biscuit equally attractive but clearly distinguishable. This was necessary so that both types of biscuit had an equal chance of being selected but, once a biscuit was identified as being unpleasant, it was easy to reidentify the palatable from the unpalatable biscuits. The iced biscuits were dried either at room temperature or in an oven at 50-60°C. Biscuits were stored out of the

light, in an airtight container and used within two weeks of preparation.

In all the following experiments alternate batches of biscuits were made with pink icing on the normal biscuit and in the other batches yellow was the normal one.

1. ESTABLISHING THE THRESHOLD CONCENTRATION IN NORMAL SUBJECTS

METHOD

Initially biscuits with a range of quinine icing concentrations were prepared and given to normal subjects to taste: seven elderly people (mean age 79.7, S.D. 4.0, range 74-85) and eight people under 70 (mean age 41.0, S.D. 14.4, range 21-57). Subjects were told it was a taste test but were not given any more information. At first each person was given a biscuit without quinine and asked to compare it with a biscuit made with 0.0012 M solution. Biscuits with progressively higher quinine concentrations were given until first a difference could be detected and then until the nature of the difference could be described.

RESULTS

When a quinine concentration of 0.04 M was used to coat the biscuits 13 out of 15 people detected a difference between the quinine and the normal biscuits. At this concentration 12 out of 15 identified the taste as bitter (see table 13.1). However, the results suggested that elderly men may have difficulty in detecting this concentration, as three of the four elderly men who were tested did not identify the taste as bitter and did not find the quinine biscuits less pleasant even at the maximum

concentration of 40 mg quinine hydrochloride per biscuit (i.e. four times the strength used in the final trial).

Table 13.1 Thresholds for detecting and identifying quinine in normal controls

- X unable to distinguish taste from normal biscuit
- D a difference detected but not identified as bitter or unpleasant.
- I bitterness described.
- * biscuit found to be as pleasant as normal biscuit.

Subject details			Quinine concentrations used to coat biscuits (M)								
Name	Age	Sex	0	0.0012	0.0025	0.005	0.01	0.02	0.04	0.08	0.16
AK	25	M	X	X	X	D	I				
SK	28	M	X	X	X	D	I				
AP	21	F	X	X	D	I					
PK	57	M	X	X	X	X	D	I			
TH	42	M	X	D	I						
KG	53	F	X	X	X	X	D	I			
SC	47	F	X	X	X	DI					
JK	55	F	X	X	X	X	D	I			
JK	85	M	X	X	X	X	X	X	?	D	D*
FW	82	M	X	X	X	D	D	?	D	D	D*
TC	77	M	X	X	X	X	X	X	X	X	X*
SH	78	M	X	X	X	X	X	DI			
NN	74	F	X	X	X	X	D	I			
JM	84	F	X	X	X	X	X	X	DI		
MM	78	F	X	X	X	DI					

DISCUSSION

This method worked well with the younger age group but if this apparent lack of discrimination in elderly men was typical, there would be no point in using quinine to test people with dementia. This extreme loss of taste in men was unexpected as the literature suggests that the ability to taste bitterness deteriorates only slightly with

age (Coward, 1989; Schiffman *et al.*, 1990; Murphy, 1992) but their experiments were done with pure compounds not a mixture of sweet and bitter. Cowart (1989), using normal subjects aged from 19-87 years, found that in taste tests for quinine sulphate there was no main effect of gender on thresholds for bitter taste and the age covariate only approached significance (ANOVA: $F [1,130] = 3.48, p = 0.064$). In her experiments the ratings of intensity of taste for sucrose were unchanged with age but, for quinine, older subjects gave lower intensity ratings than the youngest group (ANOVA: $F [2,81] = 3.79, p < 0.05$). She found there was no significant gender effect. For my experiments, it was not possible to increase the concentration further as eating more than two biscuits would exceed the level which, in discussion with the Ethics Committee, we considered safe.

2. A QUALITATIVE TEST - testing a standard biscuit

METHOD

To verify the apparent deterioration with age in the ability of men to taste bitterness a larger number of normal people, of both sexes, were given a single choice test. They included 25 people aged 18-30 (16 male and 9 female); 8 people aged 30-70 (5 male and 3 female) and 13 people aged 70-90 (6 male and 7 female). This was designed to see what proportion could distinguish normal from quinine biscuits, using the 0.04 M concentration of quinine, and to see whether there was a significant sex difference. Each person was given one normal biscuit and one biscuit with 5 g of 0.04 M quinine solution and asked if they could tell the difference between them and if so could they identify the type of taste.

RESULTS

Most people (93%) found the quinine biscuits very distasteful. Of the 46 people tested (or retested), 43 reported an unpleasantly bitter taste (see table 13.2). The numbers were too small to show whether there was a significant difference between the sexes.

Table 13.2 Ability to detect quinine

Age group	Male		Female	
	Yes	No	Yes	No
18-30	14	2	9	0
30-70	4	1	3	0
70-90	6	0	7	0

The three who could not taste quinine were two young men who were heavy smokers and a 69 year-old man (who had been a heavy smoker until ten years previously).

DISCUSSION

The biscuits made with 0.04 M quinine solution were found to be unpleasant by most people over a wide age range. The single choice test seemed to be more sensitive than the ‘staircase’ method of presentation as the three elderly men who were unable to detect bitterness when given quinine in increasing quantities, were able to tell the difference when given a single choice. The insensitivity of the ‘staircase’ method may be because of adaptation by the taste receptors as the concentration gradually increased.

3. A QUANTITATIVE TEST - How is the difference in palatability described and rated using a visual analogue scale?

METHOD

A more precise rating of taste was made using a larger sample of people. A further 198 people aged 18 to 92 were tested. The subjects were divided into three age groups to compare the effect of age and sex on taste. There were 52 in the under-40 group; 77 middle-aged and 69 aged 65 or over. Each person was asked to taste one of each type of biscuit and to fill in a form to record age, sex, smoking habits and which biscuit they preferred (see Appendix V). Having detected a difference, they were asked to rate the pleasantness or unpleasantness of each biscuit on a visual analogue scale (VAS). This scale was anchored at each end from disgusting (0) through neutral (50) to delicious (100) at the opposite end. Subjects were asked to put a cross on the bar which corresponded to how they felt about each biscuit. They were also asked to describe the taste of each biscuit, using their own words to prevent a biased answer.

RESULTS

Difference in pleasantness ratings between biscuits

In all three age groups the quinine biscuits were rated as less pleasant than normal biscuits. The difference in rating was calculated by subtracting the rating for the quinine biscuit from the rating for the normal biscuit, the results are summarised in table 13.3. There was a significant difference between the young group and the two older groups. There was a significant main effect with age (ANOVA: $F [2, 195] 6.68, p = 0.002$). The difference between the young and middle-aged was significant

(t-test $t = 3.07$, $df = 115$, $p = 0.003$). The middle-aged rated a greater difference between the two biscuits than the elderly but this was not significant ($p = 0.053$). The difference between the young and the elderly was highly significant (t-test $t = 3.53$, $df = 115$, $p = 0.001$).

Table 13.3 The effect of age on the difference in pleasantness ratings between the two types of biscuit

Age group			Rating difference (mean)	S.D.
Young	18-39	(n=52)	48.5	17.1
Middle aged	40-64	(n=77)	38.8	18.4
Elderly	65-93	(n=69)	36.8	19.0

When the difference between the sexes was examined, there was a mean difference of 42.1 points on the scale in women and 38.5 in men, however, this difference was not significant (t-test: $t = 1.36$, $df = 177.4$, $p = 0.18$).

Pleasantness ratings for the biscuits

The absolute liking for each type of biscuit was investigated to see if there was an age and sex difference in the liking for the two types of biscuit. The pleasantness rating of the sweet biscuit increased with age (Pearson correlation: 0.17, $n = 198$, $p < 0.01$) - see table 13.4.

Although the older group found the quinine biscuits significantly less unpleasant than the young there was not the complete absence of sensitivity in some older men which was suggested by the earlier pilot study. There was a very high correlation between the increase in the unpleasantness rating given to the quinine biscuit and decreasing

age i.e. younger people found the quinine biscuits significantly more unpleasant (Pearson correlation: 0.366, $n=198$, $p < 0.001$).

Table 13.4 The effect of age and sex on pleasantness ratings

Age group	VAS rating of normal biscuit		VAS rating of quinine biscuit	
	Male (n=80)	Female (n=118)	Male	Female
18-39 (n=52)	58.8	61.9	13.6	10.5
40-64 (n=77)	58.1	58.2	22.2	17.1
65-93 (n=69)	66.3	64.2	31.2	26.6

Identification of taste

The subjects were asked to describe the taste of each biscuit. Fewer of the elderly described the taste of the quinine biscuit as bitter or unpleasant. In the young and middle-aged groups 86.3% and 85.7% respectively described the taste as bitter or unpleasant, this fell to 73.5% in the old group (these differences were not significant). There was also a difference between the sexes (table 13.5), the proportion of young women who identified the quinine as bitter was greater than the proportion of young men and the difference was significant (t-test: $t = 2.41$, $df = 49$, $p = 0.02$). The proportion of young women identifying the taste as bitter was significantly greater than the elderly women (t-test: $t = 2.68$, $df = 73$, $p = 0.009$).

Table 13.5 Effect of age and sex on ability to identify taste of quinine as bitter or unpleasant (including smokers)

Age group			% finding quinine biscuit bitter or unpleasant	
			Male	Female
Young	18-39	(23M, 28F)	73.9	96.4
Middle aged	40-64	(35M, 42F)	82.9	88.1
Elderly	65-93	(21M, 47F)	76.2	72.3

The difference in rating between smokers and non-smokers was 36 points on the VAS

for smokers and 41.2 for non-smokers.

Table 13.6 Effect of age and sex on ability to identify taste of quinine as bitter or unpleasant (excluding smokers)

Age group			% finding quinine biscuit bitter or unpleasant	
			Male	Female
Young	18-39	(16M, 26F)	87.5	96.2
Middle aged	40-64	(32M, 40F)	81.3	87.5
Elderly	65-93	(19M, 43F)	73.7	79.1

As might be predicted, there was a highly significant correlation (at the $p \leq 0.001$ level) between the description of the taste as bitter or unpleasant and a higher unpleasantness rating on the VAS.

There appears to be a sex difference in ability to taste quinine, with younger females finding the sweet biscuits more pleasant than the males and, at all ages, women rated the quinine biscuits as more unpleasant. Although smoking adversely affected the ability to taste quinine, this is not relevant to the hyperphagia study as none of the subjects currently smoked.

DISCUSSION

Although the unpleasantness of quinine decreases with increasing age, presumably as the sense of taste becomes less sensitive, even in the elderly the quinine biscuit was experienced as significantly more unpalatable than the normal biscuit ($p < 0.0005$). The results of this study with normal elderly suggests that adding quinine to biscuits is a suitable method for investigating the effect of palatability on food consumption in people with dementia.

4. TO TEST THE EFFECT OF PALATABILITY IN PEOPLE WITH DEMENTIA

a) The effect of palatability on food choice and total consumption

AIM

To investigate whether people with dementia selectively choose normal biscuits in preference to quinine biscuits when given a free choice.

METHOD

Choice of palatable and unpalatable foods

It was not possible to use VAS with people with dementia (see previous chapter), therefore behavioural evidence is needed. Subjects were given a choice of two plates of food, one palatable (normal biscuits) and one less palatable, or distasteful, food (biscuits with enough quinine to make them taste bitter). The two types of biscuit were different colours to ensure that each sort could be reidentified but, to see if one type looked more palatable, six normal people were asked which biscuit they thought looked more attractive. They expressed no preference for either colour but, to avoid bias, half the subjects with dementia were offered biscuits with pink icing on the quinine biscuits and yellow icing on the normal biscuits and the rest were given the opposite combination. Also the presentation of quinine biscuits on the right side or left side was balanced. Eleven of the hyperphagic subjects and seven of the non-hyperphagic demented control group were given this test.

About one hour before normal lunch-time the room was prepared with table and video

camera in a similar way to the previous test meals. The experiment was carried out at this time so that the subjects would be moderately hungry. When the person was seated, the camera was started and two identical white plates were positioned, side by side symmetrically and equidistantly in front of the subject, one plate had one normal biscuit on it and the other had a quinine biscuit on it. A glass of water was provided and, if necessary, the subject was prompted to start. When both biscuits had been tried, each plate was replenished with a further four biscuits of each type. When one of the plates was reduced to a single biscuit, each plate was quickly 'topped up' to four again and the position of the plates was switched to eliminate any position effect of food choice. This procedure was repeated when necessary.

Some of the controls with dementia who were normal eaters ate so little that quarter biscuits were used to replenish the plates after the initial single biscuit choice. This gave a greater number of opportunities to make a choice between the palatable and unpalatable biscuits as most people finished a complete biscuit after starting to eat it.

For each test the following were noted:-

- 1 Total consumption of palatable and non-palatable foods.
- 2 Ability to continue to choose palatable foods despite switch of position.

RESULTS

Total consumption of biscuits

In the hyperphagic group a mean of 6.8 normal biscuits and 5.4 quinine biscuits were eaten (table 13.7a). This difference is not significant. In the non-hyperphagic

demented group a mean of 2.7 normal biscuits were eaten and 2.1 quinine biscuits (table 13.7b). This was not a significant difference. All subjects were non-smokers.

Only two subjects showed any sign of noticing any difference between the biscuits or of finding the quinine biscuits unpleasant, for example one said the quinine biscuit was ‘sharp’ and the other pointed to her throat.

Table 13.7 Total consumption of biscuits
a) Hyperphagic group

Subject no.	Age	Sex	MMSE	No of normal biscuits eaten	No of quinine biscuits eaten
036	75	F	0	8.0	10.0
007	85	F	0	3.0	4.0
009	73	M	0	8.0	8.0
049	78	F	0	7.0	6.5
052	80	M	0	8.0	6.0
042	79	M	0	6.0	2.0
047	77	F	7	5.0	2.0
031	55	F	7	17.0	4.5
024	85	M	0	3.0	4.0
059	84	F	2	5.0	6.0
065	75	F	12	5.0	6.0
				Mean 6.8	Mean 5.4

b) Non-hyperphagic demented group

Subject no.	Age	Sex	MMSE	No of normal biscuits eaten	No of quinine biscuits eaten
032	74	M	1	2.8	3.0
054	75	F	9	1.3	0.4
057	75	F	0	4.3	1.5
060	83	F	0	3.2	3.3
062	84	F	0	0.6	0.7
063	80	M	0	0.5	0.5
064	83	M	0	4.0	4.0
				Mean 2.7	Mean 2.1

DISCUSSION

There is no evidence that people with dementia, in either group, selected one type of biscuit rather than another. Possible explanations are:

- a) they cannot distinguish the biscuits;
- b) they can distinguish the biscuits but both are equally palatable;;
- c) quinine biscuits are less palatable but people with dementia cannot re-identify (or remember) or understand that taste depends on the type of biscuit;
- d) only when negative feedback starts to operate is palatability important.

There was little behavioural evidence to show that the majority of subjects noticed any difference between the biscuits which suggests that explanation a) is the most likely explanation. The issue was investigated further.

b) To see whether facial expression indicates that quinine is experienced as less pleasant

AIM

To observe facial expression, to see if quinine is experienced as less pleasant.

INTRODUCTION

The sensation of bitterness causes babies to react in a reliable way, making fixed and innate facial changes which are found universally in children of different ethnic groups and with a wide range of physical and mental disorders (Steiner, 1979). Perl *et al.* (1992) used a similar method for people with dementia. They used a 24-point notational system to assess the gustofacial and nasofacial reactions to common tastes

and smells for example repeated blinking, lip pursing, tongue and head movements (see Appendix VI).

METHOD

The coding system (used by Perl *et al.*, 1992) was used while looking at the videotapes of people with dementia who ate the quinine and the normal biscuits.

RESULTS

Most subjects normally showed very little change in facial expression; this may be a feature of moderate and severe dementia. Even in people who still could convey emotion by facial expression no discernable change could be seen when eating quinine biscuits. Only two people showed signs of finding the quinine biscuits unpleasant. One non-hyperphagic person expressed her dislike verbally, saying it was sharp and strong but she showed no difference in facial expression between eating normal and quinine biscuits. One person who was hyperphagic initially showed no reaction when eating quinine biscuits but, on two separate test-meals, when she was close to ceasing to eat, she said it was nasty and indicated by gesture that her mouth felt unpleasant.

DISCUSSION

There is no evidence from this study that the majority of subjects with dementia find biscuits with added quinine less palatable than normal biscuits or indeed that they can distinguish between the two biscuits.

5. EVIDENCE OF DIFFERENCES IN PALATABILITY FROM EXAMINING MICROSTRUCTURE OF EATING

INTRODUCTION

From work analysing the microstructure of eating in normal people, there are several parameters which vary with changes in palatability (Bellisle, 1989). Bellisle found that decreased palatability results in a slowing of feeding patterns, mainly due to longer chewing times. The number of chews per standard bite and the average pause duration increase whereas the size of mouthful decreases. In most people with dementia chewing movements continue after the mouth is apparently empty, therefore the number of chews per bite and the pauses are not distinct enough to measure in most people. Bellisle found that chewing rate does not change with palatability so this could not be used as a measure of perceived palatability. The only practical method was to measure the size of the mouthful.

METHOD

The number of bites per biscuit in the hyperphagic and the non-hyperphagic groups were calculated for each type of biscuit. More bites (smaller mouthfuls) would be anticipated if the food is perceived as less palatable.

RESULTS

There was no significant difference between the number of bites taken for each type of biscuit for either group (paired t-test: hyperphagic group, $t = 0.47$, $df = 9$, $p = 0.65$; non-hyperphagic group, $t = 0.12$, $df = 5$, $p = 0.912$). This showed there was no significant difference in the size of mouthful taken for the two types of biscuit.

DISCUSSION

It was not possible to show any effect of palatability on food intake in people with dementia. The aim of the study was to examine the influence of palatability on food consumption, in order to test Roger's hypothesis (1994) in the setting of hyperphagia in dementia. High palatability was expected to increase the cumulative food intake curve as a result of positive feedback. There is no evidence, from this analysis of the microstructure of eating, that there is any difference between the response to the normal and the quinine biscuits in either of the groups with dementia. These investigations were taken further because the purpose was to establish a safe method of providing foods which people with dementia would perceive to have different palatability. The hope had been that these foods could then be used to investigate the effect of palatability on total food consumption of subjects with hyperphagia but because of the lack of response, and the safety limit for quinine ingestion, it was not possible to look for evidence for differing perception of palatability between the subjects at a quinine concentration considered to be safe.

Pica in dementia

Lack of response to unpalatable substances, whether through damage to the taste receptors or through inability to respond appropriately to unpleasant stimuli, may account for the frequent reports of people with dementia eating inappropriate and unpleasant substances, particularly in those who develop hyperphagia. From carers' reports, it is known that 56% of the hyperphagic group (n=18) have eaten or attempted to eat unusual substances. Pica was reported in the non-hyperphagic control group (36%, n=14). Data, from the MRC and hyperphagia studies, were

combined and tested using the chi-square test with the Yates' correction. Pica was found to be significantly more frequent in the hyperphagic group than in the non-hyperphagic group, both for eating inappropriate foods (food pica: $\chi^2 = 12.2$, $p < 0.0005$) and for non-food pica ($\chi^2 = 10.7$, $p = 0.001$). In the hyperphagic subjects, pica was significantly more common in people who were more severely demented i.e. with an MMSE score ≤ 5 ($\chi^2 = 4.6$, $p < 0.03$).

SUMMARY

These data confirm the results from other studies that the ability to detect bitterness decreases with age. Normal elderly people were still able to detect quinine but people with dementia were not able to discriminate between the two types of biscuit. However, they might not be that different from normal elderly because the methods used may be less sensitive than visual analogue scales. Nevertheless, the lack of evidence of change in facial expression or rejection of food suggests that people with dementia are unable to respond to bitter taste.

Chapter 14 IS HYPERPHAGIA A STEREOTYPY?

AIM

To assess whether the eating behaviour, which is excessively prolonged in people with hyperphagia, is an example of stereotyped behaviour.

INTRODUCTION

In this chapter hyperphagic behaviour will be examined from a different viewpoint. The experiments so far have been designed on the assumption that hyperphagia is the result of disruption of the normal mechanisms controlling food intake, for example the mechanisms underlying hunger, satiation and satiety. The question now being considered is whether hyperphagia is an example of stereotyped behaviour with the act of eating being the behaviour which happens to be repeated. The person could be locked into a loop of behaviour, not driven to eat by hunger but trapped in a fixed pattern of movements.

The concept of a stereotypy

Gelder *et al.* (1989) define stereotypy as follows:

"Repeated patterns of behaviour which persist unaltered over days, months or even years. This behaviour is carried out repeatedly when the person is not eating, drinking or asleep. It may involve repeated movements which are not goal-directed. These movements are more complex than a tic and may be repeated in a regular sequence, for example rocking backwards and forwards and rotating the trunk."

In this definition eating behaviour is explicitly excluded. The reason for this is, presumably, because mechanisms controlling food intake are thought to make the concept of stereotyped behaviour inappropriate - stereotyped patterns are at first sight applicable to behaviour which is not controlled by powerful physiological mechanisms. Certainly, if the normal mechanisms controlling food intake were broadly intact, they would be likely to override any tendency to stereotypy. For example, the repeated (stereotyped behaviour) of eating a biscuit would be overridden by the mechanisms underlying satiation. But if those normal mechanisms are faulty, then it begins to make sense to ask whether the repeated eating is stereotyped behaviour. The question arises as to whether such a hypothesis is open to empirical investigation.

Goodall and Corbett (1982) group the hypotheses about the nature of stereotyped behaviour into three categories. The first is that stereotypies increase self-stimulation, maintaining an optimum level of arousal, in people who are understimulated and who are not able to carry out alternative activities, as a result of impaired perception or environmental deprivation. The second is that stereotyped movements are the result of increased arousal produced by drives such as hunger or intense stimulation and the third hypothesis is that stereotyped movements may block further sensory input under conditions of chronic high arousal, for example in autistic children.

Stereotypy in dementia

a) Stereotypy in the literature

In a first-hand account of the onset of his own dementing illness, Robert Davis (Davis & Davis, 1989) describes how the need for ritual gives security and comfort. He also said, 'Vigorous exercise to the point of exhaustion gets my mind out of the black hole' and a 'stretch of vigorous activity helps me to clear my head.' Perhaps people in later stages of the illness, less able to articulate their feelings, still get comfort from continuous, ritualistic, and often exhausting patterns of movement.

Very little work has been done on stereotypy in dementia. There are three papers in French which have reported stereotyped behaviour. De Ajuriaguerra and colleagues (1976) noted that stereotyped behaviour, in people with dementia, often hindered eating. Meyer and colleagues (1980) noted that most demented people with hyperphagia had different types of stereotyped behaviour involving movements of the mouth. They found that some people could not stay at the table, constantly getting up and walking round the room, whereas in others stereotyped behaviour patterns of their mouth or face interrupted eating.

Richard (1987) classified types of stereotyped behaviour that he had observed in people with AD. He included an act, movement or mannerism which:

- is repeated,
- remains a uniform, monotonous and simplified action,
- appears continuously, or intermittently, after it first starts,
- is spontaneous or triggered off by other events,

- is not appropriate to the circumstances which triggered it off originally.

Richard also adds characteristics which are more hypothetical interpretations of observed behaviour referring to:

- the automaticity of the act,
- the degree of ease which triggers it off,
- its absence of finality and obvious significance,
- its compulsive nature,
- the lack of conscious, voluntary or emotional participation of the subject,
- the disappearance of the original purpose of the action,
- the apparent compulsion to move,
- the inability to improve patterns of movements or to make new movements,
- the inability to prolong or develop the repetitive action,
- the tendency towards fixation.

b) Stereotypy reported in the MRC study

In both the MRC study and the hyperphagia study, questions were asked about repeated behaviours using the Present Behavioural Examination semi-structured interview (Hope & Fairburn, 1992). Carers reported some behaviour as stereotyped but if it did not conform to Richard's criteria it was subsequently disregarded, for example reports of playing with food, stroking things or pleating clothes were not counted if the movements were not sufficiently uniform. In both studies, many different types of stereotyped behaviour were found, especially in the later stages of dementia. Some people spent much of their time making small repeated movements

such as plucking at clothing, scratching or picking at objects, real or imaginary. Others made small movements with parts of the body, tapping or rubbing hands or feet and frequently people made chewing or lapping movements of the mouth. Sometimes a word or phrase was repeated over and over again. Often the repeated behaviour was a larger movement of the body such as crossing and uncrossing legs or it involved walking. Some people incessantly searched for objects while walking or they walked with no apparent purpose in a fixed route. If space is limited, it is often difficult to tell if the route is stereotyped because there is no alternative circuit. Also if someone repeatedly tries to open doors as they come to them, it is not obvious whether it is the sight of the door which triggers an attempt to go out or whether, in spite of the lack of rhythmicity, there is a stereotyped element to the action.

