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Review Article

The Korsakoff Syndrome

MICHAEL D. KOPELMAN

Background. Investigations of the Korsakoff syndrome by researchers from different disciplines have proliferated in recent years, making it apposite to review the various findings.
Method. This review is based on the author's knowledge of reports in the major clinical and neuropsychological journals, supplemented by Medline searches to update particular subtopics.
Results. The Korsakoff syndrome is defined as a disproportionate impairment in memory, relative to other aspects of cognitive function, resulting from a nutritional (thiamine) depletion. The initial manifestations of the disorder are variable, and a persistent memory impairment can result from a non-alcoholic aetiology, although this seems to happen much less commonly than in the past – presumably because of generally higher standards of nutrition. Although there is agreement on the underlying neuropathology, the critical lesion sites for memory disorder have been debated. Recent evidence suggests that the circuit involving the mammillary bodies, the mammillo-thalamic tract and the anterior thalamus, rather than the medial dorsal nucleus of the thalamus, is particularly critical in the formation of new memories. The relationship of these deficits to thiamine depletion remains a topic of current investigation, as does the purported role of neurotransmitter depletions in the cholinergic, glutamate/GABA and catecholamine and serotonergic systems. Neuro-imaging studies have confirmed autopsy findings of more widespread structural and metabolic abnormalities, particularly involving the frontal lobes.
Conclusions. The relationship of these neuropathological, neurochemical, and metabolic abnormalities to cognitive functioning, with particular reference to specific aspects of memory processing, has been considered in some detail. Whereas structural and/or neurochemical abnormalities within the limbic/diencephalic circuits account for anterograde amnesia, some other factor, such as frontal lobe dysfunction, must underlie the severe retrograde memory loss which is characteristically found in this syndrome.

The fascination of the Korsakoff syndrome is that relatively small, and sometimes abrupt, neuropathological lesions give rise to a severe amnesic syndrome, disproportionate to any other impairments in cognitive functioning. The neurochemical processes involved and the precise specification of the nature of the memory deficit remain topics of intense investigation. The recent emergence of neuroimaging techniques for specification of structural and metabolic abnormalitiess, as well as the existence of increasingly flexible neurochemical, neuropharmacological, and neuropsychological techniques, now provide the opportunity for relating neurobiological abnormalities to specific cognitive deficits much more closely.

This paper reviews clinical and neuropsychological findings in this disorder, relating them to observations from neuropathological, neurochemical, and neuroimaging studies. As Korsakoff's own clinical description of the syndrome has commonly been misinterpreted, and turns out to be much closer to recent neuropsychological findings than many textbook interpretations, his account would seem a suitable place to begin.

Clinical description of the syndrome

Korsakoff's description

Although earlier writers noted the association between alcohol abuse and the development of profound amnesia (e.g. Hooke, 1680; D'Assigny, 1697), the first formal descriptions in the modern scientific literature were by Lawson (1878) and Korsakoff (1887, 1889*a*,*b*). Lawson is one of the least acknowledged, and Korsakoff one of the most misquoted, authors in medical literature, and consequently it is important to clarify what they actually said.

Lawson (1878) described a syndrome, frequently but not always of alcoholic causation, in which there was a severe loss of recent memory. He distinguished cases in which there was a specific loss of memory from those in whom alcohol induced a progressive dementia, difficult to differentiate from general paresis; he also discussed a case of psychogenic amnesia. In the course of his discussion, he remarked that "in cases where organic change has been produced in the brain, the nature of the symptoms

will be caused not so much by the character of the exciting cause (e.g. alcohol), as by the physiological functions of the regions diseased".

In a series of three articles, Korsakoff (1887, 1889*a*,*b*) described a syndrome of characteristic memory disturbance, which he had witnessed in "not less than thirty" cases of chronic alcohol abuse, as well as 16 patients in whom alcohol had not played a role. The latter cases included instances in which the syndrome had developed following persistent vomiting (eight patients), postpartum (sepsis, macerated foetus), in acute or chronic infection (typhus, tuberculosis), after toxic poisoning (carbon monoxide, lead, arsenic), or other chronic disease (neoplasm, lymphadenoma, diabetes). Although Korsakoff did not make any specific reference to Wernicke's syndrome, which had been described in 1881, he did mention that a "prodromal agitation and confusion" commonly preceded the appearance of the memory disorder; that "sometimes there are ophthalmoplegia externa, nystagmus and like manifestations"; and that gait disturbance (ataxia), dysarthria and dysphagia may also be present. Furthermore, the 'psychic disturbance' was an aspect of a 'multiple neuritis' in which peripheral neuropathy was commonly, but not necessarily, present (Korsakoff, 1889*a*).