It is not clear what triggers a stereotypy and whether, if it is interrupted, how soon it restarts. It is difficult to distinguish between a 'drive' and a 'stereotypy'. Excessive walking, in its own right, could be regarded as a stereotypic movement if it is apparently purposeless and unvarying in its pace. On the other hand excessively active people could have a 'drive' to walk. Sometimes this apparent 'drive' to walk seemed to conflict with the 'drive' to eat in some people with hyperphagia (see figure 11.9).

Stereotypy in other disorders

There are several disorders which are associated with stereotyped behaviour. A subgroup of people with Gilles de la Tourette Syndrome are overactive and, in addition to the tics, they make repeated, stereotyped movements which are more complex than

tics. This has been associated with dysfunction of the serotonergic system (Cohen *et al.*, 1979; Robertson, 1990).

In Prader-Willi syndrome (PWS), which is characterised by overeating and obesity, there is some evidence of repetitive behaviour. Eighty-three per cent of males and 88% of females were reported to pick their skin, frequently and deliberately, resulting in persistent sores (Clarke *et al.*, 1989) although perhaps such self-mutilation is not a stereotypy. There are also reports of hair-pulling (trichotillomania) and hair-eating (trichophagia) in PWS (Dech & Budow, 1991). These authors describe the success of using fluoxetine to treat both these symptoms and overeating. This indicates the possible involvement of 5-HT in both overeating and stereotypy in Prader-Willi syndrome.

Goodall and Corbett (1982) found that in children with severe learning disorders and autistic children stereotypy was reduced by external sensory stimulation such as flashing lights or by proprioceptive stimulation such as holding a vibrating cylinder. Perhaps external stimulation would reduce hyperphagia in dementia, although some stereotypies are exacerbated by excessive stimulation, for example loud background noise. Goodall and Corbett suggested that stereotypy could possibly be prevented by high external stimulation early in the development of the behaviour to prevent the process of fixation.

Stereotypy and neurotransmitters

Stereotyped behaviour is a characteristic of several disorders and in some cases there seems to be a link with disturbed 5-HT function.

In animal experiments, oral stereotypy and locomotor activity is induced by cocaine, amphetamine and apomorphine, a dopamine receptor agonist. Cocaine inhibits reuptake of 5-HT, as well as the other monoamines, and in small doses it decreases activity by augmenting 5-HT (George, 1989). In large doses inhibition of dopamine uptake causes stereotypy. Stereotypy, induced by increased dopamine, is reversed by the putative 5-HT_{1A} antagonist, BMY 7378 (Sharp *et al.*, 1990). At high doses the 5-HT_{1A} receptor agonist, 8-hydroxy-di-N-propylamino tetralin (8-OH-DPAT), has a postsynaptic effect producing marked stereotypy which disrupted operant food intake. These stereotypies, the '5-HT behavioural syndrome', include gnawing and chewing, forepaw treading, head weaving and flat body posture hindlimb abduction. In low doses 8-OH-DPAT induces hyperphagia, in short-term experiments in non-deprived rats. Ebenezer (1992) has suggested that this is because of its presynaptic action, as a cell-body autoreceptor agonist it suppresses the firing of serotonergic neurones, decreasing brain 5-HT neurotransmission.

There appears to be a complex relationship between stereotypy, dopamine and 5-HT function. If hyperphagia in dementia is the result of stereotypy there could be a connection with 5-HT disturbance.

Stereotypy in hyperphagia in dementia

The concept of stereotypy is complex. It refers to repeated, purposeless behaviour. Although eating behaviour would not normally be classified as a stereotypy because of physiological control it could be meaningful to ask whether hyperphagia in dementia is an example of stereotyped behaviour because this is a group of people in whom normal physiological control is very much weakened. But the question remains as to whether the issue of hyperphagia as a stereotypy can be empirically investigated. I believe it can. This question was examined in two ways.

Eating might be one aspect of a general tendency for repeated patterns of behaviour. If overeating is an example of stereotypy it might be expected to be associated with other repeated behaviours. People with dementia who are hyperphagic might show more patterns of stereotyped behaviour than non-hyperphagic matched controls. To investigate this, evidence of other types of stereotyped behaviour, was collected from carers' reports, and also by direct observation, to see if the prevalence was significantly different from matched, non-hyperphagic, demented controls.

Secondly, if prolonged eating is a stereotyped pattern of behaviour, the initial pattern of eating, once a meal starts, may be perpetuated in a fixed 'loop' of motor actions which continue as a stereotyped pattern of behaviour rather than being driven by hunger. If this is the case, then one might expect that the behaviour could be interrupted or perhaps eating movements could be replaced by another form of stereotyped behaviour if there is no 'drive' to return to the original behaviour.

A. DESCRIPTION OF STEREOTYPED BEHAVIOUR

AIM

To record the different types of stereotyped patterns of behaviour reported by carers and observed directly. To calculate the prevalence of these behaviours in dementia and to see if there was an association between stereotypy and hyperphagia.

METHOD

(i) Carer's report

The PBE semi-structured interview was used to identify types of stereotyped behaviour (questions 193,194,195, 201, 203, 206, 207 and 210). This method was used to quantify the numbers and types of stereotyped behaviour seen in an individual. To compare the frequency of stereotyped behaviour seen in the hyperphagic with those in the non-hyperphagic group, the numbers of stereotypes reported by carers in the first interview were analysed. To look at the range of behaviour the total numbers of behaviour patterns, reported and observed, during the course of the study were analysed.

(ii) Direct observation

In order to measure frequency and periodicity of the reported stereotyped behaviour, measurements were made by direct observation. This was done using the recordings of the test meals and, in addition, on a separate occasion, four subjects were observed continuously for up to six hours, from the time they got up in the morning until the midday meal. This allowed more detailed recording of longer behaviour patterns and also types of behaviour which were not seen during meals.

Behaviour was defined as stereotypic if it followed a set pattern and was observed to occur repeatedly on at least two separate occasions or if it was reported to happen on half the days or more over a period of at least a month. Behaviour was usually unvarying, for example leg crossing or empty chewing, but it was still considered to be stereotyped despite some adaptation to the environment i.e. the form the action took changed with circumstances. For example an excessively active woman, in the hyperphagic group, walked in a set pattern round the nursing home when the doors were locked. When the doors were unlocked she followed a different, stereotyped route round the house and garden. If something occurred which partly blocked her route she would adapt her route rather than slow down or wait. Another example was seen in an overactive man, also in the hyperphagic group. Normally he walked continuously but when sitting at a table, for the test meals, he crossed and uncrossed his legs regularly throughout the meal (see Appendix VII). If he was further restricted, with his legs under a low table, with no room to cross his legs, he shuffled his feet backwards and forwards rhythmically.

RESULTS

The prevalence of stereotyped behaviour

When the results of the first interview were analysed, 11 out of 17 carers (65%) of people who were hyperphagic and 6 out of 13 carers (55%) of the carers of non-hyperphagic demented controls reported at least one pattern of stereotyped behaviour. Using t-test and chi-square test, the difference between the hyperphagic and non-hyperphagic groups was not significant (chi-square: 0.415, $p = 0.52$). If the number of behaviour patterns were considered, the mean number was 1.06 patterns for the

hyperphagic group and 0.77 for the non-hyperphagic group, this difference was not significant.

The types of behaviour were categorised into large movements (e.g. walking or repeatedly standing up and sitting down); small movements (e.g. tapping, rubbing, pleating fabric) and stereotyped verbal utterances (e.g. phrases, noises, counting). This is summarised in table 14.1 and suggests that it is large movements and verbal categories which account for the increased number of stereotypies in the hyperphagic group.

Table 14.1 Categories of stereotyped behaviour reported in first interview - with number of subjects in each group (percentage in brackets)

Group	Large move- ments	Small move- ments	Verbal
Hyperphagic demented group (n=17)	7 (41%)	4 (24%)	5 (29%)
Non-hyperphagic demented controls (n=13)	0 -	6 (46%)	0 -

There was a difference in the type of stereotypy, the non-hyperphagic group only showed small stereotyped movements whereas the hyperphagic people included verbal stereotypies and large movements such as repetitive walking routes. The probability of having large stereotyped movements is greater in hyperphagic subjects (Fisher's exact test 1-tail: $p = 0.0096$) and people with hyperphagia are significantly more likely to have verbal stereotypies (Fisher's exact test 1-tail: $p = 0.043$). There is no indication of a difference for small stereotyped movements.

As the numbers were small, the total range of behaviour in the hyperphagic group, reported or observed directly during the whole course of the study, was examined (table 14.2).

Table 14.2. Types of stereotyped behaviour (reported and observed) in the hyperphagic demented group during the course of the study

Part of body involved	Hyperphagic demented group (n=18)
Head empty chewing movements scratching/rubbing/picking lapping movements of mouth teeth grinding sucking or chewing fingers	6 1 1 1 2
Hands folding or pleating fabric scratching or rubbing skin repetitively moving objects tapping/clapping	1 1 1 2
Legs foot shuffling - seated leg crossing/swinging - seated shuffling pattern - standing walking along a fixed route apparent compulsion to walk (route is not stereotyped)	1 2 1 3 4
Voice repeated word(s), noises repetitive counting	5 2

Stereotypy was frequently observed in both groups of people with dementia. There was a trend for stereotyped behaviour to be more frequent in the hyperphagic group and for the patterns of stereotyped behaviour to be more diverse and more severe than in the matched non-hyperphagic control group. Nearly all the stereotypies in the non-hyperphagic group were intermittent, only lasting for less than a minute at a time. When observed periodically, over a period of a year or more, the patterns of

stereotyped behaviour patterns were apparently stable over time although the rate might change. If the behaviour was interrupted its form could be modified, for example a walking route might change if the route was obstructed. Although only small numbers of people were observed, patterns of behaviour seem to become more rigidly fixed with time but may become less complex as the illness progresses.

The types of stereotyped behaviour, reported and observed, in the non-hyperphagic group were all in the small movement category and were mainly movements of the hands. This is a qualitative measure and may not be valid as the period of observation was usually less in the non-hyperphagic groups as they received fewer meals and fewer interviews with carers.

No stereotyped patterns of behaviour were observed in the normal controls.

B. INTERRUPTION EXPERIMENT

AIM

As stereotyped behaviours can often be interrupted by alternative activities which are stimulating such as meals, walking or conversation, the aim was to see if continued eating is also a form of stereotyped behaviour which can be interrupted by another activity.

INTRODUCTION

There is a difference between a 'drive' which has a physiological purpose and a stereotypy which is not goal-directed. When people who showed stereotypies were observed, they usually stopped or the pattern changed its nature if there was an interruption. If hyperphagia is due not to increased hunger but to stereotyped behaviour, an experiment might show if eating could be stopped or even replaced by another activity and to see if hyperphagia is diminished if eating is interrupted. This experiment assumes that a stereotypy will not restart immediately after a distraction.

METHOD

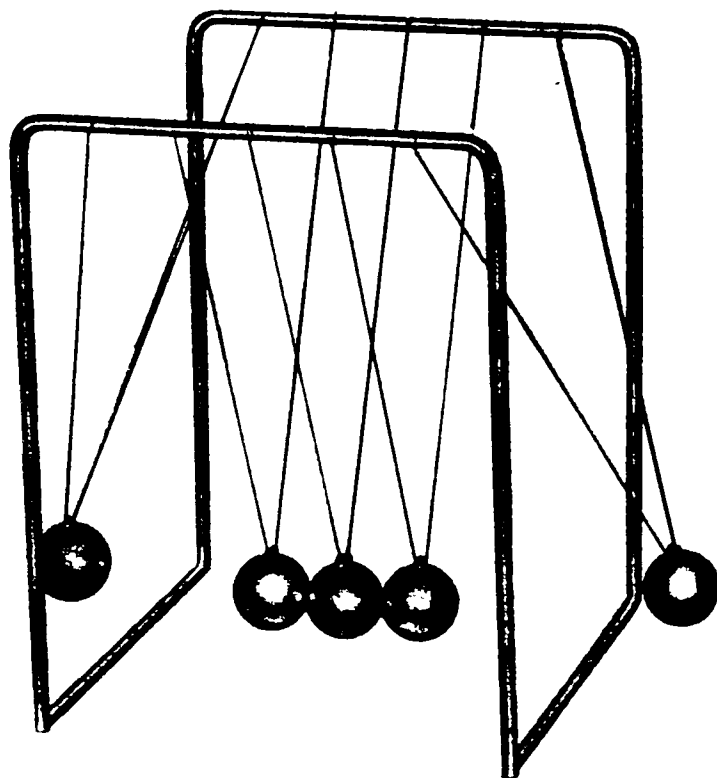
A method was devised to see if eating could be stopped by transferring attention to another activity. A sedentary distraction was needed which would attract the attention of people at all stages of dementia. It therefore needed to be eye-catching but without necessarily needing good eyesight, concentration or coordination. A shiny Newton's cradle was used; even with poor eyesight the shining, moving balls could be seen (figure 14.1).

Each time the cradle was presented the behaviour of the subject was rated. A rating of 1 was given if people continued to eat, whether or not they played with the cradle at the same time, or if eating stopped, they resumed unprompted in less than three minutes. A rating of 2 was given if they transferred stereotyped behaviour to Newton's cradle and did not resume eating in less than three minutes. A rating of 3 was given if other behaviour replaced eating e.g. falling asleep or walking away.

The latency period, before eating began, was measured from the videorecordings and

the latency, until eating restarted, was noted after each presentation of Newton's cradle.

Figure 14.1 Newton's cradle



Nine people who were in the hyperphagic demented group were tested, all but one of whom showed at least one pattern of stereotyped behaviour (not including eating behaviour). The ninth person was overactive, although he did not follow a stereotyped route.

A standardised digestive biscuit meal was given to each of the subjects as described in Chapter 9. The subject was allowed to eat five biscuits without interruption to establish the rhythm of eating, then the plate of biscuits was unobtrusively moved to one side but still within reach. Newton's cradle was put in front of the subject and the balls were set in motion. Subjects were encouraged to use it. Their attention was

continually drawn to it, both verbally and by actions, to distract them from eating. If they resumed eating the process was repeated after they had again re-established a rhythm of eating, after approximately another five biscuits. This was continued until they stopped eating or they were considered to have eaten excessively.

RESULTS

Most subjects appeared to watch the bright moving objects but the majority continued to eat, with or without a pause, while still watching the cradle (see table 14.3).

Table 14.3 The effect of Newton’s cradle on eating behaviour

Subject number	Initial latency (s)	Number of trial with Newton’s cradle						Number of biscuits eaten
		1	2	3	4	5	6	
036	10	1	1	1	1	1	-	27
037	117	1	1	1	1	1	1	28
019	0	2	2	-	-	-	-	15
007	288	3	1	1	-	-	-	11
009	7	1	1	1	1	-	-	20
049	78	2	2	2	-	-	-	13
052	28	1	1	1	-	-	-	20
042	9	3	-	-	-	-	-	6
031	-	1	1	-	-	-	-	13

Key

- 1 - Continues to eat, plays with cradle but eats at the same time or stops eating but resumes unprompted in <3 minutes.
- 2 - Interrupted or transfers stereotyped behaviour to Newton’s cradle and does not resume eating in <3 minutes.
- 3 - Other behaviour replaces eating e.g. falls asleep or walks away.

The latency periods, before eating resumed, during the meal did not change as the meal progressed (see table 14.4).

Two overactive people (052, 042) started to get up when the biscuits were removed, and one less mobile person fell asleep, the rest were interested in the balls to a greater or lesser extent. Two people (019 and 049) both had difficulty in focusing their attention on the cradle. They did not transfer their behaviour to playing with the cradle but sat still and did not resume eating within 3 minutes. However, no-one could be encouraged to transfer the stereotypy to Newton’s cradle. One of the more severely demented tried to move the balls to his mouth (009) and another tried to put them in her water glass (007).

Table 14.4 Latency periods throughout meal

Subject number	Initial latency (time to nearest half minute)	Latency after presentation of Newton’s cradle before eating resumes (time to nearest half minute)					
		1	2	3	4	5	6
036	0	0	0	0	0	0	-
037	2.0	0	0	0	0	0	0
019	0	3.5	3.5	-	-	-	-
007	5.0	10.5	0	0.5	-	-	-
009	0	0	1.0	2.0	1.0	-	-
049	1.5	6.0	7.0	6.0	-	-	-
052	0.5	0.5	3.0	3.0	-	-	-
042	0	N/A	-	-	-	-	-

DISCUSSION

It was argued in the introduction that the concept of stereotypy could, in theory, be applied to hyperphagia, i.e. hyperphagia could be regarded as resulting from the continual repetition of the act of eating. This would only apply if the physiological mechanisms which normally control food intake were weak or non-existent. The experiments reported earlier in this thesis strongly suggest that, in people who are

hyperphagic, the mechanisms of satiation and satiety are weak, or at least highly abnormal. However, the finding, reported in Chapter 11, that the latency period (the time between availability of food and the onset of eating) for hyperphagic subjects was much less than for the non-hyperphagic demented controls provides some evidence that in hyperphagic subjects the hunger mechanism is intact (and indeed may be stronger than in normal subjects). Given this, it may be questioned whether the possibility that hyperphagia is a stereotypy is tenable. However, since no other way of assessing hunger in these subjects could be devised, and given the marked abnormality in other control mechanisms, it seemed premature to rule out the possibility that hyperphagia is a stereotypy.

The Newton's cradle experiment was an attempt to investigate the question experimentally. It was reasoned that if hyperphagia is an example of stereotyped behaviour, then, if the behaviour were interrupted one would not expect the person to return quickly to eating. If hunger was driving eating then a rapid return to eating would be expected. It is not clear whether normal examples of stereotyped behaviour are like this but the idea conveyed by stereotypy is of being 'caught in a rut'. During the Newton's cradle experiment most subjects quickly resumed eating after the attempted interruption (as shown by table 14.4). The four people who did not resume eating within 3 minutes were the least hyperphagic. During the course of the meal, the latency period, before eating resumed, was short in most people and the period did not lengthen as the meal progressed. This also indicated that they remained hungry and did not show signs of satiation. Therefore this experimental design may give a way of plotting hunger through the meal as the short post-interruption latency

suggests a definite 'drive ' to eat. The other way of investigating whether excessive eating is stereotyped behaviour is to see if it is associated with other, more accepted ideas of stereotyped behaviour. This is weaker evidence as association does not necessarily imply the same mechanism.

The varied pace of eating, the searching for biscuits when they are moved to one side, and the general lack of automatism in the pattern of biscuit-eating, also points to eating being driven by hunger rather by stereotyped actions. Although not easy to prove categorically, the evidence points to hyperphagia being the result of increased hunger rather than stereotypy. The greater incidence of stereotypy in the hyperphagic group might be a response to increased arousal produced by hunger rather than hyperphagia being the result of stereotypy.

Chapter 15 THE NATURAL HISTORY OF HYPERPHAGIA

AIM

To determine the natural history of the phenomenon of hyperphagia in people with dementia.

INTRODUCTION

There has previously been no study investigating the natural history of eating changes in dementia. A retrospective study by Morris *et al.* (1989) established that 26% of a sample of people with AD showed signs of eating more at some stage in the dementing illness. There are a few reports of excessive eating in dementia in the literature (Reeves & Plum, 1969; Meyer *et al.*, 1980) but no indication of the natural history of the changes. The long-term prospective MRC study of behaviour changes in dementia has provided unique data, charting behaviour changes over many years, often from the early stages of dementia until death. Carers' reports of changes in eating behaviour have been described in Chapter 7. These show that various forms of increased eating are commonly found at some stage in the course of dementia.

The most common change, is to eat more sweet food when it is available. About a third of people, who are demented, have been reported to eat more unless restricted, to eat more than premorbidly at some stage and to show signs of wanting more food. Reports are not always reliable as each subject has a different carer and also, when people with dementia enter an institution, the new carers cannot make a comparison

with premorbid or pre-institutional food intake. Furthermore, in institutions individual carers do not have the 24-hour knowledge of the person's behaviour. It is difficult to tell whether someone is still hyperphagic if food is restricted and access to extra food is prevented.

In this thesis, I have proposed an objective way of measuring hyperphagia precisely. This has provided the opportunity of following a cohort of people over a period of time and measuring the degree of hyperphagia directly. In this chapter, data are reported on the natural history of dementia collected in two ways: first the results from direct observation and secondly the results on a larger sample from carers' reports.

1. EXAMINING THE NATURAL HISTORY OF DEMENTIA BY DIRECT OBSERVATION

METHOD

All subjects, who during the course of the studies reported in this thesis exceeded the threshold of 3337 kJ during a mixed meal were followed up for the longitudinal study. They were given identical mixed meals at four-monthly intervals during the course of the study. At the same time their carers were re-interviewed. Energy intake, macronutrient intake and sweet food intake were calculated as described previously (Chapter 10). Subjects were weighed at the time of each four-monthly test-meal.

RESULTS

The number of follow-up meals was variable, depending on when people entered the study. The most recently recruited subjects had only one mixed meal but the first subjects had up to four follow-up meals. Ten people were followed up for at least a year and the results for one year are shown in tables 15.1, 15.2 and figure 15.1.

Table 15.1 Changes in intake of 10 hyperphagic subjects followed for a year

Subject number	First mixed meal	4 months	8 months	12 months
036	8970	6758	8799	4601
037	9813	11117	8023	9359
019	7348	3134	4358	6025
007	6965	7337	4836	6890
009	9439	10141	9580	5427
049	2973	2620	3680	1651
052	7357	5881	4633	2843
042	4610	1037	1472	1054
047	3520	1574	1759	2307
031	5835	3507	5531	2985

Mean intake of normal elderly controls = 1822 kJ
 Mean intake of normal elderly controls + 1 S.E. = 2327 kJ
 Mean intake of normal elderly controls + 1 S.E. = 2832 kJ
 Mean intake of normal elderly controls + 1 S.E. = 3337 kJ (threshold for hyperphagia)

Table 15.2 Change over time (mean results for 10 hyperphagic subjects)

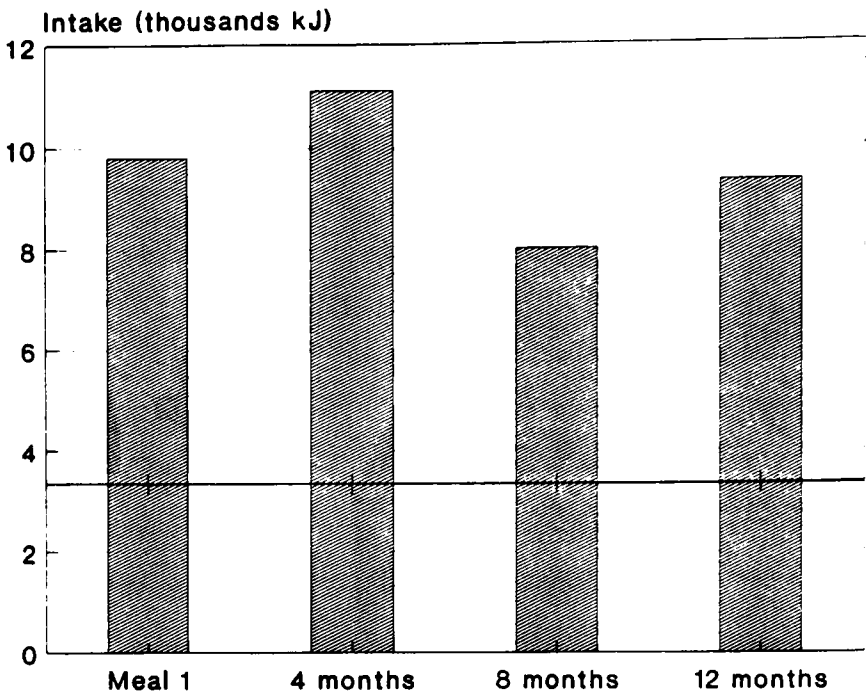
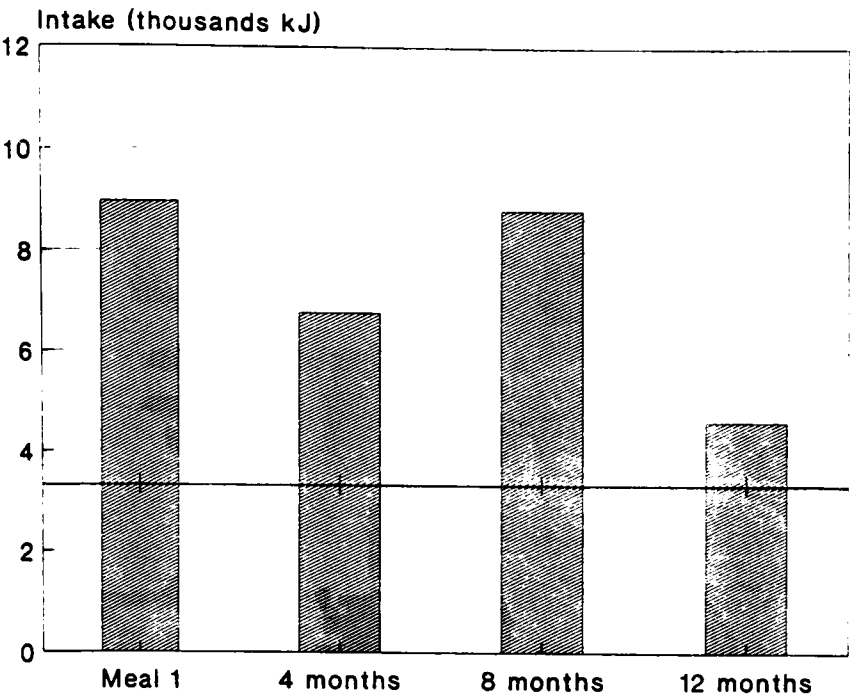
Mean results (n = 10)	First meal (time 0)	4 months	8 months	12 months
Total kJ (mixed meal)	6683	5311	5267	4314
Latency period (s) [median]	82 [7]	61 [70]	39 [8]	106 [61]
Meal length (minutes)	81	67	67	61
Sweet food intake (kJ)	2192 [30.6%]	1644 [26.7%]	1508 [27.2%]	968 [19.0%]
Protein (kJ) [%]	871 [13.3%]	686 [13.2%]	687 [12.2%]	785 [20.1%]
Fat (kJ) [%]	3519 [51.8%]	2583 [50.0%]	2616 [49.0%]	2170 [50.6%]
Carbohydrate (kJ) [%]	2292 [34.9%]	2048 [36.9%]	1964 [38.8%]	1359 [29.3%]

The results were analysed using paired t-tests. Over the course of a year, the mean intake at each successive test meal decreased and also meals ended earlier. Of the 10 people followed through for a year, 9 exceeded the threshold for hyperphagia (3337 kJ) at the first meal, 6 exceeded it after 4 months, 8 after 8 months and 5 after a year. There was a significant correlation between the intake of individuals between each meal ($p < 0.01$) but the mean of the energy of the meal after 4 months was significantly less than the first meal ($t = 2.36$, $df = 9$, $p = 0.04$), and after 8 months the difference was greater ($t = 3.2$, $df = 9$, $p = 0.01$) and after a year the mean was reduced to 65% of the original intake ($t = 4.5$, $df = 9$, $p = 0.002$).

There was no significant change between the eating rates during any of the 4 meals over the course of the year but there was a significant correlation in the eating rate in individuals between the meals. The difference in intake was accounted for by the

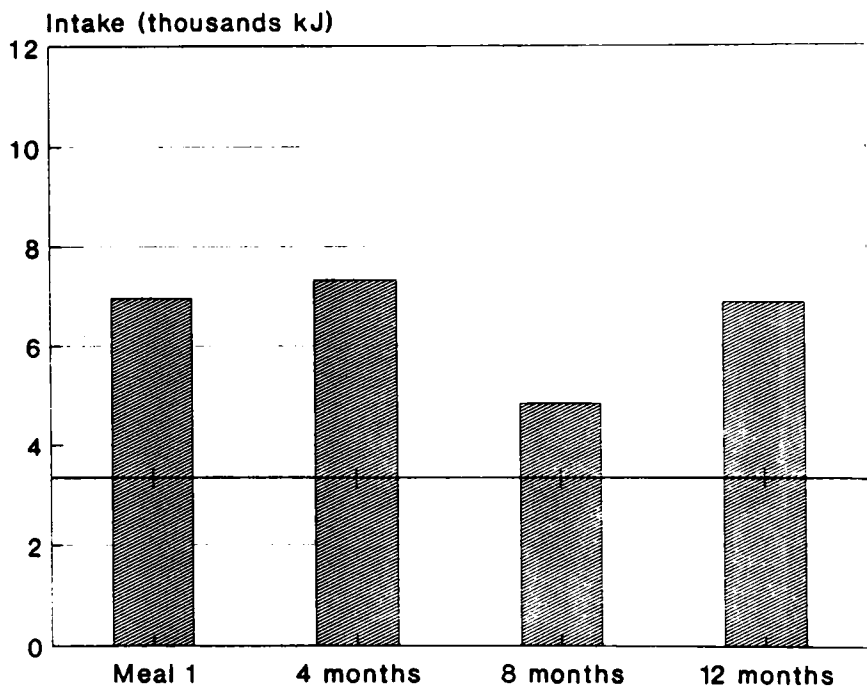
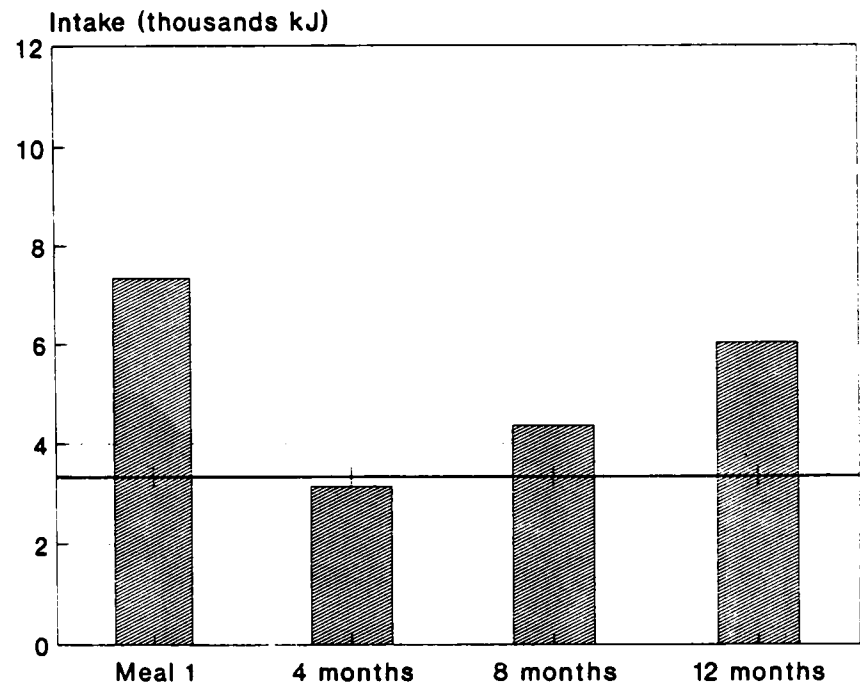
Figure 15.1 INDIVIDUAL GRAPHS
036

Threshold for hyperphagia —+—
037



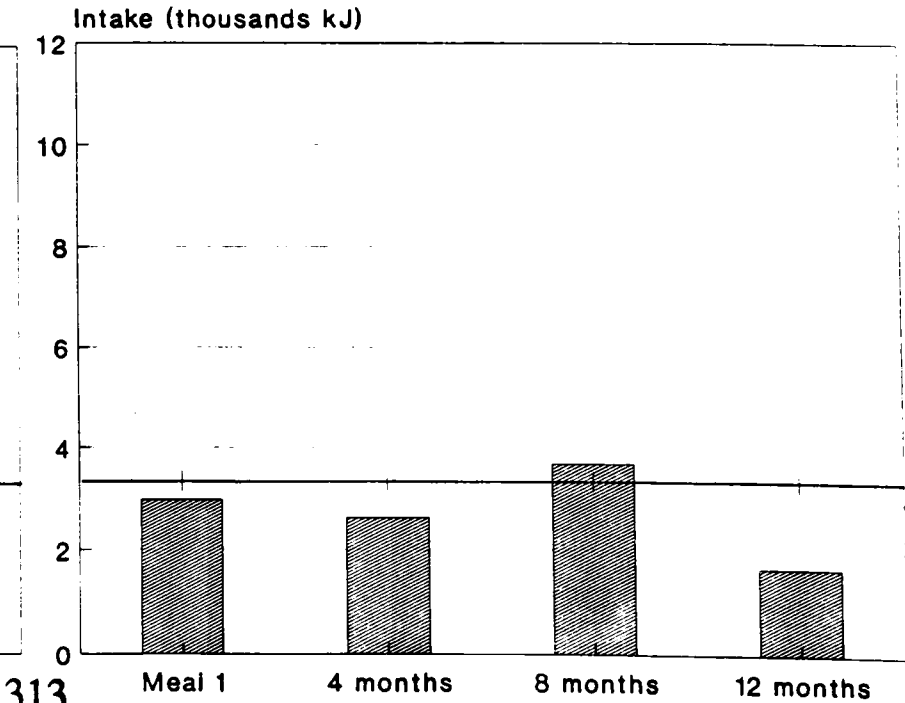
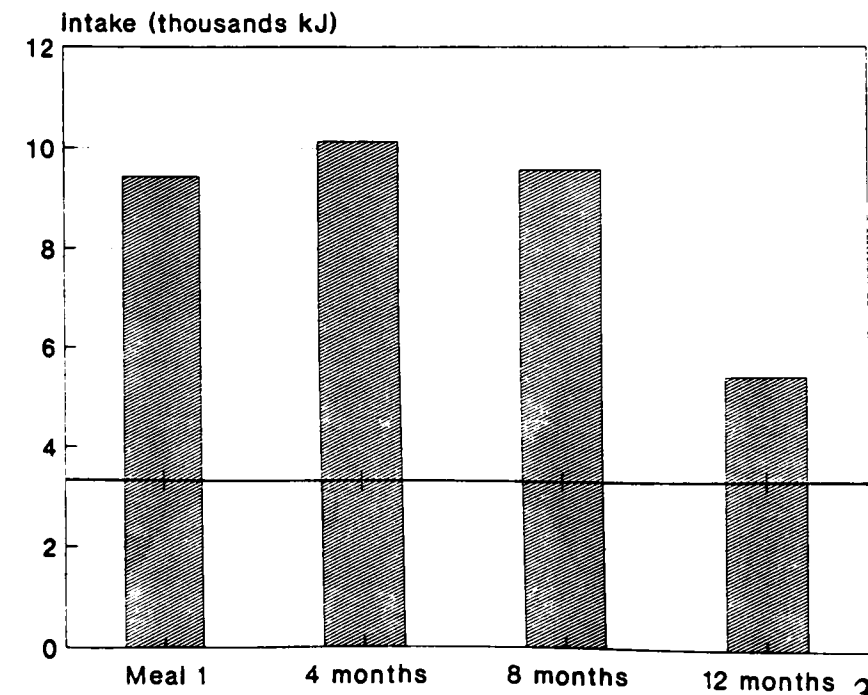
019

007

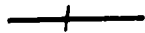


009

049

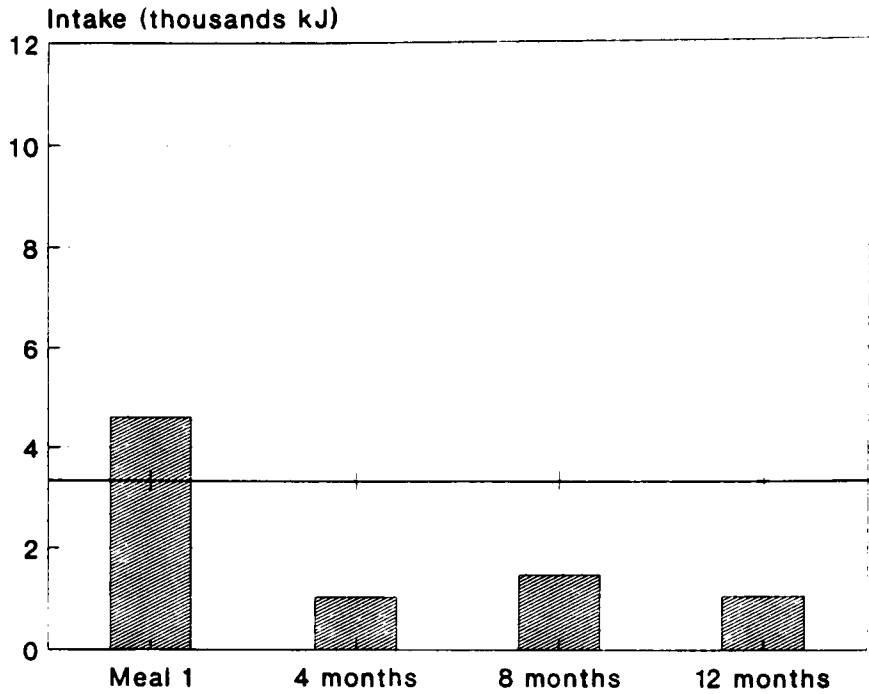
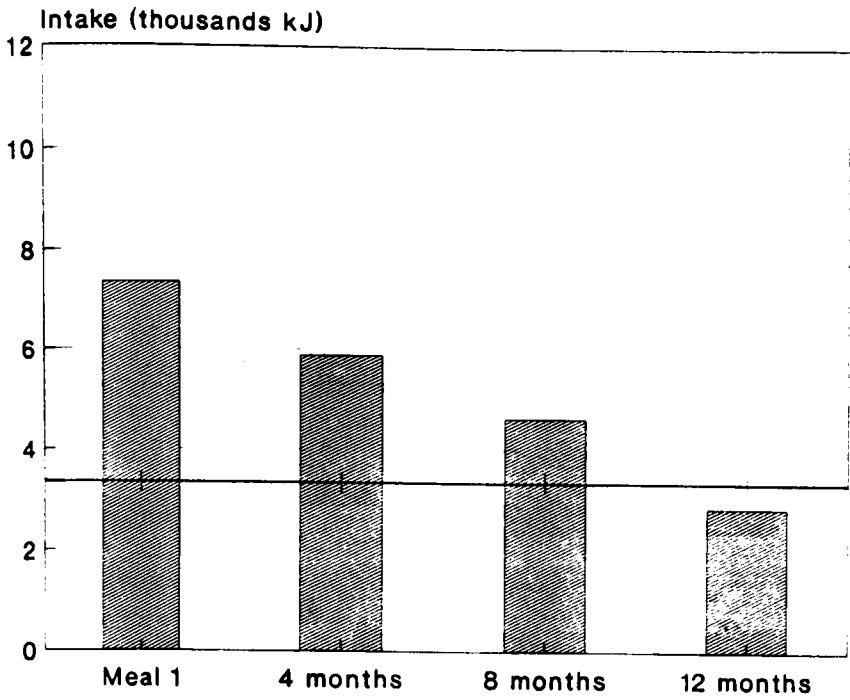


Threshold for
hyperphagia



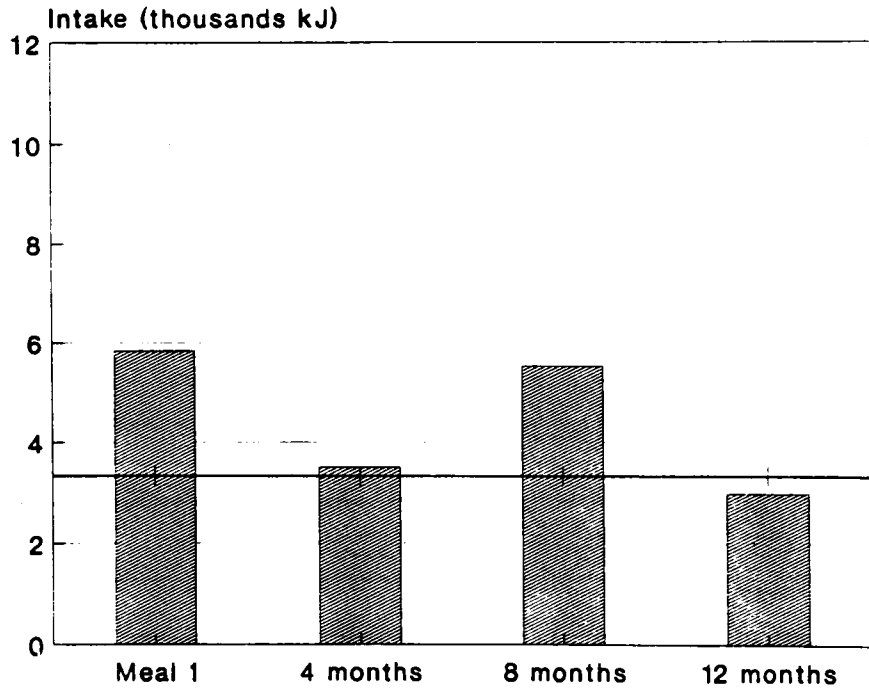
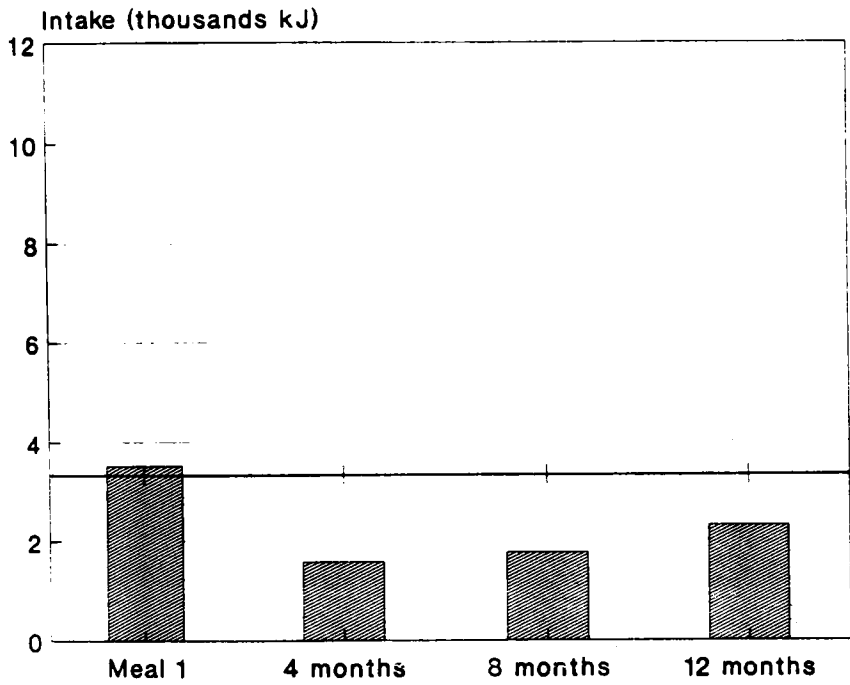
052

042



047

031



The macronutrient and sweet food intake were measured in terms of energy value and also as a percentage of the total meal (see table 15.2). The difference for the percentage intake for each of the food types was not significant between the beginning and the end of the year. Total energy intake decreased during the course of the year. Protein intake remained almost constant in terms of energy value but dropped and then rose sharply, as a percentage of the total intake, a year after the first meal, when 4 of the ten people ate over 25% of their energy intake as protein.

A record was kept of the body mass at each test meal (see table 15.3).

Table 15.3 Changes in body mass (kg) over time
(10 hyperphagic subjects followed for a year)

Subject number	First meal	4 months	8 months	12 months
036	46.0	51.0	51.5	-
037	53.0	53.5	55.5	58.0
019	70.0	70.5	73.5	74.9
007	67.0	65.0	57.5	56.0
009	81.0	↓	↓	↓
049	63.5	63.0	-	56.0
052	58.5	54.0	62.0	63.0
042	67.0	66.5	71.9	-
047	71.5	74.0	75.0	76.0
031	75.0	72.0	73.0	68.0

It was not possible to weigh some subjects who were severely demented or unable to stand. In some cases there was an obvious decrease in mass (recorded by arrows in the chart). Six subjects gained weight during the study and four lost weight but this did not correspond to changes in activity (two became overactive and lost weight and one became more active and gained weight).

At least three of the cohort became so overactive that it was difficult for them to settle long enough to eat. Two of the ten people died suddenly while still hyperphagic. Two others were hyperphagic until they declined rapidly and died. Others have remained stable or showed a gradual decline in appetite.

2. SUMMARY OF CARERS' REPORTS OF HYPERPHAGIA FROM THE MRC STUDY

INTRODUCTION

In order to obtain information about a larger number of subjects and also to chart the natural history from the onset of hyperphagia, data from the MRC study were analysed.

There is some evidence of abnormal eating in the normal population. For example a national survey by mail, in the USA, gave prevalence estimates of some deviance in food selection (Rozin, 1989). Non-food pica was reported in 4%. Food craving, was listed for at least one food by 70% of subjects. Food craving, in this study, was defined as " . . . a strong desire for a particular food or drink. This desire is so strong that it will cause a person to go out of his or her way to satisfy the craving." Sweets, vegetables and animal foods were among the most commonly craved items. Sweets and fruit were particularly craved during pregnancy. However, the data on people with dementia suggest that the abnormal eating patterns are more prevalent and more severe than those found in the general population.

METHOD

Subjects

The subjects for this study were from the MRC longitudinal study described in Chapter 7. There were 104 subjects in the cohort and, at the beginning of the study, they were living at home with a carer.

Data collection

Data were collected from carers at four-monthly intervals using the Present Behaviour Examination - PBE (Hope & Fairburn, 1992). The eating section (see Appendix I), and other relevant data from the PBE, were analysed together with information from the Past Behaviour History Interview (PBHI). The PBHI covers behaviour from the onset of the dementia up to the point of entry into the study (see Chapter 7). Data for the whole MRC cohort were analysed, using both PBHI and PBE information, to examine the differences in eating behaviour between the hyperphagic group and the non-hyperphagic group and to estimate the onset, duration and outcome of hyperphagia in the hyperphagic group.

Reports of excessive walking and the drug record at each interview were analysed to see if there was a relationship with hyperphagia. The relationship between physical aggression and hyperphagia was also examined as both aggressive behaviour and overeating might have a common cause i.e. reduction in 5-HT.

Definition

The operational definition of hyperphagia, for both the hyperphagia and the MRC

studies, was derived from the answers to some of the eating section questions of the PBE (see Appendix I). Subjects were defined as being hyperphagic if they showed signs of wanting more food, either by searching or asking for more (i.e. if PBE questions 74 or 75 were rated 3 or more), or if carers reported that subjects ate distinctly more than normal when extra food was available (i.e. question 70 was rated 4, or either of questions 76 or 77 was rated 2 or more). A single incident, which was isolated and apparently atypical, was not counted.

RESULTS

Duration of hyperphagia

Using the criteria above, 24 of the 104 subjects (23%) in the MRC study showed evidence of hyperphagia at some stage in the illness. Fifteen subjects were men and 9 were women, this did not differ significantly from the hyperphagia study. Estimates of the duration of hyperphagia are shown in table 15.4 and figure 15.2. The mean duration was 31.5 months (S.D. 23.1).