The characteristic memory disturbance occurred in a setting of clear consciousness.

> "At first, during conversation with such a patient . . . (he or she) gives the impression of a person in complete possession of his (or her) faculties; he (she) reasons about everything perfectly well, draws correct deductions from given premises, makes witty remarks, plays chess or a game of cards, in a word comports himself (herself) as a mentally sound person."

However,

> "the patient constantly asks the same questions and repeats the same stories . . . may read the same page over and again sometimes for hours . . . is unable to remember those persons whom he (she) met only during the illness, for example, the attending physician or nurse".

Characteristically, "the memory of recent events . . . is chiefly disturbed . . . everything that happened during the illness and a short time before". However, in some cases "not only memory of recent events is lost, but also that of the long past", in which case the impairment may involve memories of up to 30 years earlier. Korsakoff also emphasised the variability in the severity of the disorder. In mild cases, recent memories are "remembered vaguely . . . (without) complete abrogation . . . the forgetfulness chiefly affects the patient's own thought processes . . . (and) facts are remembered" although their retrieval requires "specially favourable conditions". In some instances, events may be remembered "but not the time when they occurred". In more severe cases, "the amnesia is much more profound . . . the memory of facts is completely lost".

As is well known, Korsakoff mentioned that "such patients invent some fiction and constantly repeat it . . . (for example) of conversations which have never occurred . . . so that a peculiar delirium develops, rooted in false recollections (pseudo-reminiscences)". However, he tended to place greater emphasis upon the confusion of "old recollections with present impressions", and he gave several examples of this:

> "In telling of something about the past, the patient would suddenly confuse events and would introduce the events related to one period into the story about another period . . . Telling of a trip she had made to Finland before her illness and describing her voyage in fair detail, the patient mixed into the story her recollections of Crimea, and so it turned out in Finland people always eat lamb and the inhabitants are Tartars".

Subsequent clinical studies

Subsequent studies have confirmed the broad outline of Korsakoff's clinical description, and that a characteristic confusional state and memory disorder and/or neuropathological changes can result from a number of factors besides chronic alcohol abuse.

Moll (1915) described 30 alcohol-related cases, of whom 25 (83.3%) were men. Like Korsakoff, he emphasised the patients' intact attention, their disorientation in time, and the variability of their retrograde loss. The disorientation in time resulted in the patients' underestimation of the duration of their hospitalisation; the retrograde component of the amnesia could sometimes be extensive. Similarly, Zangwill (1953) described two Korsakoff patients who gave a striking underestimation of their age, and whose retrograde amnesia extended back at least ten years before the onset of the disorder. Talland (1965), Victor *et al* (1971) and Luria (1976) all followed Korsakoff in arguing that confabulation often results from the inappropriate recall of genuine memories, jumbled in temporal sequence. Victor *et al* (1971) also emphasised the extensive nature of the retrograde component of the amnesia:

> "(Whilst) it is true that remote memories were better preserved than recent ones . . . it was our impression that memories of the distant past were impaired to some extent in practically all patients with Korsakoff's psychosis and seriously impaired in most of them".

Spurning an emphasis upon either a specific deficit of recent memory or the presence of confabulation, Victor *et al* (1971) defined the disorder as "an abnormal mental state in which memory and learning are affected out of all proportion to other cognitive functions in an otherwise alert and responsive patient". The diagnosis of the syndrome nowadays requires both clinical and neuropsychological evidence of this disproportionate memory impairment, as well as evidence of an underlying alcoholic or nutritional aetiology.