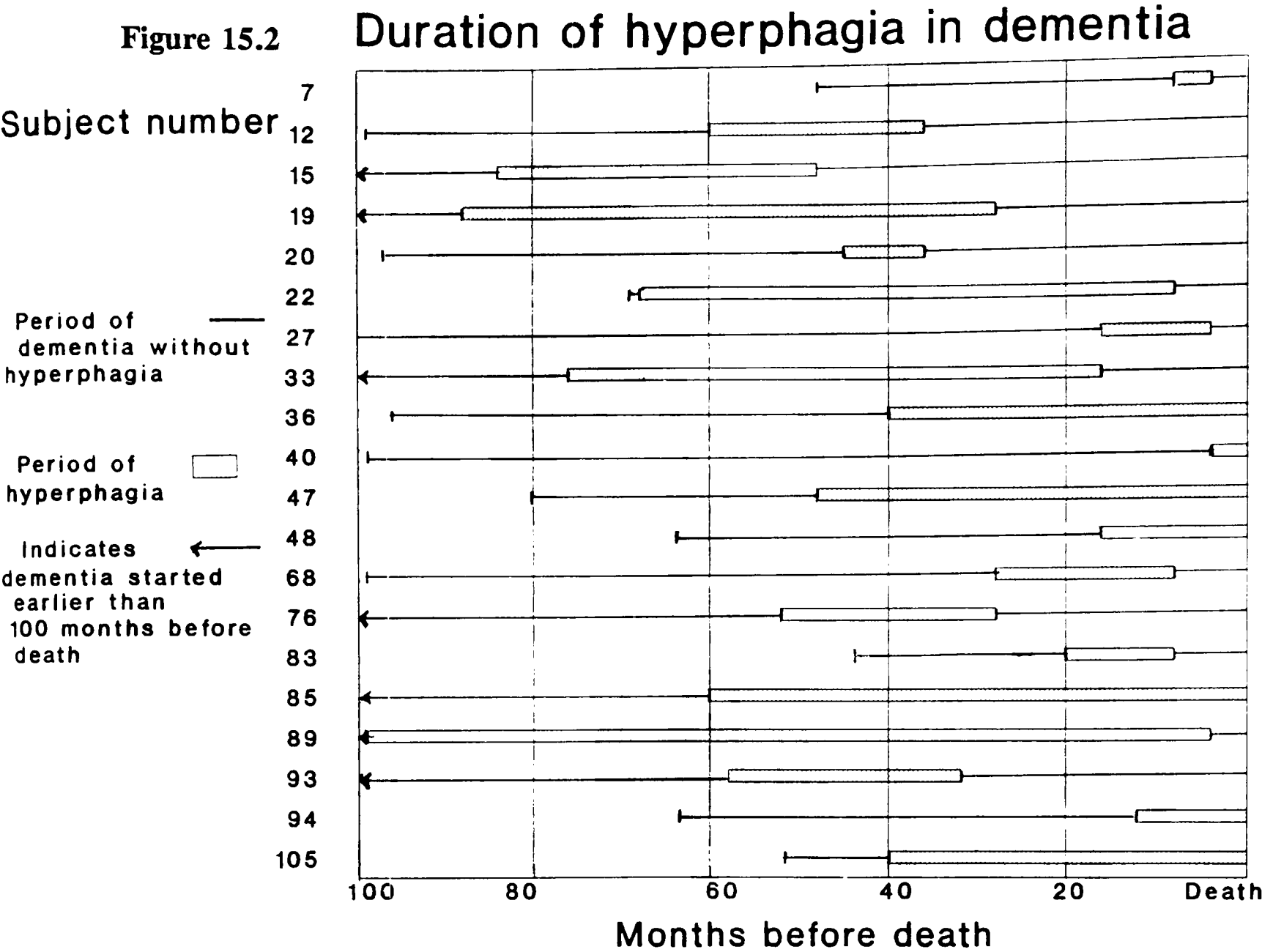


Table 15.4 Duration of hyperphagia in MRC study subjects

a)

Mean MMSE at onset of hyperphagia	13.5	(S.D. 8.48)
Mean MMSE at end of hyperphagia	7.7	(S.D. 7.61)
16.7% showed the symptoms for less than 12 months 20.8% showed symptoms for 1-2 years 25.0% showed symptoms for 2-3 years 12.5% showed symptoms for 3-4 years 4.2% showed symptoms for 4-5 years 20.8% showed symptoms for more than 5 years		

b)

Cumulative data (%)	Minimum duration
83.3%	> 1 year
62.5%	> 2 years
37.5%	> 3 years
25.0%	> 4 years
20.8%	> 5 years

Comparison between hyperphagic and non-hyperphagic group

Table 15.5 summarises the results of comparing those subjects who were hyperphagic at some stage of the dementia with those who were not. None of the eating related items, shown in table 15.5, was used as a criterion for the hyperphagic group.

Table 15.5 MRC STUDY Comparison of non-hyperphagic and hyperphagic group - PBHI and PBE data
(Significance levels between the two groups were calculated using chi-square test. N/S - no significant difference.)

	Non-hyperphagic group (n=80)	Hyperphagic group (n=24)
Sex ratio	M 50.0% : F 50.0%	M 62.5% : F 37.5% (N/S)
Age at onset	72.8 years	71.5 years (N/S)
Reported to walk excessively	34%	50% (N/S)
Physically aggressive	60%	79% (N/S)
Medication likely to increase eating	48%	63% (N/S)
Food restricted by carer	20%	58% (p = 0.0007)
Eating less then premorbidly at some stage	64%	75% (N/S)
Pica - non-food	16%	42% (p = 0.019)
Pica - inappropriate food	9%	38% (p = 0.0019)
Changed choice	38%	79% (p = 0.0008)
Oral behaviour	3%	29% (p = 0.0003)

The items for which a significant difference was found between the groups were restriction of food by the carer, pica (both food and non-food), change in food choice and oral behaviour

Hyperphagia and overactivity

Of the 12 people in the hyperphagic group who were reported to be overactive, ten were both overactive and hyperphagic at the same time.

Hyperphagia and drugs

At some time during the course of the PBE interviews 53 out of the cohort of 104 were taking drugs of a type which could increase eating. These drugs were taken by 63% of the hyperphagic group and 48% of the non-hyperphagic group. This difference was not significant (chi-square: 1.12, $p = 0.029$). Of the 9 people in the hyperphagic group who were taking these drugs at the same time as they were reported to be hyperphagic, 5 were hyperphagic before the drugs were prescribed.

Hyperphagia and aggression

Of the 24 people categorised as hyperphagic, 21 were more physically aggressive than premorbidly, at some stage. For three of them physical aggression and overeating did not occur at the same time, the overeating appeared first and aggressive behaviour came later. In 18 people the two types of behaviour overlapped. In 7 overeating was reported first, in 7 physical aggression was first and in 4 they started at the same time. In the PBHI, the different types of aggressive behaviour were not recorded, therefore only the PBE data were used. There was no significant association between hyperphagia and physical aggression (chi-square - after Yates' correction: 2.18, $p = 0.14$).

DISCUSSION

The experiments reported in this chapter were aimed at examining the course of hyperphagia in dementia. Data were collected in two ways, by direct measurement and from carers' reports from the MRC study. Both methods had some shortcomings.

Direct measurement

Because of the time-consuming method of giving test meals, the number studied was small. There was some unreliability in the test-retest data which probably makes individuals look as though they vary more than they do (but this variability should be less important in group means). This group only entered into the study once they had clearly been recognised, by the carer, as hyperphagic, therefore this study is only looking at the natural history once subjects are established hyperphagics (possibly once they are at, or past, the 'peak'). This method gives no experimental information on the onset or overall course of hyperphagia, although there is indirect evidence from carers' reports. Its main value is in looking at the pattern of the decline of hyperphagia.

MRC study

The carers' reports provide a picture of the whole course of hyperphagia. The major limitation is the validity of each carer's report and the lack of quantification. The criteria for defining hyperphagia from the PBE data treats it as a category but, as discussed in Chapter 9, the evidence suggests hyperphagia is not a categorical concept. The direct measurement study suggests, whether or not it is a category, that

there is a gradual decline over a long period, i.e. there is no definite offset. In addition, information was collected both from prospective data and from past history. These are both included to provide a picture over the entire course of dementia but with retrospective data there is a greater problem of validity.

However, putting data from both studies together, it gives a picture of the natural history of hyperphagia over the entire course of dementia.

1. At what stage in dementia is the onset of hyperphagia?

Onset can be given in three ways:

(i) Mean MMSE score

In the MRC study, the MMSE at onset was not known if hyperphagia began before the study started and it was reported during the PBHI when figures for the MMSE were not available. Therefore the data are biased, systematically tending to underestimate the influence of early onset hyperphagia. The mean MMSE score at the onset is therefore the minimum figure. From the MRC data it seems that the onset of hyperphagia occurs in the middle stages of dementia (mean MMSE 13.5, interquartile range 7-20) although it varied widely, from being one of the first signs of the illness to starting 19 years after the beginning.

(ii) Mean onset in years from the onset of dementia

The problem with this is the difficulty of determining both the onset of dementia and the onset of hyperphagia. From the best evidence, the mean onset is 5.4 years after

the onset of dementia.

(iii) Mean onset as time before death

The measurement of the onset as time before death gives a clearer comparison point but it is less meaningful because death occurs at a variety of points in dementia. From the MRC data the mean onset of hyperphagia before death was 46 months (S.D. 28.3, $n = 20$).

2. What is the course of hyperphagia in dementia?

Duration of hyperphagia varied, ranging from 4 months to prolonged overeating which sometimes lasted for up to 8 years (see figure 15.2). For the more complete MRC data this was a mean of 31.5 months (interquartile range 12 - 40 months). This is likely to be an underestimate as the end of the hyperphagia was often masked by the preventative measures taken by the carer or by the lack of opportunity in an institution. In the MRC study the mean MMSE score when hyperphagia ceased was 7.7 (interquartile range 1-10) and is probably less as hyperphagia was often not apparent once a subject entered an institution. For the direct observation study the final MMSE is lower and many of the subjects are still hyperphagic. At the last test-meal the mean MMSE was 3.3 (interquartile range 0 - 6).

The data were examined to see if there was evidence that hyperphagia had a fluctuating course, how long it lasted once it started and whether it continued to death. The subjects who were followed for 1 year, were reported by carers to have been hyperphagic for a period of several months, and sometimes several years before

the start of the study. Fifty per cent of the subjects exceeded the stringent threshold for hyperphagia at all test meals, over a period of a year or more, confirming that hyperphagia is a relatively stable pattern of behaviour.

PBE and PBHI data were examined from the MRC study and the results of test meals were calculated for the direct observation study. Both studies showed that hyperphagia is a stable condition, usually lasting for well over a year, and in some cases many years. Once hyperphagia was reported there was no clear evidence that it took a fluctuating course. In four people in the MRC study there was a slight change in the reported level of hyperphagia but this was probably because of inconsistencies in reporting. In the direct observation study, the results of test meals fluctuated but this seemed no more than chance variation, as people who failed to exceed the threshold during one of the four-monthly follow-up meals often overate on another occasion, for example during the preload series of meals. There was no evidence from carers' reports that hyperphagic behaviour stopped and restarted. Only in one person did hyperphagia clearly stop and afterwards restart. Hyperphagia stopped during the period when he was prescribed haloperidol and restarted when he stopped taking the drug. It therefore seems that hyperphagia normally lasts for a discrete period of time and once it ends it does not reoccur.

Evidence, from comparing the hyperphagic and non-hyperphagic groups suggests that overeating is not to compensate for hyperactivity and there is also evidence that drugs are unlikely to be a major cause of hyperphagia in dementia. As some hyperphagic subjects in both studies gained weight, overeating is not purely counteracting the

effects of malabsorption.

3. How does hyperphagia end?

The experimental results show that, although hyperphagia is fairly stable, it does not go on throughout the dementing process; neither does it stay at peak level and suddenly go. Typically there is a slow decline in energy intake during the course of the four-monthly test meals. In the ten people observed for a year, the mean intake dropped to 65 % of the initial intake, from a mean of 6683 kJ to 4314 kJ a year later. The fluctuation in the proportion of protein chosen may have a physiological cause but it is probably a reflection of increasing confusion. The results need to be confirmed with larger numbers.

The steady reduction in the mean of the total intake, during test meals, adds some quantification to the offset and gives some validity to carers' reports that hyperphagia is relatively long-lasting. Carers often report that people who were hyperphagic slowly decrease their intake of food, first eating a normal quantity and then eventually progressing to the undereating which typically preceded their final decline and death. Hyperphagia sometimes stopped during an illness such as influenza, or following an incapacitating fall and did not restart afterwards.

Of the 42 people in the two studies who were hyperphagic 2 of the 18 who are still alive, continue to be actively hyperphagic. In 7 people (17%) there was no clear evidence of the outcome of hyperphagia; 1 withdrew from the study and for 6 people the carers could not be sure if they would still overeat if given the chance. In at least

10 of the group (23.8%), there was a period of hypophagia in the terminal stages when swallowing became difficult, and they refused to eat.

Seven (17%) died suddenly e.g. from a stroke, while still hyperphagic. One man who was still hyperphagic choked to death on a piece of chicken. For the rest overeating was reported to have stopped. This change often happened when the person entered a nursing home or hospital. This apparent change probably reflected the lack of opportunity to have access to extra food and, with physical and mental deterioration, people were less able to know how to ask for, or to find, food if they wanted it. The duration of hyperphagia was uncertain for those who went into nursing homes, or for those who had to be fed, as there was little opportunity to see signs of hyperphagia.

Of the 23 people in the two studies who have died, the latest evidence of hyperphagia was a mean of 12.9 months before death (interquartile range 0 - 20 months) showing that it frequently stops before death.

Hyperphagia seems to occur over a single restricted period, mainly during the middle stages of dementia and is not significantly related to age, sex, diagnosis or activity.

SECTION 3 SUMMARY AND DISCUSSION

SUMMARY OF MAIN FINDINGS

The principal findings from the experiments reported in this thesis are summarised below.

- 1 a) Eating changes are common in dementia.
b) There is a wide range of such changes.
c) Thirty-three percent of the MRC subjects ate more than premorbidly at some stage in their illness (Chapter 7).
- 2 Hyperphagia can be studied in detail using standardised meals, with high test-retest reliability (Chapter 9).
- 3 a) A definition of hyperphagia, for the purpose of detailed research, is proposed. This is based on the mean plus 3 standard errors of the energy value of food eaten during a test meal, by a group of age and sex-matched normal elderly controls.
b) There appears to be a continuum of severity in hyperphagia; overeating in dementia does not appear to form a distinct category of behaviour. At the mild end of the spectrum there are people who eat more than before the onset of dementia when attractive foods, such as sweets or biscuits, are available. At the other extreme are people who, if given the opportunity, eat until they reach the limit of their physical capacity. If they cannot find food these

subjects may eat anything which can be chewed and swallowed (Chapter 9).

- 4 a) Food choice changes with age. Elderly subjects eat a lower proportion of protein and a higher proportion of sweet food than middle-aged controls.
 - b) People with dementia eat less protein and more sweet food than the normal elderly. With respect to food choice, dementia may represent an extreme form of ageing.
 - c) For people in the hyperphagic group, the changes were more extreme still. They ate significantly less protein and more sweet food, as a proportion of their total intake, than either the normal elderly or non-hyperphagic demented control groups (Chapter 10).
-
- 5 a) Hyperphagia appears to result from delayed satiation. The evidence for this is that eating rates were normal but showed no evidence of slowing down during the course of the meal.
 - b) There was, however, some evidence that subtle changes in hunger and satiation occurred during the course of the meal in a sub-group of hyperphagic subjects who were also hyperactive. The 'drive' to walk seemed to win increasingly against the 'drive' to eat as the meal progressed, suggesting that there was some relative reduction in the drive to eat (Chapter 11).
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- 6 There is evidence, based on the short latency period before eating begins, that there is a marked increase in hunger in the hyperphagic group, in comparison

with non-hyperphagic demented controls (Chapter 11 and Chapter 14).

- 7 a) Satiety, measured by the effect of a preload on subsequent intake, appears to decrease with age. Young people compensate accurately for the energy content of previous food intake but the normal elderly showed evidence of only a weak satiety mechanism.
- b) No compensation for earlier food intake was demonstrated in those with dementia, whether they were hyperphagic or not (Chapter 12).
- 8 It seems unlikely that hyperphagia is an example of stereotyped behaviour (Chapter 14).
- 9 a) Hyperphagia usually occurs during the middle stages of dementia, over a single restricted period (mean duration 31.5 months; mean MMSE at onset 13.5 and at offset ≤ 7.7).
- b) Hyperphagia is not significantly related to age, sex, diagnosis or activity.
- c) The level of hyperphagia does not generally fluctuate and eventually over-eating decreases and, unless the person dies suddenly, hyperphagia is often replaced by hypophagia in the terminal stages of the disease (Chapter 15).
- 10 There was no evidence that hyperphagia was caused by increased activity, medication or lack of restraint in former dieters, although they may be contributory factors.

Chapter 16 FINAL DISCUSSION

I have already discussed the results of each experiment in the relevant chapters. This approach seemed clearer because the aims and design of one experiment often depended on the conclusions from the discussion of a previous experiment. In the previous pages I have summarised what I believe to be the main conclusions from the series of experiments described in this thesis. In this final chapter, I will discuss three general issues relevant to the range of experiments reported, rather than specific to a particular experiment. The three general issues are: methodological problems; the possible mechanisms underlying hyperphagia and future research.

The purpose of the study was to develop an objective way to diagnose hyperphagia in dementia and to study the phenomenon in detail. The study has shown that there are a number of abnormalities in the control mechanisms in people with dementia (summarised above). Some of these changes are unique to hyperphagia, for example the lack of satiation during a meal; some changes are an aspect of dementia, for example the apparent absence of a satiety mechanism and still other changes seem to be an exaggeration of normal ageing, for example the changes in food choice.

The definition of hyperphagia, proposed in Chapter 9, is based on the arbitrary threshold of food intake during a test meal. It is intended for detailed research, not for epidemiological purposes. Although such objective definitions are likely to result in some false negatives, they do enable a hyperphagic group to be classified for experimental purposes. Descriptions from carers, however, may be a better method

for epidemiological studies.

METHODOLOGICAL ISSUES

Hyperphagia has not been investigated experimentally before. Previous research relied on anecdotal evidence from relatives and nursing staff and, more recently, in the MRC study, a semi-structured interview with carers was used. To test the validity of carers' reports, and to make accurate quantitative measures needed for experimental work, standardised methods needed to be developed to carry out research by direct observation. The nature of the illness meant that procedures normally used in human eating research had to be modified and new methods devised. These raised a number of methodological problems.

Small subject and control groups

The subject and control groups used in the experiments were small. The main reason for this was that the work was very time-consuming as only one test meal could be given each day. Test meals on young people can be carried out in a laboratory on a large group simultaneously. In people with dementia there were frequently severe problems which were related to ageing, for example poor eyesight, hearing, absence of teeth or poorly fitting dentures, poor coordination and reflexes. This meant that subjects were given meals, in their own home or ward, one at a time, as they had to be monitored the whole time to prevent spillages and the risk of choking.

Although hyperphagia was shown to be a relatively stable condition, there was the problem that, in a series of experiments, the baseline level changed as time passed.

For example by the time some subjects who were originally classified as hyperphagic by the initial meals were tested in the preload experiments (Chapter 12) and the Newton's cradle experiment (Chapter 14), some of the subjects were past the peak of hyperphagia and were more borderline. This may have affected the results, for example people showing signs of satiation would be more easily distracted from eating by an interruption, such being shown Newton's cradle. The constraint of time prevented the recruitment of additional subjects because of the lengthy process of the initial diagnostic interviews and test meals.

The chief disadvantages of small groups is the danger of type II errors. A positive result is valid and the significance levels confirm the validity. However, estimates of values will be less certain, i.e. the confidence limits are wider. A non-significant result, on the other hand, may be an artefact of the small sample size, resulting in conclusions which are falsely negative. However, in spite of the small numbers, many of the statistical analyses of the experiments described in this thesis revealed significant differences between the hyperphagic group and the two control groups.

Matching with controls

Although controls were matched for age and sex and, in the case of the non-hyperphagic demented controls, matching was also carried out for type and degree of dementia, there were other variables which might influence food intake. These variables include physical activity levels, metabolic rate, body weight and prescribed drugs as well as mood and state of health on the day of the test meals. From data collected from carers, it was possible to confirm, *post hoc*, that there was no

significant difference in weight, activity and medication between the two groups with dementia. This might be an example of a type II error as there was a trend for the hyperphagic group to be more active, to be taking more major tranquillisers and to have a slightly higher BMI. Larger numbers are needed to verify whether this is a spurious observation or a significant difference. The effect of temporary changes in mood and health would also have less influence on results if the groups were larger. Although the individual subjects were closely matched with controls, each group, as a whole, was heterogeneous in age and activity, and, for the two groups with dementia, in cognitive ability. As the age range of the experimental subjects was from 54-91 and activity varied from people who were immobile to those who walked several miles a day, it meant that it was difficult to quantify what level of food intake should be regarded as normal. For experimental purposes individuals were treated as equal but, in a more fine-grained analysis, allowances should be made for such variables as gender, age and activity.

Diagnosis (diversity and uncertainty)

Subjects did not have the same diagnosis. However, in the group of reported hyperphagic subjects the people who were classified as 'observed' hyperphagic and included in the experimental group, all had a clinical diagnosis of Alzheimer's disease and some probably had dementia of mixed origin; there were no subjects with a clinical diagnosis of vascular disease on its own. The diagnosis might affect results if the eating behaviour associated with AD is different from that seen in people with vascular dementia. Clinical diagnosis is uncertain, without post-mortem investigation it is difficult to verify the precise cause of dementia. However, from the post-mortem

results of the MRC study it seems there is evidence of AD in most subjects, even when the clinical diagnosis had been vascular dementia.

Limitations imposed by safety limits

Safety considerations limited the methods which could be used. The provision of food *ad libitum*, to test satiety, was not possible because a safe limit of intake would be exceeded by some subjects. This was evident as some individual meals could not be allowed to run their full course, either because subjects appeared to be uncomfortably full or they were reaching the maximum limit considered to be safe (set at 12 000 kJ). This means that the total level of food intake in people who were severely hyperphagic is an underestimate and also the apparent lack of satiation (Chapter 9) and satiety (Chapter 12) may also be misleading as some subjects were not allowed to finish their meals. Another limitation was that the quantity of quinine needed to render food less palatable would be so high that the number of quinine biscuits considered to be safe would be too small to allow people to eat more than a few. This therefore prevented their use in experiments investigating the effect of palatability on satiation (Chapter 13).

Limitations imposed by cognitive impairment

Cognitive impairment ruled out many of the standard methods used in research into eating in humans, such as the subjective methods used to assess hunger and palatability. Some established but less sensitive methods could be adapted but these methods had to assume that verbal instructions would not necessarily be understood and responses given to questions or prompts could not be taken as reliable. This

meant, for example, that the end-point of a meal was not easy to judge and the reason for the lack of response to unpalatable food could not be determined.

The inferences made by observation methods alone may not always be valid, for example lack of understanding and poor concentration meant that some subjects were reluctant to start eating or stopped eating prematurely, before they had satiated. This meant that the measurement of latency period and measurements of eating rates were erratic and probably sometimes random.

Consent and ethical considerations

Consent posed an ethical problem. As people with dementia were not able to give informed consent, the next-of-kin needed to give consent on their behalf. It was important that methods used did not intrude on the subject's dignity and that the carer should be satisfied that the person concerned would have been happy to help with the research, had they been able to understand. This meant that methods needed to be as unobtrusive and non-invasive as possible. The experimental condition, and in particular the use of videorecordings, did stop some people from giving consent on behalf of their relative. This excluded some people who seemed to be severely hyperphagic.

IS HYPERPHAGIA DUE TO A SINGLE MECHANISM?

The main abnormalities in control mechanisms underlying hyperphagia are:

Food choice - low-protein foods and high-sweet foods are chosen.

Satiation - there seems to be an absence of satiation.

Hunger - there seems to be increased hunger.

Satiety - the satiety mechanism is weak or absent.

Can these changes be explained by a common mechanism? Although cognitive impairment could account for eating at abnormal times (because people had forgotten when they had last eaten) and for the greater variation in behaviour seen in dementia groups, it does not seem adequate to account for this range of abnormalities in control mechanisms. If there is a common mechanism it is best looked for in terms of neurotransmitter abnormalities or specific brain lesions.

The most likely candidates for a unifying mechanism are reduced 5-HT and hypothalamic damage.

Reduced 5-HT

The evidence which supports reduced 5-HT being responsible for the changes in eating are that 5-HT is reduced in at least some people with AD (Chapter 6). Reduced 5-HT is known to result in a change in food choice i.e. carbohydrate satiety is diminished, there is a craving for sweet food and there is a low intake of protein (Chapter 5). In hyperphagic subjects there was a significant decrease in the proportion of protein eaten and increase in sweet food intake compared with matched,

normal, elderly controls (Chapter 10). Although the proportion of carbohydrate chosen was greater than normal controls the difference was not significant but this might be a type II error.

Reduced 5-HT causes an increase in total intake of food through a relative loss of the satiation mechanism (Chapter 5). Meals go on for longer, although the rate of eating is unchanged, and this results in obesity. The experimental results confirm that eating goes on for longer, i.e. satiation is delayed (Chapter 11). Eating rate was very variable in the hyperphagic group and it was not easy to separate the effect of hyperphagia from the effect of dementia on the various methods of measuring the rate of food intake. It was clear, for the majority of subjects in the hyperphagic group, that their eating rate was not faster than the normal controls.

The evidence against 5-HT being the sole cause of hyperphagia is that hyperphagia is usually followed by hypophagia in the final stages of dementia. It is unlikely that 5-HT decreases and then increases later in dementia. There are two likely explanations. First, given the range of neurotransmitter damage in AD, and, in view of the complex nature of the control of eating, the changes are unlikely to be due to a single neurotransmitter. It is probably the relative balance and the interaction of many neurotransmitters that is important and which determines the increase or decrease of eating. There is little good evidence to give any detail to this. The second explanation is that the neurotransmitters of the brain form a complex, interdependent control system and their functions are not fixed but depend on the location in the brain.

Hypothalamic damage

In terms of the region of the brain affected, the hypothalamus is severely damaged in AD. In animals, hypothalamic lesions destroy the satiation mechanism, which is possibly cued by metabolites or gut hormones. This system only operates after food has been swallowed, and if the control mechanism is lost, eating continues. The range of eating changes in dementia may be due to differential damage to the hypothalamic nuclei. This may account for the onset and offset of hyperphagia (Chapter 15). In experimental animals, lesion of the ventro-medial hypothalamus (VMH) is followed by a new, high set-point in body weight (Chapter 5). They also become finicky eaters, eating palatable, easily accessible food. Therefore in AD, if neuronal damage is concentrated in the VMH it may cause hyperphagia and may account for the increased consumption of sweet foods. Experimental lesions in animals in the region of the lateral hypothalamus (LH) result in reduced feeding. Therefore if, in dementia, the neuronal damage is predominantly in the LH it is likely to cause hypophagia.

The onset and offset of hyperphagia in dementia might be explained if the initial damage is greatest in the VMH and then the offset could be accounted for as there is progressively more damage to other areas, for example the LH.

As the temporal lobe is often severely affected in AD, it is possible that this also might contribute to the increased eating, as well as the hyperorality, seen in many subjects with hyperphagia. These symptoms form part of the Klüver-Bucy syndrome, which were seen originally described in monkeys after bilateral temporal lobe removal

(Chapter 4).

It is unlikely that hyperphagia is due to a single mechanism but 5-HT and hypothalamic damage are probably implicated in the observed changes.

THE FUTURE

This study had shown the characteristics of hyperphagia in dementia. Possible causes of the phenomenon have been suggested such as increased hunger, lack of satiation during a meal, disruption of the satiety mechanism and lack of response to taste. It has demonstrated that some factors, such as lack of social restraint, overactivity, stereotypy, addiction, drugs or lack of inhibition in previous dieters, are not the sole cause of hyperphagia although they may be contributory factors.

The non-invasive, observational methods, used in this series of experiments, gave some clear and reliable behavioural results but did not allow direct measures of any putative causative factors. Some possible further experiments are suggested below.

1. Further observational methods

In view of the small size of the subject groups, and their heterogeneous nature, larger and more homogeneous experimental groups would confirm the validity of these findings and correct any type II errors. Further work could evaluate the contribution of such variables as overactivity and medication to hyperphagia and also whether the increase in the proportion of carbohydrate chosen is significantly greater than in control groups.

2. Study of eating over a longer time-period

a) Diurnal eating patterns

The present study only involved a maximum of one meal a week. It did not prove that the excessive intake was not just temporary compensation after relative food deprivation, although circumstantial evidence suggests otherwise, as subjects had sometimes been reported to have helped themselves to considerable quantities of food both before and immediately after the test meal. Ideally, further tests should be done giving a subject access to unlimited quantities of food over a long period of time. This would help to establish the intrinsic eating pattern. In subjects with dementia, mealtimes and the quantity of food is usually controlled by the carer. If 'free-range' cafeteria eating conditions could be approximated, this would show if there was still a normal meal pattern i.e. if there was a normal period of satiety before eating was resumed even though satiation was delayed.

b) Long-term macronutrient intake

On the evidence of a single meal, macronutrient choice is abnormal both in dementia and even more so, in people who are hyperphagic but the question remains as to whether the change in macronutrient choice is stable over a prolonged period. An extended experiment would also show whether there was an abnormal pattern of macronutrient intake in the long term and whether there was a diurnal fluctuation in macronutrient choice, as in normal eaters.

3. Investigating the mechanisms responsible for hyperphagia

a) Drug studies

The test meals, used in this series of experiments, proved to be a reliable objective measure of hyperphagia in general and could be used as a basis for assessing the effect of drugs.

- (i) After a series of test meals, to assess the baseline level of food intake, drugs, known to have anorexic effects could be used. Subsequent test meals would show which drugs were efficacious. A reduction in food intake in hyperphagia has already been demonstrated in a detailed case study on a subject with Pick's Disease (Hope & Allman, 1991) and in two pilot case studies, carried out in the course of this present study, one using fluoxetine and one fluvoxamine. This suggests the involvement of 5-HT.
- (ii) There is a wide range of selective agonists and antagonists, which are currently being used on normal subjects, to investigate the effect of different neurotransmitter receptor sub-types. The effect of some of these drugs, such as *m*-CPP (a 5-HT_{1C} agonist), on hyperphagic subjects might reveal which neurotransmitter mechanism is responsible for hyperphagia in dementia and whether hyperphagia is the result of decreased release of a neurotransmitter or whether the sensitivity of the post-synaptic receptors has altered. A 5-HT releaser, such as d-fenfluramine, and reuptake inhibitors such as fluoxetine might maximise the effect of the remaining 5-HT, curb hyperphagia and sweet-food craving, as well as reducing some of the other side-effects of low 5-HT, such as aggressive behaviour.

b) Post-mortem studies

In post-mortem studies, it is probably important to have evidence that the person was hyperphagic at the time of death, otherwise any observed changes are unlikely to be related to overeating. It is usually only in the case of sudden death that this would happen, as the terminal illness or the final stages of dementia are likely to be characterised by hypophagia.

- (i) **Biochemical investigation** of different regions of the brain, in people who were hyperphagic, could be compared with age-matched normal controls to determine which neurotransmitter systems were deficient. Again it is probably important to have evidence that the person was hyperphagic at the time of death, in order to correlate neurotransmitter deficiencies with eating behaviour.
- (ii) **Behavioural data could be related to anatomical changes** found in the brain during post-mortem examination. Areas of neuronal damage, shown by an increased density of plaques and tangles, or by the areas damaged by infarction, might correlate with observed changes of behaviour. For example damage to the ventro-medial hypothalamus might correlate with people who showed hyperphagic behaviour. A high degree of neuronal damage in the lateral hypothalamus might be expected to correlate with people who had been hypophagic before death.

c) Non-CNS control

Numerous mechanisms controlling food intake are found outside the CNS (see Chapter 5). This has not been investigated in people with dementia and it would be

interesting to determine which changes are due to dementia and which are specific to hyperphagia.

- (i) **Hormonal imbalance** could be investigated by biochemical means, for example reduced breakdown of CCK, a satiety hormone, may influence eating patterns in people with dementia.
- (ii) **Gastro-intestinal receptors** may not be functioning normally and therefore sensory information will not be relayed to the CNS to bring about satiation.
- (iii) **Physiological investigations**, for example to measure activity and metabolic rate, could confirm that hyperphagia was not just the result of compensating for hyperactivity. Tests similar to the pilot work by Lehmann (1979) need to be repeated to investigate whether hyperphagia is the result of compensating for malabsorption. The apparent lack of satiation, seen in hyperphagia, could be a side-effect of rapid gastric emptying. This would need to be confirmed experimentally.

CLINICAL IMPORTANCE AND TREATMENT OF HYPERPHAGIA

Hyperphagia is clinically significant as it can lead to a dramatic increase in weight. This weight increase creates problems for carers, who are often elderly themselves, particularly when the carer needs to help the person physically in such situations as bathing, washing, dressing or toileting. Increasing weight is likely to lead to decreased mobility which in turn exacerbates problems for carers as well as adding to health problems, for example by leading to pressure sores.

Additional strains are imposed on carers if food has to be permanently hidden or locked up. The most difficult situation arises when discrimination goes and the person with hyperphagia tries to eat any substance. This means that a round-the-clock watch has to be maintained to avoid the danger of poisoning. There is also a risk of choking; one person who was hyperphagic was found with her mouth stuffed to capacity with boiled sweets and another choked to death on a lump of chicken.

From the evidence of the experiments described in this thesis, possible treatment could be based on:

a) Drug treatment

If hyperphagia is due to lack of 5-HT, drugs such as fluvoxamine or fluoxetine might reduce overeating.

b) Dietary treatment

Levels of 5-HT could possibly be boosted by dietary means such as a high carbohydrate/low protein diet or by tryptophan loading.

c) Photo-therapy

Photo-therapy has been used successfully to boost 5-HT in people with seasonal affective disorder (Wurtman & Wurtman, 1989). It might possibly improve 5-HT function in people with dementia.

The problems created by hyperphagia are particularly exacting where the person is still living at home and a carer is often coping single-handed for 24 hours a day. There is an pressing need for a successful way of treating hyperphagia in dementia.

ACKNOWLEDGEMENTS

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The Medical Research Council funded the three year D.Phil. studentship to study hyperphagia in dementia.

Oxfordshire Health Authority granted money to cover the expenses involved in providing test meals, buying and servicing equipment and paying for transport to visit subjects.

Duphar gave money to buy the Noldus 'Observer' package used in behaviour analysis.

ACADEMIC AND EXPERIMENTAL ADVICE

Peter Rogers of the Institute of Food Research at Reading gave me invaluable advice on suitable preload meals and helped to develop a taste test suitable for people with dementia. I am also very indebted to Peter Rogers and Nicky Elliman for carrying out preload experiments on the younger controls and for their advice and expertise in analysing hunger ratings.

I am grateful for Philip Cowen's sound suggestions and advice at the planning stage which helped to shape the project.

John Blundell of the University of Leeds helped in the initial stages, in devising eating experiments to demonstrate satiation and macronutrient choice.

Lynne Murray and her team at Cambridge University, together with Alan Stein and Helen Woolley of the University of Oxford introduced me to methods of recording and coding behaviour using videotapes.

Paul Griffiths gave me very valuable advice on statistical analyses.

RECRUITING

The difficult task of recruiting suitable subjects and controls was made possible by the help and suggestions given by the OPTIMA team, Dr Catherine Oppenheimer, the Oxford CPNs and the staff of many local hospital wards and nursing homes. Angela Tremaine and Mrs Critchley helped to recruit large numbers for the taste test by nobly persuading their friends to taste biscuits containing quinine.

PRACTICAL HELP

I am grateful for permission to use of the software program written by Andrew Leech, originally developed for use with Automated Food Dispenser (Goodall *et al.*, 1992).

OPTIMA helped me by sharing CAMDEX data on some of our joint subjects.

Sandra Cooper gave me indispensable advice and timely help with computing and statistics. Kathy Gedling assisted with the reliability study and with analysis of some of the MRC data. I have enjoyed being able to continue to work as part of the 'dementia team' and greatly appreciate their friendship and support.

Heather Jones kindly volunteered to proof-read the thesis. I must thank my family and numerous volunteers who took part, as controls, in the test meals and taste tests and all the carers who allowed me to give the meals and who gave up their time to be interviewed.

Finally I am deeply indebted to Tony Hope for his unfailing patience and reassurance in supervising this study. Without his help and encouragement this thesis would not have been written.

APPENDIX I Extracts from PRESENT BEHAVIOURAL EXAMINATION

Tony Hope and Christopher Fairburn

Oxford University Department of Psychiatry
Warneford Hospital
Oxford

(7th Edition March 1988)

SECTION B: WALKING

Now I would like to find out about {...subject...}'s walking
TIME SPENT WALKING

- 38 *** On average, over the past four weeks, how much of the time has {...subject...} spent walking around?**

If we go through an average day; first of all, between breakfast and the midday meal. What is the pattern of walking? (Then ask similarly about the rest of the day.)

[Obtain an overall picture of how long the subject spends walking around before first sitting down; how long s/he is then likely to sit before getting up and walking again (and whether whilst sitting s/he is asleep, or eating or drinking); and then for how long s/he is walking before next sitting down. On the basis of this information give brief description of walking pattern and then rate.

N.B. What is being rated is the amount of walking initiated by the subject. If person can only walk with the help of someone else, rate {0}, not {7}.

Rate as follows:

- {0} - doesn't walk at all without help
- {1} - minimal walking (enough to get from bed to sitting-room, no walking without encouragement except to go to the lavatory)
- {2} - sedentary, but does walk spontaneously to perform specific activities on up to two occasions between meals
- {3} - walks a normal amount for someone of similar age (but more than ratings {0},{1},{2})
- {4} - walks distinctly more than is normal (i.e. time spent walking is more than normal).]

If above is rated {4} then find out:

- 39 Time spent sitting

On a typical day how long would s/he normally sit down for, while awake but not eating or drinking before s/he gets up again?

[Rate median time of continuous sitting (awake and not eating or drinking) in an average day in minutes (the median time is the most common length of time).

Do not include in these ratings sitting in a car, where it would be impossible for the subject to get up.]

SECTION C: EATING

I would like to ask you about {...subject...}'s eating over the past four weeks.

FACTORS CONFOUNDING EATING

- 64 * **Over the past four weeks, has {...subject...} had any difficulties in swallowing either solids or liquids?**

[Rate only physical difficulties, not e.g. cramming so much food in mouth that there is difficulty in swallowing.]

Rate as follows:

- {0} - no
- {1} - yes, establish what the difficulties are and how they might interfere with other ratings (e.g. with the types of food eaten). A dry mouth causing difficulty in swallowing should rate here.]

- 65 * **Does {...subject...} wear false teeth to eat?**

Do they interfere with his eating at all?

[Rate as follows:

- {0} - no
- {1} - yes, but they probably do not interfere with eating
- {2} - yes, and this has substantially influenced eating (e.g. food has to be specially prepared or liquidised). Specify.]

If {...subject...} does not have or use false teeth or if subject has some of own teeth in addition to false teeth ask:

- 66 * **Has {...subject...}'s dentition (state of his teeth) affected his eating over the past four weeks?**

Do you prepare, or cut up food specially in any way?

[Rate as follows:

- {0} - no
- {1} - yes, establish what the difficulty is and how it might interfere with other ratings (e.g. with the types of food eaten). N.B. Only rate here if special preparation of food is because of problems with dentition
- {7} - has none of own teeth and uses false teeth.]

- 67 * **Are there any other problems (e.g. mouth ulcers) that may have affected how {...subject...} has eaten, chewed or swallowed food over the last four weeks?**

[Rate as follows:

- {0} - no (or has had ulcers etc. but these have not affected eating)
- {1} - yes, establish what the difficulties are and how they might interfere with other ratings (e.g. with the types of food eaten).]

68 * Is {...subject...} on any special diet?

[Rate as follows:

{0} - no

{1} - yes (specify), rate only diet imposed on subject - e.g. because of diabetes. Rate 'slimming diet' only if this pre-dates the dementia. Otherwise rate below. Do not rate here restriction of food from choice.]

69 * Do you/{...relevant carer...} tend to restrict {...subject...}'s food because s/he tends to eat too much?

[Rate here if carer restricts food (even if only saccharin in tea) because of eating too much since onset of dementia.

Rate as follows:

{0} - no

{1} - yes (specify).]

AMOUNT EATEN

70 * Over the past four weeks, has {...subject...} in general eaten about the same amount that s/he did before s/he began to have memory problems, or not?

If answer is no, ask:

How much more, or less, does s/he now eat?

[Rate in comparison with the subject before the onset of dementia. Make sure that the informant is clear that comparison is between the last four weeks and the premorbid level. Judge overall food intake e.g. if subject eats less at meals but more between meals, totalling about the same overall as premorbid level, rate {0}. Rate {8} if carer does not know pattern of eating before onset of memory problems.

Rate as follows:

{0} - no change

{1} - eats a little less than prior to memory problems

{2} - eats two thirds or less, than prior to memory problems

{3} - eats a little more than prior to memory problems

{4} - eats half as much again or more, than prior to memory problems.]

FOOD CHOICE

71 * Over the past four weeks, has {...subject...} in general eaten the same kinds of food that s/he did before the onset of the problems with memory, or not?

Is there anything s/he now dislikes but used to enjoy - or vice versa?

If answer is no change, then probe:

For example does {...subject...} eat more sweet things, or, perhaps fewer sweet things than before?

[Rate any change even to sugar in tea, if different to pre-morbid diet.

Rate {8} if physical problem, e.g. mouth ulcer, poor gums, probably affects the answer. Also rate {8} if carer does not know pattern of eating before onset of memory problems.

Rate as follows:

{0} - no change

{1} - change (specify with examples).]

EATING BETWEEN MEALS

- 72 * **Over the past four weeks, has {...subject...} eaten food between meals apart from a routine snack?**

Did s/he do this before the memory problems?

[Do not rate if no more than one snack between each main meal. Only rate changes from premorbid eating pattern, i.e. do not rate two snacks between meals if this was the routine premorbid pattern of eating. Sweets by themselves do not rate as snacks.

Specify and rate on seven-point scale:

- {0} - not at all
- {1} - on 5 or fewer days per 28 days
- {2} - on more than 5 but fewer than half the days per 28 days
- {3} - on about half the days (see note in Instructions to Interviewers)
- {4} - on more than half the days (6 - 13 exceptions)
- {5} - on almost every day (up to five exceptions)
- {6} - on every day.]

- 73 **How often between main meals has {...subject...} eaten?**

[Rate as follows:

- {1} - has eaten between meals in excess of routine snacks, but not to extent rated {2}
- {2} - four or more episodes of eating spread out over a 3 hour period (between meals)
- {7} - no episodes of eating between meals (except for routine snacks).]

SEARCHING FOR FOOD

- 74 * **Over the past four weeks, has {...subject...} searched for food?**

[The purpose behind this question is to rate evidence that the person wants more food than s/he can get, e.g. will even try to find food which carer has had to lock away.

Rate {0} if subject knows where food is, so does not have to search.

Rate {0} if subject is sedentary.

Specify and rate on seven-point scale.]

REQUESTS FOR FOOD

- 75 * **Over the past four weeks, has {...subject...} asked specifically for food?**

[This question is to pick up evidence that the subject wants more food but may not search. Do not rate "When is dinner?" or "Isn't it dinner time?", etc. Rate {0} if subject mute.

Specify and rate on seven-point scale.]

ABUNDANCE OF FOOD

*** Over the past four weeks, if faced with a large amount of food, has {...subject...} eaten more than s/he would normally?**

For example, what has s/he done if there has been more than the usual amount of food around at meal times?

Has this actually happened (over the past four weeks)?

What about sweet things, for example biscuits, sweets or cakes? What has {...subject...} done if there is an open packet of sweets or biscuits around?

[Rate sweet foods separately from other foods.

Rate even if only one type of food is eaten excessively, when available e.g. sweets but not biscuits.

To rate {2} or {3} there must be evidence that the subject has eaten much more than a large single portion of some type(s) of food when the opportunity was there.

To rate {3} there must be evidence that subject would either eat all of the food that was available (eat through an entire open packet of biscuits without leaving any) or appears to be insatiable.

76 (a) Other foods

Specify and rate as follows:

{0} - eaten his/her normal amount and left the excess food or refused more food if offered

{1} - eaten a little more food than normal

{2} - eaten considerably more than normal but has not eaten all the food that was available

{3} - carried on eating until there was no more food

{8} - there has not been any occasion when {...subject...} has been faced with an excess of food.

77 (b) sweet foods

Specify and rate as follows:

{0} - eaten his/her normal amount and left the excess food or refused more food if offered

{1} - eaten a little more food than normal

{2} - eaten considerably more than normal but has not eaten all the food that was available

{3} - carried on eating until there was no more food

{8} - there has not been any occasion when {...subject...} has been faced with an excess of food.]

INAPPROPRIATE PLACING OF FOOD

78 * Over the past four weeks, has {...subject...} put food in odd places? For example, in his/her pocket, or down the side of chairs, or in the clothes cupboard?

[Specify the variety of food, the variety of places and whether the food tends to be collected together and any evidence of the purpose. Do not rate if inappropriate placing of food appears to be part of moving other objects around rather than collecting food specifically, possibly for eating later.

Rate on seven-point scale (see question 72):

EATING STYLE

79 * Does {...subject...} have to be fed?

[Rate as follows:

{0} - no

{1} - yes.

If subject is always fed, rate {7} for following questions.]

80 Over the past four weeks, when {...subject...} has eaten, has s/he ever used his/her hands inappropriately for putting food in his/her mouth or to help in eating?

[e.g. used hands to shovel food on spoon.

Rate {8} if sight interferes with eating.

Rate on seven-point scale as question 72.]

81 Has s/he ever used an unusual utensil for putting food in his/her mouth, over the past four weeks?

[Rate on seven-point scale as above. By 'unusual utensil' is meant one which is not normally used for eating.]

82 Has s/he ever used a normal utensil in an unusual way (for example using his/her knife for putting the food in his/her mouth or using a spoon to cut up food when a knife is available)?

[If carer only gives subject a spoon rate {7}.

Rate on seven-point scale as question 72.]

FOOD LEFT IN MOUTH

83 * Over the past four weeks, has {...subject...} left food in his/her mouth unswallowed for an inappropriate length of time?

[Rate on a seven-point scale as question 72].

OTHER ABNORMALITIES

84 * Over the past month, has {...subject...} shown any (other) odd behaviour in the way in which s/he has eaten (e.g. spitting out food, or gulping or tipping food on the floor)?

[Rate tipping a spoonful of food over the table etc. or the deliberate throwing of food. Also rate if spilling of food is due to bad coordination. Specify and rate on seven-point scale]

PUTTING INEDIBLE OBJECTS IN MOUTH

- 85 * **Over the past four weeks, has {...subject...} chewed or eaten anything that is not food?**

[List objects; note their colour.

Specify and rate on seven-point scale as question 72].

- 86 **For each object specify whether {...subject...} has:**

{0} - put it in his/her mouth but not chewed or swallowed it

{1} - put it in his/her mouth and chewed it

{2} - put it in his/her mouth and swallowed it (with or without chewing).]

INAPPROPRIATE FOOD

- 87 * **Over the past four weeks, has {...subject...} ever tried to eat food that seems odd to you? For example, uncooked meat, a whole jar of pickled onions, or raw potatoes.**

[Specify and rate on seven-point scale.]

ORAL BEHAVIOUR

- 88 * **Over the past four weeks, has {...subject...} touched or examined with his/her mouth any inappropriate object?**

[What is being rated here is apparently using the mouth or lips to 'explore' objects - in a way analogous to the method a blind person might use the sense of touch.

Specify the objects that have been so examined and rate on seven-point scale.]

AMOUNT OF ALCOHOL DRUNK

- 89 * **How much alcohol has {...subject...} had to drink on average over the past four weeks?**

[Rate average number of units per week. One unit is equivalent to half a pint of beer, a single measure of spirit or a glass of wine.]

REQUESTS FOR ALCOHOLIC DRINK

- 90 * **Over the past four weeks, has {...subject...} asked specifically for an alcoholic drink?**

[Do not rate if asking near a time when s/he normally has a drink if this could be just time orientation.

Specify and rate on seven-point scale.]

AMOUNT OF NON-ALCOHOLIC LIQUID DRUNK

- 91 * **Turning now to non-alcoholic drink, over the past four weeks has {...subject...} drunk more, the same or less than an average person?**

[Rate as follows:

{0} - normal

{1} - a little (possibly) less

{2} - substantially less (to the extent that dehydration is a problem)

{3} - a little (possibly) more

{4} - substantially more.]

REQUESTS FOR NON-ALCOHOLIC DRINK

- 92 * **Over the past four weeks, has {...subject...} asked specifically for drink?**

[Rate only those days on which subject has asked for some drink on three or more times between two main meals. Do not include drink requested with, or immediately after the end of a meal. Do not include requests specifically for alcoholic drink.

Specify and rate on seven-point scale as question 72.]

DRINKING STYLE

- 93 * **Have you noticed anything odd or peculiar in the way that {...subject...} has been drinking over the past four weeks, for example: in his/her choice of drink; or how s/he drinks?**

[The amount drunk is rated in 91 above. Do not rate problems due to physical difficulties. The purpose of this is to rate abnormalities in drinking which are, at least to some extent, intentional. By 'drink' is meant any drink, not just alcoholic drinks.

Specify abnormality and rate on seven-point scale as question 72.]

210 OBSESSIONAL BEHAVIOUR

- * **Over the past four weeks, has {...subject...} been particularly "obsessional" about anything. For example, having to go to the toilet on the hour; or having to carry out some task in a particular way?**

What would s/he do if prevented?

[Rate here any behaviour in which the subject carries out a task in an excessively rigid manner, and would resist attempts by the carer to stop the behaviour.

Specify and rate on seven-point scale as question 72.]

STEREOTYPED BEHAVIOUR

*** Over the past four weeks, has {...subject...} shown patterns of stereotyped behaviour?**

Supplementary questions were asked about picking, rubbing, plucking or garnering behaviour, repeated grunting or verbal utterances and stereotyped walking patterns.

[Specify and rate on seven-point scale as question 72.]

APPENDIX II EATING BEHAVIOUR RATING SCALE

EBRS SCALE (Wilson *et al.*, 1989)

Subject Number : _____

EBRS Score: _____

EBRS Score + Affect: _____

t-eat: _____ minutes, _____ seconds
t-drink: _____ minutes, _____ seconds
t-total: _____ minutes, _____ seconds

1. Global assesment of eating

0 1 2 3 4 5

2. Picking at food

5 4 3 2 1 0

3. Poor table manners
involving eating utensils

0 1 2 3 4 5

4. Alternation between foods

0 1 2 3 4 5

5. Food disposal

5 4 3 2 1 0

6. Distaste for food

5 4 3 2 1 0

7. Abnormal verbalization
during a meal

5 4 3 2 1 0

8. Preference for low
calorie foods

0 1 2 3 4 5

9. Abnormally slow eating

5 4 3 2 1 0

10. Abnormally rapid eating

0 1 2 3 4 5

11. Ritualistic eating

0 1 2 3 4 5

12. Excessive activity
during the meal

5 4 3 2 1 0

13. Affect during the meal

0 1 2 3 4 5

APPENDIX III EATING QUESTIONNAIRE FOR NORMAL ELDERLY CONTROLS

NAME..... SUBJ. NO DATE.....