Two topics in which clinical findings have been more conflicting are the mode of onset of the disorder and the prevalence of Wernicke features. Moll (1915) followed Kraepelin (1910) in arguing that the disorder can have either an acute or an insidious onset, and he also noted a better prognosis in women. Cravioto *et al* (1961) emphasised that the disorder most commonly first appears as an 'organic mental syndrome' (confusion, disorientation, memory impairment, and dyscalculia) with or without peripheral neuropathy, and that eye signs and ataxia were relatively rare. The full Wernicke 'triad' (confusion, eye signs, ataxia) was present in only four (14.3%) of their 28 (pathologically-confirmed) cases, and in none of 42 cases described in an earlier series by Riggs & Boles (1944). On the other hand, 96% of the Korsakoff patients described by Victor & Adams (1953) and Victor *et al* (1971) had manifested signs of a preceding Wernicke syndrome, and only 10% of these patients had exhibited an insidious onset (Victor & Adams, 1985). However, Cravioto *et al* (1961) pointed out that the prevalence figures obtained in the Victor & Adams (1953) series would have reflected the nature of the referrals and the diagnostic criteria employed within an acute neurological service; in short, this series may have represented a selected subsample of a wider population of Korsakoff patients.

Consistent with this view, Cutting (1978*a*) found that, in a retrospective series of 50 Korsakoff patients diagnosed within a psychiatric service, the disorder sometimes had an acute onset and sometimes an insidious onset, defined in terms of the interval between the onset of symptoms and admission to hospital. An 'acute' onset (less than eight weeks between onset and admission) was more commonly associated with the classical Wernicke eye signs, whereas an 'insidious' onset (more than eight weeks between onset and admission, the mean being one year) occurred more commonly in women and had a better long-term prognosis. More recent studies have indicated that some patients, in whom a pathological diagnosis of Wernicke's encephalopathy is eventually made, may first appear in coma (Torvik *et al*, 1972; Wallis *et al*, 1978), whereas others may never have been diagnosed in life, surviving in the community with (presumably) a milder degree of memory impairment (Harper, 1979, 1983; Torvik *et al*, 1982). In short, it appears that the initial clinical manifestation of the disorder may vary from acute coma, through the classical Wernicke syndrome, to an insidious onset of memory impairment, and that, in some cases, the disorder may not be identified until the subject comes to autopsy.

Furthermore, various modern writers have confirmed that the Wernicke-Korsakoff pathology can result from a number of debilitating disorders, all of which produce malnutrition or malabsorption. De Wardener & Lennox (1947) described 52 prisoners-of-war in south-east Asia who developed a Wernicke encephalopathy as a result of malnutrition, of whom 32 (61.5%) developed loss of recent memory. The onset was 6–14 weeks after the start of captivity, and was usually preceded by episodes of diarrhoea and vomiting, self-starvation, or concurrent infection (Cruikshank, 1950). Interestingly, in the early stages, the subjects *complained* of wavering vision on looking sideways, double vision, memory loss, and impaired time appreciation, indicating that 'insight' was initially preserved. Other writers have described Wernicke symptoms and/or pathology occurring after: self-starvation (Devathason & Koh, 1982; Pentland & Mawdsley, 1982); intravenous feeding, especially in the presence of a glucose load (Wallis *et al*, 1978; Harper, 1980; Luda, 1980); the persistent vomiting of hyperemesis gravidarum (Campbell & Russell, 1941; Nightingale *et al*, 1982; Wood *et al*, 1983); and carcinoma of the oesophagus, stomach, or intestine (Campbell & Russell, 1941; Malamud & Skillicorn, 1956; Ebels, 1978). Ebels (1978) reported 29 cases of Wernicke-Korsakoff pathology detected at autopsy, in whom chronic alcohol abuse had been excluded. He subdivided the underlying clinical disorders into four main groups: (a) gynaecological (hyperemesis gravidarum, malignancy); (b) gastrointestinal (carcinoma, other causes of malabsorption); (c) other malignancy; and (d) other causes of debility and malnutrition (e.g. haemodialysis, severe self-neglect).