1 Weight?Kg 2 Height? cm BMI.....

3 Have you dieted or attempted to lose weight in the last five years?
{0} - no
{1} - yes (specify)

4 During the last five years has your eating, at any stage, changed?
(Obtain description and rate as appropriate below.)
{0} - no
{1} - yes (specify)

INCREASE

5 At any time in the last five years has there ever been a period when you have eaten definitely more than you did before?
(Rate only if for a sustained period, not just a feast.)
{0} - no
{1} - yes
If {1} ask the following questions:

6 Why do you think that was?
(Probe about exercise, bereavement etc.)

7-8 At that time did your weight change?
{1} - stayed the same - then 7 is 0
{2} - increase in weight {specify amount}
{3} - decrease in weight {specify amount}

DECREASE

9 At any time in the last five years has there ever been a period when you have eaten definitely less than you did before?
{0} - no
{1} - yes
If {1} ask the following questions:

10 Why do you think that was?
(Probe about exercise, bereavement etc.)

11-12 At that time did your weight change?
{1} - stayed the same - then 12 is 0
{2} - increase in weight {specify amount}
{3} - decrease in weight {specify amount}

13 In the last five years has there been a change in the sort of food you like for example sweet or strongly flavoured food.
{0} - no
{1} - yes (specify)

AT TIME OF TEST MEAL

14 Have you had any problems eating in the last week for example problems with your teeth or mouth ulcers?
{0} - no
{1} - yes (specify)

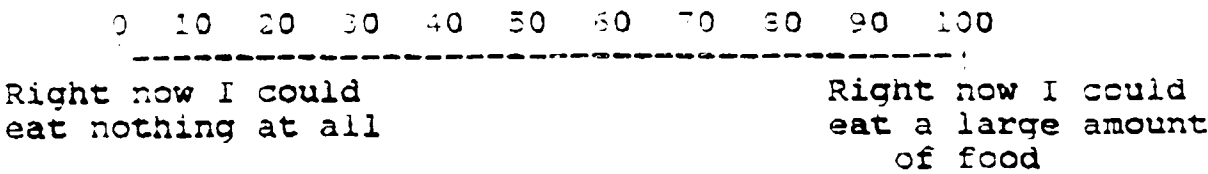
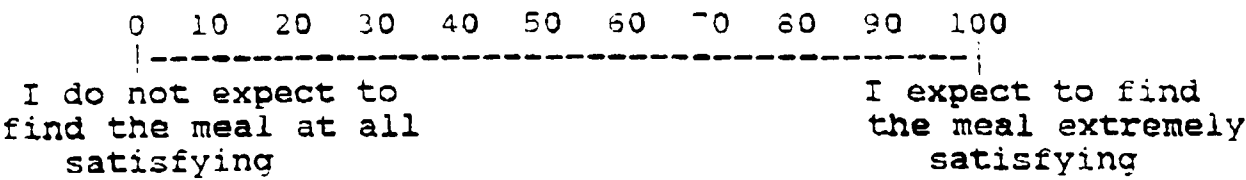
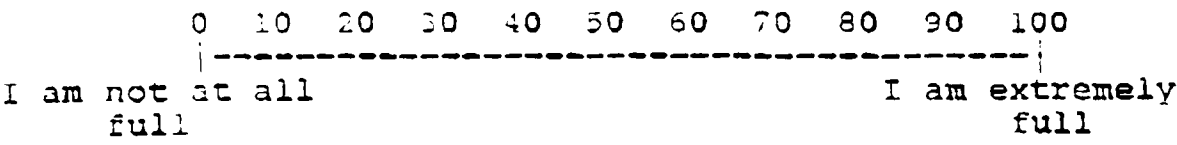
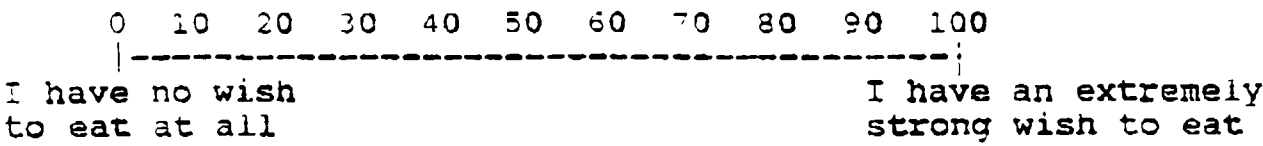
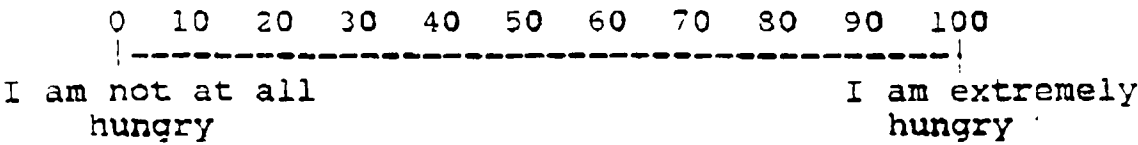
15 Are you on any special diet at the moment?
{0} - no
{1} - yes (specify)

APPENDIX IV VISUAL ANALOGUE SCALES FOR
PRELOAD MEALS (sample page)

Name..... Date..... Code.....

CIRCLE THE NUMBER WHICH BEST INDICATES HOW
YOU FEEL RIGHT NOW

1 Before milkshake



APPENDIX V TASTE TEST QUESTIONNAIRE FOR NORMAL SUBJECTS

TASTE TEST

I am carrying out a taste test on people of all ages to see if taste differs between men and women and to see if the sense of taste varies with age.

Please would you taste each of the biscuits in turn and see if they taste different to you, afterwards fill in the answers below.

Are you male or female?.....

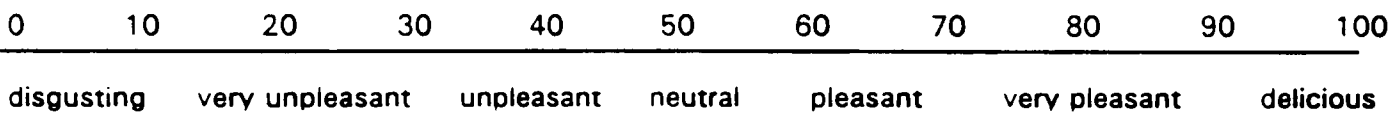
How old are you?.....

Delete as applicable.

Which biscuit did you prefer? YELLOW / PINK

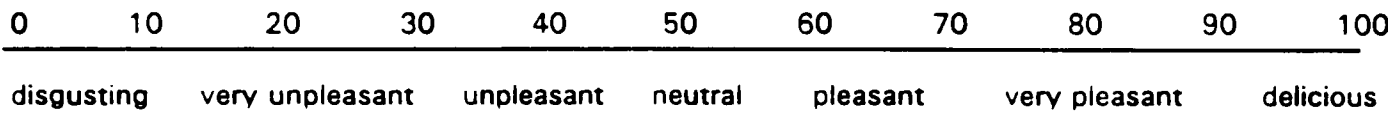
Please put a cross on the bar which corresponds to how you felt about each biscuit.

YELLOW BISCUIT



Can you describe the taste?.....

PINK BISCUIT



Can you describe the taste?.....

PLEASE DELETE AS APPLICABLE

Are you a smoker? YES / NO

If you smoke do you smoke more than 20 a day? YES / NO

What do you smoke mainly? FILTER TIPS / NON FILTER-TIPS / ROLL-YOUR-OWN

If you cannot taste the difference DON'T worry! Many others cannot either.
If you would like to know the reasons for doing this test and results please fill in your name and address below
.....
.....
.....

Please return the form to: Janet Keene, University Department of Psychiatry, Warneford Hospital, Headington, Oxford OX3 7JX

APPENDIX VI CODES FOR FACE OR BODY MOVEMENTS

Perl *et al.* (1992)

(modified from Ganchrow *et al.*, 1983)

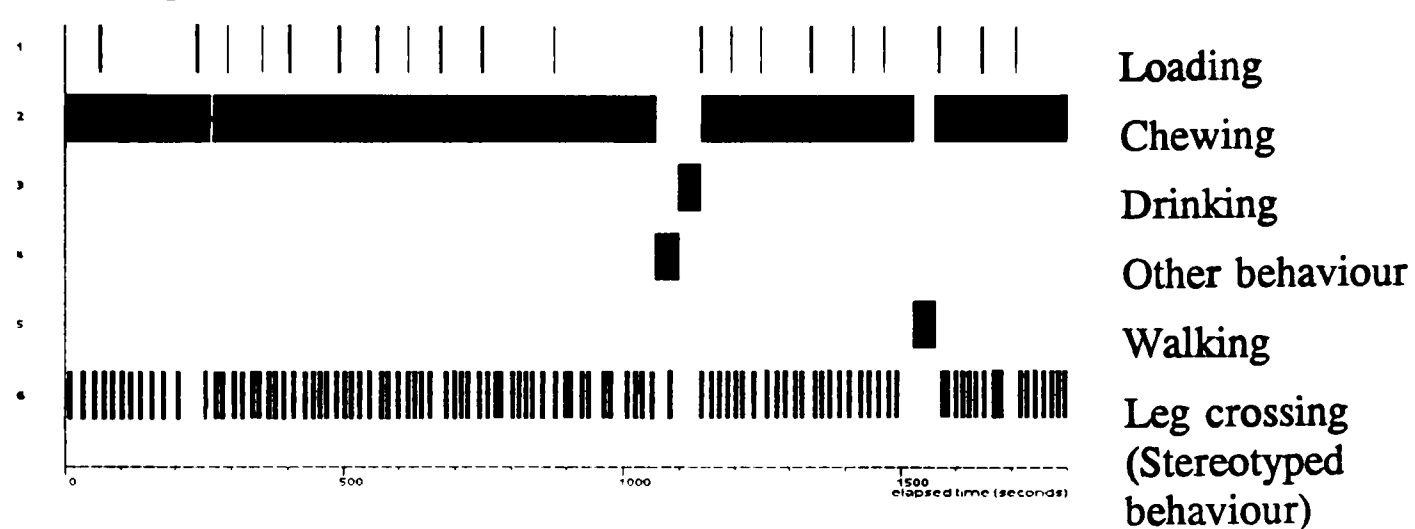
- | | |
|------------------------------------|---------------------------------|
| (1) Furrowing of forehead | (13) Mouth open |
| (2) Eyes open | (14) Gaping |
| (3) repeated blinking | (15) Drool long and/or spitting |
| (4) Eyes tightly closed | (16) Flat tongue out |
| (5) Nose wrinkled | (17) Rolled tongue out |
| (6) Moving of <i>alae-nasi</i> | (18) Head turn |
| (7) Closed lips | (19) Head up or down |
| (8) Lips apart/mouthing | (20) Horizontal head shake |
| (9) Lip pursing | (21) Mouth cleaning |
| (10) Lip licking/rubbing | (22) Hand to face or mouth |
| (11) Smile/laughter (satisfaction) | (23) Nose rubbing or cleaning |
| (12) Mouth corners down | (24) Resting face |

APPENDIX VII ANALYSIS OF BEHAVIOUR

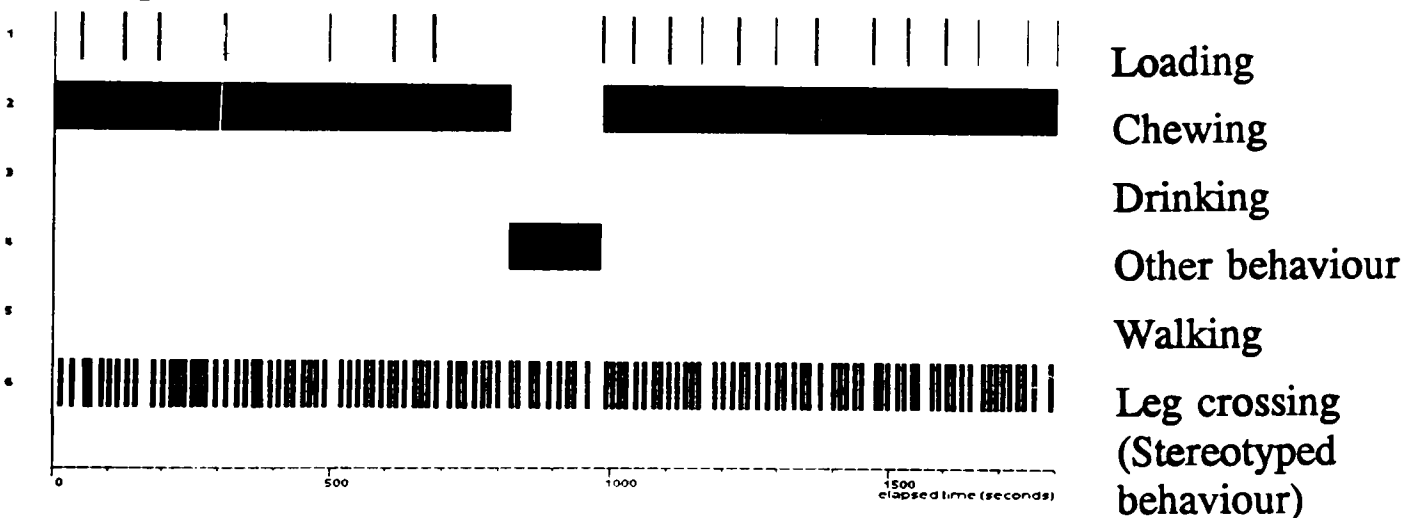
First quarter of meal



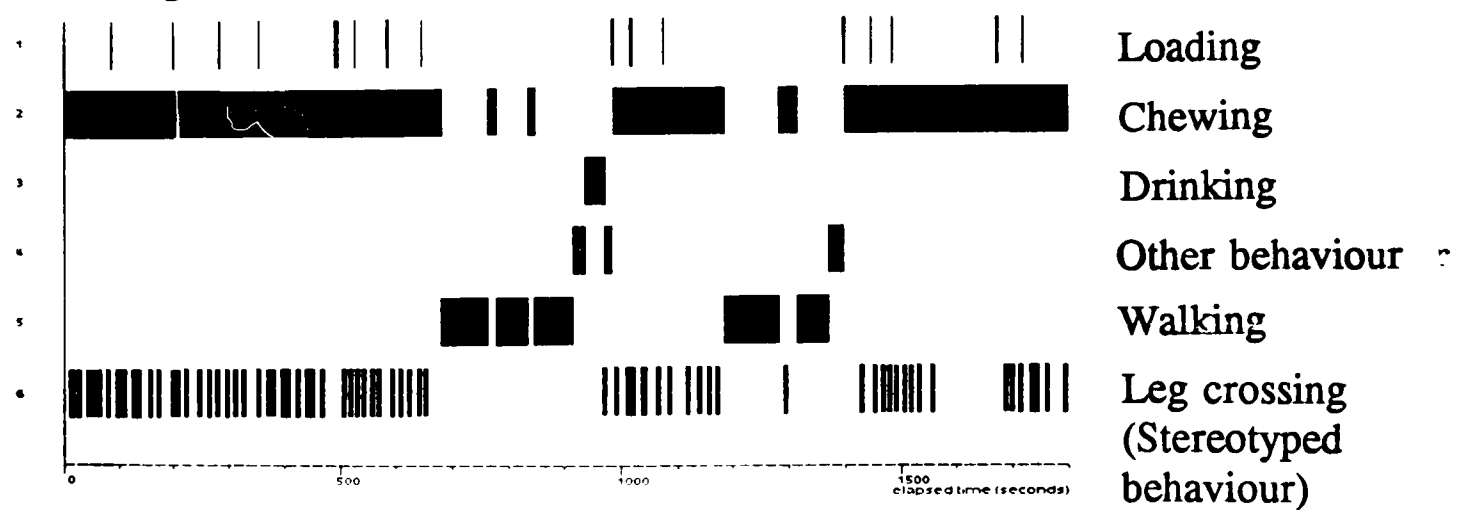
Second quarter of meal



Third quarter of meal



Fourth quarter of meal



BIBLIOGRAPHY

- Abalan, F. (1984). Alzheimer's Disease and malnutrition: a new etiological hypothesis. *Medical Hypotheses*, **15**, 385-393.
- American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders, (Fourth Edition)*. American Psychiatric Association, Washington D.C.
- Anand, B.K. and Brobeck, J.R. (1951). Hypothalamic control of food intake in rats and cats. *Yale J. Biol Med.*, **24**, 123-140.
- Anderson, I.M., Parry-Billings, M., Newsholme, E.A., Fairburn, C.G. and Cowen, P.J. (1990). Dieting reduces plasma tryptophan and alters brain 5-HT function in women. *Psychological Medicine*, **20**, 785-91.
- Ashley, D.V.M., Coscina, D.V. and Anderson, G.H. (1979). Selective decrease in protein intake following brain serotonin depletion. *Life Sciences*, **24**, 973-984.
- Bartoshuk, L.M. (1989). Taste. Robust across age span? *Annals New York Academy of Sciences*, **561**, 65-75.
- Bartoshuk, L.M., Rifkin, B., Marks, L.E. and Bars, P. (1986). Taste and aging. *J. Gerontol*, **41**, 51-7.
- Beal, M.F., Kleinman, G.M., Ojemann, R.G. and Hochberg, F.H. (1981). Gangliocytoma of third ventricle: hyperphagia, somnolence, and dementia. *Neurology (Ny)*, **31**, 1224-8.
- Beck, C., Rossby, L. and Baldwin, B. (1991). Correlates of disruptive behavior in cognitively impaired elderly nursing home residents. *Arch. Psychiatr. Nurs.*, **5(5)**, 281-291.
- Bellisle, F. and Le Magnen, J. (1980). The analysis of human feeding patterns: the Edogram. *Appetite*, **1**, 141-150.
- Bellisle, F. and Le Magnen, J. (1981). The structure of meals in humans: eating and drinking patterns in lean and obese subjects. *Physiology and Behavior*, **27**, 649-658.
- Bellisle, F. (1989). Quantifying palatability. *Annals of the New York Academy of Sciences*, **575**, 363-75.
- Berntson, G.G., Zipf, W.B., O'Dorisio, T. M., Hoffman, J.A. and Chance, R.E. (1993). Pancreatic polypeptide infusions reduce food intake in Prader-Willi Syndrome. *Peptides*, **14**, 497-503.

- Berry, E.M. (1992). Undernutrition in the elderly: a physiological or pathological process. In *Nutrition of the Elderly*, (H. Munro & G. Schlierf, eds.) Nestlé Nutrition Workshop Series, Vevey/Raven Press, 29, 65-73.
- Birch, L.L. (1987). The acquisition of food acceptance patterns in children. In *Eating Habits - Food, Physiology and Learned Behaviour*, (R.A. Boakes, D.A. Popplewell & M.J. Burton eds.) John Wiley & Sons, 107-130.
- Blass, E.M. (1991). Suckling: Opioid and Nonopioid Processes in Mother-Infant Bonding. In *Chemical Senses, Volume 4 Appetite and Nutrition*, (M.I. Friedman, M.G. Tordoff, & M.R. Kare, eds.), Marcel Dekker, New York, 283-302.
- Blass, J. (1980). Food selection in the aged. *International Journal of Obesity*, 4, 377-380.
- Blass, J.P. and Zemcov, A. (1984). Alzheimer's disease. A metabolic systems degeneration? *Neurochem. Pathol.* 2(2), 103-14.
- Bliwise, D.L. (1993). Sleep in normal aging and dementia. *Sleep (American Sleep Disorders Association and Sleep Research Society)*, 16(1), 40-81.
- Blundell, J.E. (1977). Is there a role for serotonin (5-hydroxytryptamine) in feeding? *Int. J. of Obesity*, 1, 15-42.
- Blundell, J.E. (1984). Serotonin and appetite. *Neuropharmacology*, 23, 1537-1551.
- Blundell, J.E. (1988). Understanding anorexia in the elderly: formulating biopsychological research strategies. *Neurobiology of aging*, 9, 18-20.
- Blundell, J.E. (1991a). Pharmacology of appetite control. Poster *Trends in Pharmacological Sciences*, Elsevier Trends Journals.
- Blundell, J.E. (1991b). The biology of appetite. *Clinics in Applied Nutrition*, 1(2), 21-31.
- Blundell, J.E. and Halford, J.C.G. (1994). Regulation of nutrient supply: the brain and appetite control. *Proc. Nut. Soc.*, 53, 407-418
- Blundell, J.E. and Hill, A.J. (1987a). Nutrition, serotonin and appetite: case study in the evolution of a scientific idea. *Appetite*, 8, 183-194.
- Blundell, J.E. and Hill, A.J. (1987b). Serotonergic modulation of the pattern of eating and the profile of hunger - satiety in humans. *International Journal of Obesity*, 11, Suppl. 3, 141-155.

Blundell, J.E., Rogers, P.J. and Hill, A.J. (1987). Evaluating the satiating power of foods: implications for acceptance and consumption. In *Chemical composition and Sensory Properties of Food and their Influence on Nutrition*, (J. Solms, ed.), London Academic Press, 205-219.

Booth, D.A. (1972) Postabsorptively induced suppression of appetite and the energostatic control of feeding. *Physiology and Behavior*, **9**, 199-202

Booth, D.A. (1977). Satiety and appetite are conditioned reactions. *Psychosomatic Medicine*, **39** (2), 76-81.

Booth, D.A. (1989). Mood- and nutrient-conditioned appetites: cultural and physiological bases for eating disorders. *Annals New York Academy of Science*, **575**, 122-135.

Booth, D.A. (1992). Integration of internal and external signals in intake control. *Proceedings of the Nutrition Society*, **51**, 21-28.

Booth, D.A., Conner, M.T. and Gibson, E.L. (1989). Measurement of food perception, food preference and nutrient selection. *Annals New York Academy of Science*, **561**, 226-242.

Bowman, B.A., Rosenberg, I.H. and Johnson, M.A. (1992). Gastrointestinal function in the elderly. In *Nutrition of the Elderly*, (H. Munro and G. Schlierf, eds.), Nestlé Nutrition Workshop Series, Vevey/Raven Press, **29**, 43-50.

Bray, G.A. (1984). Syndromes of hypothalamic obesity in man. *Pediatr. Ann.*, **13**, 525-536.

Brobeck, J.R. (1948). Food intake as a mechanism of temperature regulation. *Yale J. Biol. Med.* **20**, 545-52.

Bruch, H. (1974). *Eating disorders: obesity, anorexia and the person within*, Routledge and Kegan Paul, London.

Burns, A., Jacoby, R. and Levy, R. (1990a). Psychiatric phenomena in Alzheimer's Disease. III: Disorders of mood. *Br. J. Psychiatry*, **157**, 81-86.

Burns, A., Jacoby, R. and Levy, R. (1990b). Psychiatric phenomena in Alzheimer's Disease. IV: Disorders of behaviour. *Br. J. Psychiatry*, **157**, 86-94.

Busse, E.W. (1980). Eating in late life: physiologic and psychologic factors. *New York State Journal of Medicine*, **4**, 1496-7.

Campfield, L.A., Brandon, P. and Smith, F.J. (1985). On-line continuous measurement of blood glucose and meal pattern in free-feeding rats: the role of glucose in meal initiation. *Brain Research Bulletin*, **14**, 605-616.

Celesia, G.G., Archer, C.R. and Chung, H.D. (1981). Hyperphagia and obesity: relationship to medial hypothalamic lesions. *Journal of the American Medical Association*, **246**, 151-153.

Chesson, A.L. Jr., Levine, S.N., Kong, L.S. and Lee, S.C. (1991). Neuroendocrine evaluation in Kleine-Levin syndrome: evidence of reduced dopaminergic tone during periods of hypersomnolence. *Sleep*, **14**, 226-32.

Christensen, C.M., (1984). Food texture perception. *Advances in Food Research*, **29**, 159-199.

Chung-A-On, K.O. Thomas, D.E., Tidmarsh, S.F. *et al.* (1985). Vitamin deficiencies: a factor in senile dementia. In *Psychopharmacology and food*, (M. Sandler & T. Silverstone eds.), OUP, 162-174.

Clarke, D.J., Waters, J. and Corbett J.A. (1989). Adults with Prader-Willi syndrome: abnormalities of sleep and behaviour. *Journal of the Royal Society of Medicine*, **82**, 21-24.

Coccaro, E.F., Siever, L.J., Klar, H.M. *et al.* (1989). Serotonergic Studies in Patients with Affective and Personality Disorders. *Arch. Gen. Psychiatry*, **46**, 587-599.

Cohen, D.J., Shaywitz, B.A., Young, J.G. *et al.* (1979). Central biogenic amine metabolism in children with the syndrome of chronic multiple tics of Gilles de la Tourette. *J. American Academy of Child Psychiatry*, **18**, 320-341.

Cohen-Mansfield, J., Marx, M.S. and Rosenthal, A.S. (1990). Dementia and agitation in nursing home residents; how are they related? *Psychol. Aging*, **5**(1), 3-8.

Cooper, J.K. and Mungas, D. (1992). Serotonin response in sweet-food craving Alzheimer's disease subjects, *Aging Clin. Exp. Res.*, **4**, 165-169.

Cooper, M.J. and Fairburn, C.G. (1992). Thoughts about eating, weight and shape in anorexia nervosa and bulimia nervosa. *Behaviour Research and Therapy*, **30**, 501-511.

Cooper, Z. and Fairburn C.G. (1987). The Eating Disorder Examination: a semi-structured interview for the assessment of the specific psychopathology of eating disorders. *International Journal of Eating Disorders*, **6**, 1-8.

Cooper, Z., Cooper, P.J. and Fairburn C.G. (1989). The validity of the Eating Disorder Examination and its subscales. *British Journal of Psychiatry*, **154**, 807-812.

Copeland, J.R.M. (1994). Epidemiology: Prevalence and incidence. In *Principles and Practice of Geriatric Psychiatry*, (J.R.M. Copeland, M.T. Abou-Saleh and D.G. Blazer, eds.), John Wiley & Sons Ltd, 273-277.

Copeland, J.R.M., Gurland, B.J., Dewey, M.E. *et al.* (1987). Is there more dementia, depression and neurosis in New York? A comparative study of the elderly in New York and London using the computer diagnosis AGECAT. *Br J. Psychiatry*, **151**, 466-473.

Copeland, J.R.M., Kelleher, M.J., Kellett, J.M. *et al.* (1976). A semi-structured interview for the assessment of diagnosis and mental state in the elderly: the Geriatric Mental State Schedule. *Psychological Medicine*, **6**, 439-449.

Cosford, P. and Arnold, E. (1992). Eating disorders in later life: a review. *International Journal of Geriatric Psychiatry*, **7**, 491-498.

Cowart, B.J. (1989). Relationship between taste and smell across the adult lifespan. *Annals New York Academy of Sciences*, **561**, 39-55.

Cowen, P.J. (1991). Serotonin receptor subtypes: implications for psychopharmacology. *British Journal of Psychiatry*, **159** (suppl. 12), 7-14.

Cowen, P.J. (1993). Serotonin receptor subtypes in depression: evidence from studies in neuroendocrine regulation. *Clin. Neuropharmacol.*, **16** (Suppl. 3), S6-S18.

Cowen, P.J. and Anderson, I.M. (1991). Abnormal 5-HT neuroendocrine function in depression: association or artefact? In *5-Hydroxytryptamine in Psychiatry: a spectrum of ideas*. (M. Sandler, A. Coppen and S. Harnett eds.) Oxford Medical Publications, 124-137.

Cross, A.J. (1990). Serotonin in Alzheimer-type dementia. *Annals New York Academy of Science*, **600**, 405-417.

Curzon, G. (1985). Effect of food intake on brain transmitter amine precursors and amine synthesis. In *Psychopharmacology and food*, (M. Sandler and T. Silverstone, eds.), OUP, 59-70.

Davis, R. and Davis, B. (1989). *My journey into Alzheimer's disease*. Tyndale House Publishers Inc., Illinois.

De Ajuriaguerra, J., Richard, J., Tissot, R. *et al.* (1976). Les conduites alimentaires dans les démences dégénératives ou mixtes à prédominance dégénérative du grand âge. *Annales médico-psychologiques*, **2**, 213-241.

De Vries, B.B., Fryns, J.P., Butler, M.G. *et al.* (1993). Clinical and molecular studies in fragile X patient with a Prader-Willi-like phenotype. *J. Med. Genet.*, **30**, 761-6.

Dech, B. and Budow, L. (1991). The use of fluoxetine in an adolescent with Prader-Willi Syndrome. *J. Am. Acad. Child Adolesc. Psychiatry*, **30**, 298-302.

- Deutsch, J.A. (1987). Signals determining meal size. In *Eating Habits - Food, Physiology and Learned Behaviour* (R.A. Boakes, D.A. Popplewell and M.J. Burton, eds.), John Wiley & Sons, 155-173.
- Donnelly, M., Rapoport, J.L., and Potter, W.Z. (1989). Fenfluramine and dextroamphetamine treatment of childhood hyperactivity. *Arch. Gen. Psychiatry*, **46**, 205-212.
- Doty, R.L., Reyes, P.F. and Gregor, T. (1987). Presence of both odor identification and detection deficits in Alzheimer's disease. *Brain Research Bulletin*, **18**, 597-600.
- Drake, M.E. (1987). Kleine-Levin syndrome after multiple cerebral infarctions. *Psychosomatics*, **28**, 329-330.
- Ebenezer, I.S. (1992). Effects of the 5-HT_{1A} agonist, 8-OH-DPAT, on operant food intake in non-deprived rats. *NeuroReport*, **3**, 62-4.
- Erb, J.L., Gwirtsman, H.E., Fuster, J.M. and Richeimer, S.H. (1989). Bulimia associated with frontal lobe lesions. *International Journal of Eating Disorders*, **8** (1), 117-121.
- Esiri, M. (1991). Neuropathology. In *Psychiatry in the Elderly*, (Jacoby, R. and Oppenheimer, C. eds.) Oxford Medical Publications, 113-147.
- Esiri, M.M. and Wilcock, G.K. (1984). The olfactory bulbs in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, **47**, 56-60.
- Fairburn, C.G. (1993). Eating disorders. In *Companion to Psychiatric Studies*, (R.E. Kendell and A.K. Zealley, eds.), Churchill Livingstone, Edinburgh, 525-541.
- Fairburn, C.G. and Cooper, Z. (1993). The Eating Disorder Examination (12th Edition). In *Binge Eating: Nature, Assessment and Treatment*, (C.G. Fairburn and G.T. Wilson, eds.), Guilford Press, New York, 317-360.
- Fairburn, C.G. and Hope, R.A. (1988a). Changes in behaviour in dementia: a neglected research area. *British Journal of Psychiatry*, **152**, 406-407.
- Fairburn, C.G. and Hope, R.A. (1988b). Changes in eating in dementia. *Neurobiology of Aging*, **9**, 28-29.
- Feinberg, M.J., Ekberg, O., Segall, L. and Tully, J. (1992). Deglutition in elderly patients with dementia: findings of videofluorographic evaluation and impact on staging and management. *Radiology*, **183**, 811-814.
- Fernstrom, J.D. and Wurtman, R.J. (1971). Brain serotonin content: increase following ingestion of carbohydrate diet. *Science*, **174**, 1023-1025.

Fernstrom, J.D., Wurtman, R.J., Hammarstrom-Wiklund *et al.* (1979). Diurnal variations in plasma concentrations of tryptophan, tyrosine and other neutral amino acids: effect of dietary protein intake. *American Journal of Clinical Nutrition*, **32**, 1912-1922.

Fineberg, N. and Montgomery, S.A. (1990). Neuroendocrine response to serotonergic challenge in obsessive-compulsive disorder. In *Obsessive Compulsive Disorder*, (S.A. Montgomery, W.K. Goodman & N. Goeting, eds.), 19-25.

Fisman, M., Gordon, B., Feleki, V., Helmes, E., McDonald T. and Dupre, J. (1988). Metabolic changes in Alzheimer's disease. *J. Am. Geriatr. Soc.*, **36**, 298-300.

Folstein, M.F., Folstein, S.E. and McHugh, P.R. (1975). Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.*, **12**, 189-198.

Fraser, C. and Durnin, J.V.G.A. (1993). The diet, physical activity patterns and anthropometry of a group of free-living elderly people. *Proceedings of the Nutrition Society*, **52** (3), 344A.

Friedman, M.I., Tordoff, M.G. and Ramirez, I. (1986). Integrated metabolic control of food intake. *Brain Res. Bull.*, **17**, 855-859.

Ganchrow, J. R., Steiner, J.E. and Daher, M. (1983). Neonatal facial expressions in response to different qualities and intensities of gustatory stimuli. *Infant Behav. Develop.*, **6**, 189-200.

Garner, D.M. and Garfinkel, P.E. (1979). The Eating Attitudes Test: an index of the symptoms of anorexia nervosa. *Psychological Medicine*, **9**, 273-279.

Garner, D.M. and Garfinkel, P.E. (1980). Socio-cultural factors in the development of anorexia nervosa. *Psychological Medicine*. **10**, 647-656.

Garry, P.J., Rhyne, R.L., Halioua, L. and Nicholson, C. (1989). Changes in dietary patterns over a 6-year period in an elderly population. *Annals New York Academy of Science*, **561**, 104-112.

Gelder, M., Gath, D. and Mayou, R. (1989). *Oxford Textbook of Psychiatry*, second edition. Oxford Medical Publications, OUP.

George, F.R. (1989). Cocaine produces low dose locomotor depressant effects in mice. *Psychopharmacology*, **99**, 147-150.

Ghaziuddin, N. and McDonald, C. (1985). A clinical study of adult coprophagics. *Br. J. Psychiatry*, **147**, 312-313.

Glick, Z. (1982). Inverse relationship between brown fat thermogenesis and meal size: the thermostatic control of food intake revisited. *Physiology and Behavior*, **29**, 1137-1140.

Glick, Z. (1992). Energy balance in the elderly. In *Nutrition of the Elderly*, (H. Munro & G. Schlierf, eds.), Nestlé Nutrition Workshop Series, **29**, Vevey/Raven Press, 99-108.

Goodall, E. and Corbett, J. (1982). Relationships between sensory stimulation and stereotyped behaviour in severely mentally retarded and autistic children. *J. Ment. Defic. Res.*, **26**, 163-75.

Goodall, E., Feeney, S., McGuirk, J. and Silverstone, T. (1992). A comparison of the effects of *d*- and *l*-fenfluramine and *d*-amphetamine on energy and macronutrient intake in human subjects. *Psychopharmacology*, **106**, 221-7

Goodwin, F.G. and Post, R.M. (1983). 5-Hydroxytryptamine and depression: a model for the interaction of normal variance with pathology. *Br. J. Clin. Pharmac.*, **15**, 393S-405S.

Greenwood, R., Bhalla, A., Gordon, A. and Roberts, J. (1983). Behaviour disturbances during recovery from herpes simplex encephalitis. *Journal of Neurology, Neurosurgery, and Psychiatry*, **46**, 809-817.

Hachinski, V.C., Iliff, L.D., Zilhka, E., Du Boulay, G.H., McAllister, V.L., Marshall, J., Ross Russel, R.W. and Symon, L. (1975). Cerebral blood flow in dementia. *Arch. Neurol.*, **32**, 632-637.

Hardy, J., Adolfsson, R., Alafuzoff, I. *et al.* (1985). Transmitter deficits in Alzheimer's disease. *Neurochem. Int.*, **7**, 545-563.

Healy, K., Conroy, R.M. and Walsh, N. (1985). The prevalence of binge-eating and bulimia in 1063 college students. *Journal of Psychiatric Research*, **19**, 161-166.

Herman, C.P. and Mack, D. (1975). Restrained and unrestrained eating. *Journal of Personality*, **43**, 647-660.

Herman, C.P. and Polivy, J. (1984). A boundary model for the regulation of eating. In *Eating and its Disorders*, (A.J. Stunkard & E. Stellar, eds), Raven Press, New York, 141-156.

Herman, C.P. and Polivy, J. (1988). Studies of eating in normal dieters. In *Eating Behaviour*, (B.T. Walsh, ed.), 97-111.

Herzog, A.G. and Kemper, T.L. (1980). Amygdaloid changes in aging and dementia. *Archives of Neurology*, **37**, 625-629.

- Hetherington, A.W. and Ranson, S.W. (1940). Hypothalamic lesions and adiposity in the rat. *Anat. Res.*, **78**, 149-72.
- Hetherington, M. and Rolls, B.J. (1989). Sensory-specific satiety in anorexia and bulimia nervosa. *Annals of the New York Academy of Sciences*, **575**, 387-398.
- Hetherington, M.M and Rolls, B.J. (1991). Eating behavior in eating disorders: response to preloads. *Physiology and Behavior*, **50**, 101-108.
- Hetherington, M., Rolls, B.J. and Burley, V.J. (1989). The time course of sensory-specific satiety. *Appetite*, **12**, 57-68.
- Hetherington, M.M., Spalter, A.R., Bernat, A.S., Nelson, M.L. and Gold, P.W. (1993). Eating pathology in bulimia nervosa. *Int.J. Eating Disorders*, **13**, 13-24.
- Hierons, R., Janota, I. and Corsellis, J.A.N. (1978). The late effects of necrotising encephalitis of the temporal lobes and limbic areas: a clinicopathological study of 10 cases. *Psychological Medicine*, **8**, 21-42
- Hill, A.J. and Blundell, J.E. (1986). Macro-nutrients and satiety: the effects of a high-protein or high-carbohydrate meal on subjective motivation to eat and food preferences. *Nutrition and Behaviour*, **3**, 133-144.
- Hill, A.J., Leathwood, P.D. and Blundell, J.E. (1987). Some evidence for short-term caloric compensation in normal weight human subjects: the effects of high- and low-energy meals on hunger, food preference and food intake. *Human nutrition: Applied Nutrition*, **41**, 244-57.
- Hirano, A. and Zimmerman, H.M. (1962). Alzheimer's neurofibrillary changes. *Archives of Neurology*, **7**, 227-242.
- HMSO (1991). *Dietary reference value for food energy and nutrients for the United Kingdom*, HMSO (COMA Rpt), Unipub, London.
- Hoebel, B.G., Hernandez, L., Schwartz, D.H. *et al.* (1989). Microdialysis studies of brain norepinephrine, serotonin and dopamine release during ingestive behavior. *Annals of the New York Academy of Sciences*, **575**, 171-193.
- Holland, A.J., Treasure, J., Coskeran, P. *et al.* (1993). Measurement of excessive appetite and metabolic changes in Prader-Willi syndrome. *Int. J. Obes. Relat. Metab. Disord.*, **17(9)**, 527-32.
- Hope, R.A. and Allman, P. (1991). Hyperphagia in dementia: fluvoxamine takes the biscuit. *Journal of Neurology Neurosurgery & Psychiatry*, **54**, 88.
- Hope, R.A. and Fairburn, C.G. (1990). The nature of wandering in dementia: a community-based study. *International Journal of Geriatric Psychiatry*, **5**, 239-245.

- Hope, R.A., Fairburn, C.G and Goodwin, G.M. (1989). Increased eating in dementia. *International Journal of Eating Disorders*, 8, 111-115.
- Hope, R.A., Morris, C.G. and Fairburn, C.G. (1991a). Eating abnormalities in Dementia. *Clinics in Applied Nutrition*, 1(2), 55-62.
- Hope, R.A., Patel, V. and Series, H., (1991b). Dexamphetamine may reduce hyperactivity in dementia - a case study using direct observation. *International Journal of Geriatric Nutrition*, 6, 165-169.
- Hope, T. and Fairburn, C.G. (1992). The Present Behavioural Examination (PBE): the development of an interview to measure current behavioural abnormalities. *Psychological Medicine*, 22, 223-230.
- Hope, T. and Patel, V. (1993). Assessment of behavioural phenomena in dementia. In *Ageing and Dementia - a methodological approach*, (A. Burns ed.), Edward Arnold, London, 221-236.
- Hope, T., Tilling, K.M., Gedling, K., Keene, J.M., Cooper, S.D. and Fairburn, C.G. (1994). The structure of wandering in dementia. *International Journal of Geriatric Psychiatry*, 9, 149-155.
- Hsu, L.K.G. and Zimmer B. (1988). Eating disorders in old age. *Int. J. Eating Disorders*, 7 (1), 133-138.
- Huppert, F. A. and Brayne, C. (1994). What is the relationship between dementia and normal aging? In *Dementia and Normal Aging*, (F.A. Huppert, C.Brayne & D.W. O'Connor, eds.), Cambridge University Press, 3-11.
- Ishii, T. (1966). Distribution of Alzheimer's neurofibrillary changes in the brain stem and hypothalamus of senile dementia. *Acta Neuropathologica*, 6, 181-187.
- Janati, A. (1985). Klüver-Bucy syndrome in Huntington's chorea. *J. Nerv. Mental Dis*, 173, 632-635.
- Jelgersma, H.C. (1964). Ein Fall von juveniler hereditärer Demenz vom Alzheimer Typ mit Parkinsonismus und Klüver-Bucy-Syndrom. *Archiv für Psychiatrie und Zeitschrift f. d. ges. Neurologie*, 205, 262-266.
- Jorm, A.F., Korten, A.E. and Henderson A.S. (1987). The prevalence of dementia; a quantitative integration of the literature. *Acta Psychiatrica Scandinavica*, 76, 465-79.
- Jorm, A.F., Scott, R. and Jacomb, P.A. (1989). Assessment of cognitive decline in dementia by informant questionnaire. *International Journal of Geriatric Psychiatry*, 4, 35-39.

- Khachaturian, Z.S. (1985). Diagnosis of Alzheimer's disease. *Archives of Neurology*, **42**, 1097-1105.
- Kim, R.C., Collins, G.H., Parisi, J.E., Wright, A.W. and Chu, Y.B. (1981). Familial dementia of adult onset with pathological findings of a non-specific nature. *Brain*, **104**, 61-78.
- Kissileff, H.R. (1984). Satiating efficiency and a strategy for conducting food loading experiments. *Neuroscience & Biobehavioral Reviews*, **8**, 129-135.
- Kissileff, H.R. and Thornton, J. (1982). Facilitation and inhibition in the cumulative food intake curve in man. In *Changing concepts of the Nervous System*, Academic Press, 585-607.
- Kissileff, H.R., Gruss, L.P., Thornton, J. and Jordan, H.A. (1984). The satiating efficiency of foods. *Physiology and Behavior*, **32**, 319-332.
- Kissileff, H.R., Klingsberg, G. and Van Itallie, T.B. (1980). Universal eating monitor for continuous recording of solid or liquid consumption in man. *Am.J.Physiol.*, **238**, R14-R22.
- Kissileff, H.R., Thornton, J. and Becker, E. (1982). A quadratic equation adequately describes the cumulative food intake curve in man. *Appetite*, **3**, 255-272.
- Klüver, H. and Bucy, P.C. (1938). An analysis of certain effects of bilateral temporal lobectomy in the rhesus monkey, with special reference to psychic "blindness". *J. Psychology*, **5**, 33-54.
- Knupfer, L. and Spiegel, R. (1986). Differences in olfactory test performance between normal aged, Alzheimer and vascular type dementia individuals. *International Journal of Geriatric Psychiatry*, **1**, 3-14.
- Kopelman, M.D. (1993). The effect of drugs on memory. In *Ageing and Dementia - a methodological approach*, (A. Burns, ed.), Edward Arnold. 193-220.
- Koss, E., Weiffenbach, J.M., Haxby J.V. and Freidland, R.P. (1988). Olfactory detection and identification performance are dissociated in early Alzheimer's disease. *Neurology*, **38**, 1228-1232.
- Krahn, D.D. and Mitchell, J.E. (1984). Case report of bulimia associated with increased intracranial pressure. *American Journal of Psychiatry*, **141**, 1099-1100.
- Kräuchi, K. and Wirz-Justice, A. (1988). The four seasons: food intake frequency in seasonal affective disorder in the course of the year. *Psychiatry Research*, **25**, 323-338.

- Kritchevsky, D. (1992). Protein requirements of the Elderly. In *Nutrition of the Elderly*, (H. Munro and G. Schlierf, eds.), Nestlé Nutrition Workshop Series, **29**, Vevey/Raven Press 109-127.
- Kyriakides, M., Silverstone, T., Jeffcoate, W. and Lawrance, B. (1980). Effect of naloxone in hyperphagia in Prader-Willi syndrome. *Lancet*, **8173**, 876-7.
- Lawless, H.T. (1979). Evidence for neural inhibition in bittersweet taste mixtures. *Journal of Comparative and Physiological Psychology*, **93**, 538-547.
- Lawless, H.T. (1987). Gustatory psychophysics. In *Neurobiology of Taste and Smell*, (T.E Finger & W.L. Silver, eds.), John Wiley & Sons, New York, 401-420.
- Le Magnen, J. (1983). Body energy balance and food intake: a neuroendocrine regulatory mechanism. *Physiol. Rev.*, **63**, 314-86.
- Le Magnen, J. (1985). Hunger. *Problems in Behavioural Science*, Camb. Univ. Press.
- Le Magnen, J. (1987). Central processing of sensory information in the control of feeding. *Progress in Sensory Physiology*, **8**, 95-128.
- Lehmann, J. (1979). How to investigate tryptophan malabsorption and the value of repeated tryptophan loads. In *Origin, Prevention and Treatment of Affective Disorders*, (M. Schou & E. Strömngren, eds.), Academic Press, London, 125-138.
- Lehmann, J., Persson, S., Wålinder, J. and Wallin, L. (1981). Tryptophan malabsorption in dementia. Improvement in certain cases after tryptophan therapy as indicated by mental behaviour and blood analysis. *Acta Psychiat. Scand.*, **64**, 123-131.
- Leibowitz, S.F. (1985). Brain neurotransmitters and appetite regulation. *Psychopharmacology Bulletin*, **21**, 412-418.
- Leibowitz, S.F. (1988). Brain neurotransmitters and eating behavior in the elderly. *Neurobiol. Aging*, **9**, 20-22.
- Leibowitz, S.F. (1989). Hypothalamic neuropeptide Y, galanin and amines: concepts of co-existence in relation to feeding behaviour. *Annals of the New York Academy of Sciences*, **575**, 221-235.
- Leibowitz, S.F. (1990). Neurochemical control of macronutrient intake. In *Progress in Obesity Research*, (Y. Oomura *et al.* eds.), John Libby & Company Ltd, 13-18.
- Leibowitz, S.F. and Shor-Posner, G. (1986). Brain serotonin and eating behavior. *Appetite*, **7**, Supplement, 1-14.

- Levine, A.S. and Billington, C.J. (1991). Stress and feeding behaviour. *Clinics in Applied Nutrition*, 1(2), 32-39.
- Liddle, R.A., Goldfine, I.D., Rosen, M.S. *et al.*, (1985). Cholecystokinin bioactivity in human plasma. Molecular forms, responses to feeding and relationship to gall bladder contraction. *Journal of Clinical Investigation*, 75, 1144-1152.
- Lipschitz, D.A. (1992). Nutrition and ageing. In *Oxford Textbook of Geriatric Medicine* (J.G. Evans & T.F. Williams, eds.), 119-127.
- Lishman, W.A. (1987). *Organic Psychiatry, the psychological consequence of cerebral disorder*, Second Edition. Blackwell Scientific Publications.
- Litchford, M.D. and Wakefield, L.M. (1987). Nutrient intakes and energy expenditures of residents with senile dementia of the Alzheimer's type. *Journal of the American Dietetic Association*, 87, 211-213.
- Lotter, E.C., Krinsky, R., McKay, J.M. *et al.* (1981). Somatostatin decreases food intake of rats and baboons. *J.Comp. Physiol. Psychol.* 95, 278-87.
- Louis-Sylvestre, J. and Le Magnen, J. (1980). A fall in blood glucose level immediately precedes meal onset in free-feeding rats. *Neurosci. Biobehav. Res.*, 4 (Suppl. 1), 13-16.
- MacKenzie, J.M. (1994). Neuropathology. In *Principles and Practice of Geriatric Psychiatry*, (J.R.M. Copeland, M.T. Abou-Saleh & D.G. Blazer, eds.), John Wiley & Sons Ltd, 349-51.
- Magalini, S.I., Magalini, S.C. and Francisci, G. (eds.) (1990). *Dictionary of Medical Syndromes*. 3rd edition, Lippincott, Philadelphia.
- Margo, J.L., Robinson, J.R. and Corea, S. (1980). Referrals to a psychiatric service from old people's homes. *British Journal of Psychiatry*, 136, 396-401.
- Mattes, R.D. and Cowart, B.J. (1994). Dietary assessment of patients with chemosensory disorders. *Journal of the American Dietetic Association*, 94, 50-56.
- Mayer, J. (1953). Glucostatic mechanism of regulation of food intake. *New England Journal of Medicine*, 249, 13-16.
- Mayer, J. (1955). Regulation of energy intake and body weight: glucostatic and lipostatic hypothesis. *Annals New York Academy of Science*, 63, 15.
- McDonald, W.M. and Nemeroff, C.B. (1991). Neurotransmitters and neuropeptides in Alzheimer's disease. *The Psychiatric Clinics of North America*, 14, 421-442.