Although the above papers described Wernicke symptoms and/or Wernicke-Korsakoff pathology resulting from nutritional disorders, most did not provide sufficient or unequivocal evidence of persistent memory impairment, except for Korsakoff himself (1889), De Wardener & Lennox (1947), and Cruikshank (1950). Three recent papers have attempted to do this, using modern neuropsychological techniques (Beatty *et al*, 1989; Becker *et al*, 1990; Parkin *et al*, 1991). Beatty *et al* (1989)

described a patient with a "Korsakoff-like amnesic syndrome" following severe anorexia and vomiting, but this patient had very abnormal liver function tests, including a very high gamma glutanyl transferase (γGT), which raises the suspicion of past alcohol misuse. Becker *et al* (1990) described a woman with malabsorption from an inflammatory cause in the small intestine, who had a past history of heavy drinking, although that seems to have resolved by the time of her amnesic disorder. Parkin *et al* (1991) described a patient who had had prolonged intravenous feeding, but the amnesia appeared following a surgical operation, in which she had to have a blood transfusion, and there were multiple small lesions in the deep white matter on a magnetic resonance imaging (MRI) scan, probably vascular in origin, making unclear the possible contribution of hypotension and/or hypoxia during the operation. In short, it is surprisingly hard to find unequivocal cases of the amnesic syndrome from non-alcoholic nutritional depletion nowadays, presumably because of generally higher standards of nourishment than when Korsakoff himself was writing. However, there is little doubt that non-alcoholic causes may complicate and compound alcoholic causation, and the present author has seen one case in whom a previous gastrectomy, and another case in whom carcinoma of the stomach, probably contributed to the onset of Wernicke and Korsakoff symptoms.

Finally, various forms of localised brain pathology can, of course, produce an amnesic syndrome, although the term 'Korsakoff syndrome' is nowadays best reserved for those cases of persistent memory impairment with the characteristic pathological changes (discussed below), resulting from nutritional (thiamine) depletion.

Case examples

Case 1

Patient B, who was born in 1925, has been included in studies of the Korsakoff syndrome by various authors. He has consistently claimed that he consumed ten pints of beer per night for 20–25 years, but only at weekends. If true, the effects of this alcohol consumption may have been exacerbated by a partial gastrectomy which was performed in 1952 for a perforated duodenal ulcer. However, it is clear that B went on a four-week alcoholic binge following the death of his wife in 1970, and this culminated in an admission, in which nystagmus, ataxia, and confusion were noted, as well as a peripheral neuropathy. When last seen by the author, B was living in a long-stay hospital, where he was able to find his way about within the immediate vicinity, but would get lost if he travelled further.

B was formerly an electrician, and he had a full scale IQ of 99 with an anterograde memory quotient (AMQ) of approximately 51. He also showed fairly severe impairment across various tests of retrograde memory with a pronounced 'temporal gradient' (relative sparing of early memories). On tests of frontal lobe function, he was also quite severely impaired, scoring only 19 on FAS verbal fluency, and obtaining only two out of six categories on a card-sorting test with 81% perseverative errors.

Case 2

Born in 1936, C had been a receptionist and secretary. She had consumed one bottle of sherry or as much as two-and-a-half bottles of wine per day for approximately 15–20 years, and then consumed three-quarters of a bottle of gin plus half a bottle of wine per day for seven years until her admission. In June 1983, her general practitioner made a domicilary visit and found that she had opthalmoplegia, marked ataxia, confusion, and profuse confabulation. The opthalmoplegia and confabulation resolved over the course of a month, following thiamine administration, but some degree of nystagmus and a pronounced ataxia remained, the latter of which was secondary to both a sensory and a motor neuropathy. She was first seen by the present author in a general hospital, and, when visited in a long-stay psychiatric hospital two years later, she had no memory of ever having been in the general hospital.

C had a full scale IQ of 115 and an AMQ of 70. On retrograde memory tests, she showed moderately severe impairment with a pronounced sparing of early memories. For example, she was able to describe how she had won a tennis cup at the age of 15, beating "Gorgeous Gussie" on the way, and how, after the prize-giving, her father had made a derogatory comment about her maths. On the other hand, she was able to give only a very fragmentary account of her current daily life, and was unable to recognise the author from previous visits. On frontal lobe tests, she showed relative preservation, scoring 45 on FAS verbal fluency and obtaining six out of six categories on card-sorting with no perseverative errors.

Case 3

D was a school teacher who had been born in 1923. His drinking history was somewhat unclear. It was probable that he had started consuming alcohol fairly

heavily either while in the Fleet Air Arm during the Second World War, or during three years in the Merchant Navy following that, but he admitted to drinking heavily for only about seven years before the onset of his disorder. During that time, he said that he had been drinking eight or nine pints of beer a night, plus a third of a bottle of spirits daily. The onset of his disorder had occurred when he was staying in a hotel in Lagos in 1976, when he suddenly became ataxic, abusive and excessively talkative. Medical details of his admission were lacking, but in the 1980s he still showed evidence of nystagmus, marked ataxia, and some degree of disorientation. In the past, he had been described as confabulating. D was a linguist, who had previously been accomplished in current European, classical, and several African languages. These linguistic skills appeared to be largely intact, providing evidence of the relative preservation of the more semantic (conceptual/linguistic) aspects of memory.