- McGuirk, J., Goodall, E., Silverstone, T. and Willner, P. (1991). Differential effects of *d*-fenfluramine, *l*-fenfluramine and *d*-amphetamine on the microstructure of human eating behaviour. *Behavioural Pharmacology*, **2**, 113-119.
- McHugh, P.R. and Moran, T.H. (1986). The stomach, cholecystokinin and satiety. *Federation Proceedings*, **45**, 1384-1390.
- McKhann, G., Drachman, D., Folstein, M., *et al.* (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*, **34**, 939-944.
- Meyer, J.E. and Pudel, V.E. (1972). Experimental studies on food intake on obese and normal weight subjects. *Psychosomatic Medicine*, **16**, 305-308.
- Meyer, J.E., Pudel, V. and Huszarik-Felgenendreher, M. (1980). Zum Eßverhalten im höheren Lebensalter: Experimentelle Studien an gesunden und dementen alten Menschen. *Der Nervenarzt*, **51**, 493-497.
- Mitchell, J.E., Hatsukami, D., Eckert, E.D. and Pyle, R.L. (1985). Characteristics of 275 patients with bulimia. *American Journal of Psychiatry*, **142**, 482-485.
- Morley, J.E. and Silver, A.J. (1988). Anorexia in the elderly. *Neurobiol. Aging*, **9**, 9-16.
- Morley, J.E., Silver A.J., Miller, D.K. and Rubenstein, L.Z. (1989). The anorexia of the elderly. *Annals of the New York Academy of Sciences*, **575**, 50-59.
- Morris, C.H. and Hope, R.A. (1990). Alteration in eating behavior following head injury: a case report. *International Journal of Eating Disorders*, **9**, 463-467.
- Morris, C.H. and Hope, R.A. (1992). A review of the management of eating and weight changes in dementia. *British Journal of Clinical and Social Psychiatry*, **8**, 67-71.
- Morris, C.H., Hope, R.A. and Fairburn, C.G. (1989). Eating habits in dementia: a descriptive study. *British Journal of Psychiatry*, **154**, 801-806.
- Morris, C., Hope, T., Gedling, K. and Keene, J. (1993). Dementia and eating abnormalities. *Int. J. Geriatr. Psychiatry*, **8**, 441-443.
- Mungas, D., Cooper, J.K., Weiler, P. G., Gietzen D. *et al.* (1990). Dietary preference for sweet foods in patients with dementia. *Journal of the American Geriatrics Society*, **38**, 999-1007.

- Murphy, C. (1992). Age-associated changes in taste and odor sensation, perception, and preference. In *Nutrition of the Elderly*, (H. Munro & G. Schlierf, eds.), Nestlé Nutrition Workshop Series, Vevey/Raven Press, **29**, 79-87.
- Murphy, C. and Withee, J. (1986). Age-related differences in the pleasantness of chemosensory stimuli. *Psychology and Aging*, **1**, 312-318.
- Nazerali, A.J. and Reynolds, G.P. (1992). Monoamine neurotransmitters and their metabolites in brain regions in Alzheimer's disease. *Cellular and Molecular Neurobiology*, **12**, 581-587.
- Neary, D., Snowden, J.S., Northen, B. and Goulding, P. (1988). Dementia of the frontal lobe type. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 353-361.
- Nelson, H.E. and O'Connell, A. (1978). Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex*, **14**, 234-244.
- Nes, M., Sem, S.W., Rousseau, B. *et al.* (1988). Dietary intakes and nutritional status of old people with dementia living at home in Oslo. *European Journal of Clinical Nutrition*, **42**, 581-593.
- Neumann, M.A. and Cohn, R. (1967). Progressive subcortical gliosis. A rare form of presenile dementia. *Brain*, **90**, 405-418.
- Nidiffer, F.D. and Kelly, T.E. (1983). Developmental and degenerative patterns associated with cognitive, behavioural and motor difficulties in the Sanfilippo syndrome: an epidemiological study. *J. Ment. Defic. Res.*, **27**, 185-203.
- Norberg, A. and Athlin, E. (1989). Eating problems in severely demented patients: issues and ethical dilemmas. *Nursing Clinics of North America*, **24** (3), 781-789.
- Nordström, G., Lundgren, B.K., Nilsson, B. *et al.* (1988). Dietary habits in the eighth decade of life. *Compr. Gerontol.* **2**, 29-39.
- O'Brien, G. and Whitehouse, A.M. (1990). A psychiatric study of deviant eating behaviour among mentally handicapped adults. *British Journal of Psychiatry*. **157**, 281-284.
- Oomura, Y. (1988). Chemical and neuronal control of feeding motivation. *Physiology and Behaviour*, **44**, 555-560.
- Orford, J. (1985). *Excessive Appetites: a psychological view of addictions*, John Wiley & Sons.

- Palmer, A.M., Stratmann, G.C., Procter, A.W. and Bowen, D.M. (1988). Possible neurotransmitter basis of behavioural changes in Alzheimer's disease. *Annals of Neurology*, **23**, 616-620.
- Patel, V. and Hope, R.A. (1992a). Aggressive behaviour in elderly psychiatric inpatients. *Acta Psychiatr. Scand.*, **85**, 131-135.
- Patel, V. and Hope, R.A. (1992b). A rating scale for aggressive behaviour in the elderly - the RAGE. *Psychological Medicine*, **22**, 211-221.
- Paul, A.A. and Southgate, D.A.T. (1991). *McCance and Widdowson's The Composition of Foods* 5th Revised Edition, HMSO.
- Peabody, C.A. and Tinklenberg, J.R. (1985). Olfactory deficits and primary degenerative dementia. *Am. J. Psychiatry*, **142**, 524-5.
- Perl, E., Shay, U., Hamburger, R. and Steiner, J.E. (1992). Taste- and odor-reactivity in elderly demented patients. *Chemical Senses*, **17** (6), 779-794.
- Perry, E.K., Court, J.A., Piggott, M.A. and Perry, R.H. (1994). Cholinergic component of dementia and aging. In *Dementia and Normal Aging*, (F.A. Huppert, C.Brayne & D.W. O'Connor, eds.), Cambridge University Press. 437-469.
- Pilleri, G. (1966). The Klüver-Bucy Syndrome in man. *Psychiatrica Neurologica* (Basel), **152**, 65-103.
- Platt, S., Weyman, A., Hirsch, S. and Hewett, S. (1980). The Social Behaviour Assessment Schedule (SBAS): rationale, contents, scoring and reliability of a new interview schedule. *Social Psychiatry*, **15**, 43-55.
- Prentice, A.M., Leavesley, K., Murgatroyd, P.R. *et al.* (1989). Is severe wasting in elderly mental patients caused by an excessive energy requirement? *Age and Ageing*, **18**, 158-167.
- Price, L.H., Charney, D.S., Delgado, P.L. and Heninger, G.R. (1991). Serotonin function and depression: neuroendocrine and mood responses to intravenous L-tryptophan in depressed patients and healthy comparison subjects. *Am. J. Psychiatry*, **148**, 1518-1525.
- Prinz, P.N. and Vitiello, M.V. (1993). Sleep in Alzheimer's Disease. *Sleep disorders and Insomnia in the Elderly, Facts and Research in Gerontology*, **7**(S), 33-54.
- Prinz, P.N., Peskind, E.R., Vitaliano, P.P. *et al.* (1982). Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. *Journal of the American Geriatrics Society*, **30**(2), 86-93.

- Rau, J.H. and Green R.S. (1975). Compulsive eating: a neurophysical approach to certain eating disorders. *Comprehensive Psychiatry*, **16**, 223-231.
- Rayner, D.V. (1992). Gastrointestinal satiety in animals other than man. *Proceedings of the Nutrition Society*, **51**, 1-6.
- Read, N.W. (1992). Role of gastrointestinal factors in hunger and satiety in man. *Proceedings of the Nutrition Society*, **51**, 7-11
- Reeves, A.G. and Plum, F. (1969). Hyperphagia, rage and dementia accompanying a ventromedial hypothalamic neoplasm. *Archives Neurology (Chicago)*, **20**, 616-624.
- Reisburg, B., Borenstein, J., Salob, S.P. *et al.* (1987). Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J. Clin. Psychiatry*, **48:5 (Suppl.)**, 9-15.
- Renvall, M.J., Spindler, A.A., Ramsdell, J.W. and Paskvan, M. (1989). Nutritional status of free-living Alzheimer's patients. *The American Journal of the Medical Sciences*, **298**, 20-27.
- Rheame, Y., Riley, M.E. and Volicer, L. (1987). Meeting nutritional needs of Alzheimer's patients who pace constantly. *J. Nutr. Elderly*, **7**, 43-52.
- Richard, J. (1987). De la valeur séméiologique et de la signification pathogénique de la stéréotypie dans la maladie d'Alzheimer. *Archives Suisses de Neurologie et de Psychiatrie*, **138 (4)**, 71-80.
- Robertson, M.M. (1990). Obsessional disorder and the Gilles de la Tourette syndrome. In *Obsessive Compulsive Disorder*, (S.A. Montgomery, W.K. Goodman & N. Goeting, eds.), 74-81.
- Rodin, J. (1990). Behavior: Its definition and measurement in relation to dietary intake. In *Diet and Behaviour: Multidisciplinary Approaches*, (G. Harvey Anderson, ed.), Springer-Verlag, 57-72.
- Rogers, P.J. (1990a). Dietary fat, satiety and obesity. *Food Quality and Preference*, **2**, 103-110.
- Rogers, P.J. (1990b). Why a palatability construct is needed. *Appetite*, **14**, 167-170.
- Rogers, P.J. (1993). The experimental investigation of human eating behaviour. *Human Psychopharmacology*, **4**, 123-142.
- Rogers, P.J. (1994). Mechanisms of moreishness and food craving. In *Pleasure, the Politics and the Reality*. (D.M. Warburton and M. Kew, eds.), John Wiley, Chichester, 38-49.

Rogers, P.J., and Blundell, J.E. (1979). Effect of anorexic drugs on food intake and the micro-structure of eating in human subjects. *Psychopharmacology*, **66**, 159-65.

Rogers, P.J. and Blundell, J.E. (1989a). Evaluation of the influence of intense sweeteners on the short-term control of appetite and caloric intake: a psychobiological approach. In *Progress in Sweeteners* (T.H. Grenby, ed.), Elsevier Applied Science, London & New York, 267-289.

Rogers, P.J. and Blundell, J.E. (1989b). Separating the actions of sweetness and calories: effects of saccharin and carbohydrates on hunger and food intake in human subjects. *Physiology and Behavior*, **45**, 1093-1099.

Rogers, P.J. and Blundell, J.E. (1990). Umami and appetite: effects of monosodium glutamate on hunger and food intake in human subjects. *Physiology and Behavior*, **48**, 801-804.

Rogers, P.J. and Hill, A.J. (1989). Breakdown of dietary restraint following mere exposure to food stimuli: interrelationships between restraint, hunger, salivation, and food intake. *Addictive Behaviors*, **14**, 387-397.

Rogers, P.J. and Lloyd, H.M. (1994). Nutrition and mental performance. *Proc. Nut. Soc.*, **53**, 443-456.

Rogers, P.J., Edwards, S., Green, M.W. and Jas, P. (1992). Nutritional influences on mood and cognitive performance: the menstrual cycle, caffeine and dieting. *Proceedings of the Nutrition Society*, **51**, 343-351.

Rogers, P.J., Keedwell, P. and Blundell, J.E. (1991). Further analysis of the short-term inhibition of food intake in humans by the dipeptide L-aspartyl-L-phenylalanine methyl ester (Aspartame). *Physiology and Behavior*, **49**, 739-743.

Rolls, B.J., Hetherington, M. and Burley, V.J. (1988). The specificity of satiety: the influence of foods of different macronutrient content on the development of satiety. *Physiology & Behaviour*, **43**, 145-153.

Rolls, B.J., Rowe, E.A., Rolls, E.T. *et al.* (1981). Variety in a meal enhances food intake in man. *Physiology & Behaviour*, **26**, 215-221.

Rolls, E.T. (1981). Central nervous mechanisms related to feeding and appetite. *Br. Med. Bull.*, **37**, 131-134.

Rolls, E.T. (1986). Neuronal activity related to the control of feeding. In *Neural and Humoral Controls* (R.C. Ritter, S. Ritter & C.D. Barnes, eds.), Academic Press, 163-190.

- Rosenberg, P., Herishanu, Y. and Beilin, B. (1977). Increased appetite (bulimia) in Parkinson's disease. *Journal of the American Geriatrics Society*, **25**, 277-278.
- Roth, M., Tym, E., Mountjoy, C.Q. *et al.* (1986). CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *British Journal of Psychiatry*, **149**, 698-709.
- Rozin, P. (1976). The selection of food by rats, humans and other animals. *Advances in the Study of Behavior*, **6**, 21-76.
- Rozin, P. (1989). Disorders of food selection: the compromise of pleasure. *Annals of the New York Academy of Sciences*, **575**, 376-86.
- Rubenstein, L.Z. (1990). An overview of aging - demographic, epidemiological and health service. In *Geriatric Nutrition*. (J.E. Morley, Z. Glick & L.Z. Rubenstein, eds.), Raven Press, New York, 1-10.
- Ryden, M.B. (1988). Aggressive behavior in persons with dementia who live in the community. *Alzheimer Dis. Assoc. Disord.*, **2**(4), 342-355.
- Sandman, P.O., Adolfsson, R., Nygren, C., Hallmans, G. and Winblad B. (1987). Nutritional status and dietary intake in institutionalized patients with Alzheimer's disease and multiinfarct dementia. *J. Am. Geriatr. Soc.*, **35**, 31-38.
- Sanford, J.R.A. (1975). Tolerance of debility in elderly dependents by supporters at home: its significance for hospital practice. *British Medical Journal*, **3**, 471-473.
- Schiffman, S.S. and Warwick, Z.S. (1988). Flavor enhancement of foods for the elderly can reverse anorexia. *Neurobiology of Aging*, **9**, 24-26.
- Schiffman, S.S., Clark, C.M. and Warwick, Z.S. (1990). Gustatory and olfactory dysfunction in dementia: not specific to Alzheimer's disease. *Neurobiology of Aging*, **11**, 597-600.
- Sclafani, A. and Kirchgessner, A. (1986). The role of the medial hypothalamus in feeding behaviour. In *Neural and Humoral Controls* (R.C. Ritter, S. Ritter & C.D. Barnes, eds.), Academic Press 27-66.
- Serby, M. (1986). Olfaction and Alzheimer's disease. *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **10**, 579-586.
- Shader, R.I., Harmatz, J.S. and Saltzman, C. (1974). A new scale for clinical assessment in geriatric populations - Sandoz Clinical Assessment-Geriatric (SCAG). *J. Amer Geriatr. Soc.*, **22**, 107-113.

- Sharp, T., Backus, L.I., Hjorth, S. *et al.* (1990). Further investigation of the *in vivo* properties of the putative 5-HT_{1A} antagonist, BMY 7378. *Eur. J. Pharmacol.*, **176**, 331-40.
- Shaw, D.M., Sweeney, E.A., Tidmarsh, S.F. *et al.*, (1981). Pilot study of amino acids in senile dementia. *Brit. J. Psychiatr.*, **139**, 580-582.
- Silver, A.J. (1990). Anorexia of aging and protein-energy malnutrition. In *Geriatric Nutrition*, (J.E. Morley, Z. Glick & L.Z. Rubenstein, eds.), Raven Press, New York, 105-115.
- Silverstone, T. (1985). Psychotropic drugs, appetite, and body weight. In *Psychopharmacology and food*, (M. Sandler & T. Silverstone, eds.), OUP, 139-145.
- Sims, N.R., Bowen, D.M., Smith, C.C.T. *et al.* (1980). Glucose metabolism and acetylcholine synthesis in relation to neuronal activity in Alzheimer's disease, *The Lancet*, Feb 16, 1980, 333-336.
- Sims, N.R., Finegan, J.M. and Blass. J.P. (1987). Altered metabolic properties of cultured skin fibroblasts in Alzheimer's disease. *Annals of Neurology*, **21**, 451-457.
- Singh, S., Mulley, G.P. and Losowsky, M.S. (1988). Why are Alzheimer's patients thin? *Age and Ageing*, **17**, 21-28.
- Sinha, D., Zemlan, F.P., Nelson, S., Bienenfeld, D., *et al.* (1992). A new scale for assessing behavioral agitation in dementia. *Psychiatry Research*, **41**, 73-88.
- Sourander, P. and Sjögren, H. (1970). The concept of Alzheimer's disease and its clinical implications. In *Alzheimer's Disease and related conditions*, (G.E.W. Wolstenholme & M. O'Connor), Churchill, London, 11-36.
- Spiegel, T.A. (1973). Caloric regulation of food intake in man. *Journal of Comparative and Physiological Psychology*, **84**, 24-37.
- Stähelin, H.B., Hofer, H.O., Vogel, M. *et al.* (1983). Energy and protein consumption in patients with senile dementia. *Gerontology*, **29**, 145-148.
- Stein, E.M., Stein, S. and Linn, M.W. (1985). Geriatric sweet tooth. A problem with tricyclics. *J. American Geriatr. Soc.*, **33**, 687-92.
- Steiner, J.E. (1979). Human facial expressions in response to taste and smell stimuli. *Advances in Child Development and Behavior*, **13**, 257-295.
- Stevens, J.C., Bartoshuk, L.M. and Cain, W.S. (1984). Chemical senses and aging: taste versus smell. *Chemical Senses*, **9**, 167-179.

- Stricker, E.M. (1978). Hyperphagia. *N. Engl. J. Med.*, **298**, 1010-1013.
- Stunkard, A.J. (1975). Satiety is a conditioned reflex. *Psychosom. Med.*, **37**, 383-387.
- Swearer, J.M., Drachman, D.A., O'Donnell, B.F. and Mitchell, A.L., (1988). Troublesome and disruptive behaviors in dementia. *J. American Geriatr. Soc.*, **36**, 784-790.
- Teff, K.L., Young, S.N., Marchand, L. and Botez, M.I. (1989). Acute effect of protein or carbohydrate breakfasts on human cerebrospinal fluid monoamine precursor and metabolite levels. *J. Neurochem*, **52**, 235-241.
- Teri, L., Boroson, S., Kiyak, A. and Yamagishi, M. (1989). Behavioral disturbance, cognitive dysfunction, and functional skill. *J. Am. Geriatr. Soc.*, **37**, 109-116.
- Thomas, D.E., Chung-A-On, K.O., Dickerson, J.W.T., Tidmarsh S.F. and Shaw D.M. (1986). Tryptophan and nutritional status of patients with senile dementia, *Psychological Medicine*, **16**, 297-305.
- Thompson, C., Obrecht, R., Franey, C. *et al.* (1985). Neuroendocrine rhythms in a patient with Kleine-Levine syndrome. *British Journal of Psychiatry*, **147**, 440-3.
- Tierney, M.C., Fisher, R.H., Lewis, A.J., Zoritto, M.L. *et al.* (1988). The NINCDS-ADRDA Work Group criteria for the clinical diagnosis of probable Alzheimer's disease: a clinicopathologic study of 57 cases. *Neurology*, **38**, 359-64.
- Trinkle, D.B., Burns, A. and Levy, R. (1992). Abnormal eating behaviour in dementia - a descriptive study. *Int. J. Geriatr. Psychiatry*, **7**, 799-803.
- van der Ster Wallin, G., Norring, C. and Holmgren, S. (1994). Binge eating versus nonpurged eating in bulimics: is there a carbohydrate craving after all? *Acta Psychiatr. Scand.* **89**, 376-381.
- van Praag, H.M. (1991). Serotonergic dysfunction and aggression control. *Psychological Medicine*, **21**, 15-19.
- Volicer, L., Selzer, B., Rheaume, Y. *et al.* (1989). Eating difficulties in patients with probable dementia of the Alzheimer type. *Journal of Geriatric Psychiatry and Neurology*, **2**, 188-195.
- Waldbillig, R.J., Bartness, T.J. and Stanley, B.G. (1981). Increased food intake, body weight, and adiposity in rats after regional neurochemical depletion of serotonin. *J. Comparative and Physiological Psychology*, **95**, 391-405.

- Walsh, B.T., Hadigan, C.M., Kissileff, H.R. *et al.* (1992). Eating behaviour in bulimia nervosa. In *The Biology of Feast and Famine - Relevance to eating disorders*. (G.H. Anderson & S.H. Kennedy, eds.), Academic Press, 4-20.
- Ware, C.J.G., Fairburn, C.G. and Hope, R.A. (1990). A community-based study of aggressive behaviour in dementia. *International Journal of Geriatric Psychiatry*, **5**, 337-342.
- Watson, R. (1993). Measuring feeding difficulty in patients with dementia: perspectives and problems. *Journal of Advanced Nursing*, **18**, 25-31.
- Watson, R. (1994a). Measuring feeding difficulty in patients with dementia: developing a scale. *Journal of Advanced Nursing*, **19**, 257-263.
- Watson, R. (1994b). Measuring feeding difficulty in patients with dementia: replication and validation of the EdFED Scale #1. *Journal of Advanced Nursing*, **19**, 850-855.
- Weiffenbach, J.M., Tylanda, C.A. and Baum, B.J. (1990). Oral sensory changes in aging. *Journal of Gerontology*, **45**, M121-125.
- Westerterp-Plantenga, M.S., van den Heuvel, E., Wouters, L. and ten Hoor, F. (1992). Diet-induced thermogenesis and cumulative food intake curves as a function of familiarity with food and dietary restraint in humans. *Physiology and Behavior*, **51**, 457-465.
- Westerterp-Plantenga, M.S., Westerterp, K.R., Nicolson, N.A. (1990). The shape of the cumulative intake curve in humans during basic and manipulated meals. *Physiology and Behavior*, **47**, 569-576.
- Wiepkema, P.R. (1971). Positive feedback at work during feeding. *Behavior*, **39**, 266-273.
- Wilson, A.J., Touyz, S.W., Dunn, S.M. and Beumont, P. (1989). The Eating Behavior Rating Scale (EBRS): A measure of eating pathology in anorexia nervosa. *International Journal of Eating Disorders*, **8**(5), 583-592.
- Wilson, W., Marsden, C.A. and Maughan, R.J. (1994). The effect of prolonged exercise on selected brain monoamine concentrations in the rat. *Proceedings of the Nutrition Society*, **53**, 83A.
- Winograd, C.H., Jacobson, D.H., Butterfield, G.E. *et al.* (1991). Nutritional intake in patients with senile dementia of the Alzheimer type. *Alzheimer Disease and Associated Disorders*, **5**, 173-180.

- Wirz-Justice, A. and Richter, R. (1979). Seasonality in biochemical determinations: a source of variance and a clue to temporal incidence of affective illness. *Psychiatry Research*, **1**, 53-60.
- Wolf-Klein, G.P., Silverstone, F.A. and Levy, A.P. (1992). Nutritional patterns and weight change in Alzheimer's patients. *International Psychogeriatrics*, **4**, 103-118.
- World Health Organisation (1992). *International Classification of Disease (ICD-10) Classification of Mental and Behavioural Disorders: clinical descriptions and diagnostic guidelines*. World Health Organisation, Geneva.
- Wurtman, J.J. (1988a). Carbohydrate craving, mood changes and obesity. *J.Clin. Psychiatry*, **49**, 37-39.
- Wurtman, J.J. (1988b). The Anorexia of aging: a problem not restricted to low calorie intake. *Neurobiology of aging*, **9**, 22-23.
- Wurtman, R.J. (1978). Effects of nutrients and circulating precursors on the synthesis of brain neurotransmitters. In *Central mechanism of Anorectic Drugs*, (S. Garattini & R. Samanin, eds.), Raven Press, New York. 267-294.
- Wurtman, R.J. (1983). Behavioural effects of nutrients. *The Lancet*, **May 21**, 1145-1147.
- Wurtman, R.J. and Wurtman, J.J. (1989). Carbohydrates and depression. *Scientific American*, **260**, 50-57.
- Wurtman, R.J. and Wurtman, J.J. (1992). Dietary carbohydrates, mood, and obesity. In *The Biology of Feast and Famine - Relevance to eating disorders*. (G.H. Anderson & S.H. Kennedy, eds.), Academic Press, 151-156.
- Young, S.N., Tourjman, S.V., Teff, K.L, *et al.* (1988). The effect of lowering plasma tryptophan on food selection in normal males. *Pharmacology, Biochemistry and Behavior*, **31**, 149-152.
- Zipf, W.B. and Berntson G.G. (1987). Characteristics of abnormal food-intake patterns in children with Prader-Willi syndrome and study of effects of naloxone. *Am. J. Clin. Nutr*, **46**, 277-281.
- Zipf, W.B., O'Dorisio, T.M. and Berntson, G.G. (1990). Short-term infusion of pancreatic polypeptide: effect on children with Prader-Willi syndrome. *American Journal of Clinical Nutrition*, **51**, 162-166.
- Zubenko, G.S., Moossy, J. and Kopp, U., (1990). Neurochemical correlates of major depression in primary dementia. *Arch. Neurol.*, **47**, 209-214.