Current full scale IQ was 129, and his AMQ was 69. On retrograde memory tests, he showed fairly severe impairment across all tests, with a marked temporal gradient. On tests of frontal lobe function, he showed fairly severe impairment, scoring 24 on FAS verbal fluency and obtaining only two out of six categories on card-sorting, with 45% perseverative errors.

Neuropathology of the Wernicke-Korsakoff syndrome

Type and distribution of lesions

Bender & Schilder (1933) established that patients with a *pathological* diagnosis of Wernicke's encephalopathy had often displayed a "mental picture . . . like that of a Korsakoff psychosis". Consistent with this, Jolliffe *et al* (1941) reported that of 27 patients who were given a *clinical* diagnosis of Wernicke's syndrome, 13 survived, of whom 12 were left with a residual Korsakoff syndrome. Subsequently, the pathological series of Malamud & Skillicorn (1956) and Victor *et al* (1971) clearly established that the distribution and nature of the pathological lesions in the two disorders were virtually identical, resulting in the coining of the term 'the Wernicke-Korsakoff syndrome'.

These studies, and also that of Cravioto *et al* (1961), confirmed that the pathological abnormalities lay in the paraventricular and peri-aqueductal grey matter, the walls of the third ventricle, the floor of the fourth ventricle, and the cerebellum. The mammillary bodies and the thalamus were among the sites most commonly affected (Malamud & Skillicorn, 1956; Cravioto *et al*, 1961; Victor *et al*, 1971; Harper, 1983). There were petechial haemorrhages, endothelial proliferation, focal areas of parenchymal necrosis, demyelination, gliosis, and variable degrees of neuronal loss (Jolliffe *et al*, 1941; Malamud & Skillicorn, 1956; Cravioto *et al*, 1961; Victor *et al*, 1971). As mentioned above, similar changes have also been observed in subjects in whom a diagnosis was not made during life, but in whom there had been a history of alcohol abuse (Harper, 1979, 1983; Torvik *et al*, 1982). In some of these latter subjects, acute or 'active' pathological changes (haemorrhages, endothelial proliferation) were prominent, but, more commonly, chronic or 'inactive' changes (necrosis, gliosis) were predominant (Torvik *et al*, 1982; Harper, 1983).

In addition, Malamud & Skillicorn (1956) reported that cortical atrophy was present in 8.5% of their Wernicke-Korsakoff cases, Victor *et al* (1971) in 26% of their series, and Harper (1983) in 21% of his subjects. More recently, Harper *et al* (1987, 1988) have drawn attention to the gross atrophy, reduced neuron count and increased hydration of the frontal lobes in alcoholic subjects at autopsy, particularly those in whom a pathological diagnosis of Wernicke's encephalopathy has been made.

Critical lesion sites for memory disorder

Although there is now general agreement about the overlapping distribution of the lesions in Wernicke's encephalopathy and Korsakoff's syndrome, debate has ensued regarding the critical lesion(s) for the development of an amnesic syndrome, the thalamus and the mammillary bodies being the sites most commonly implicated. Victor *et al* (1971) pointed out that of 24 cases in whom the medial-dorsal nucleus of the thalamus was affected, all had a clinical history of persistent memory impairment (Korsakoff's syndrome), whereas five cases in whom it was unaffected had a history of Wernicke features without any recorded clinical history of subsequent memory disorder. By contrast, the mammillary bodies were implicated in all the Wernicke cases examined, whether or not there was subsequent memory impairment. Amnesia in association with unilateral or bilateral involvement of the thalamic nuclei, with apparent sparing of the mammillary bodies, has also been described in cases of tumour or infarction (McEntee *et al*, 1976; Speedie & Heilman, 1982; Guberman & Stuss, 1983; Winocur *et al*, 1984; Graff-Radford *et al*, 1985, 1990; Katz *et al*, 1987; Parkin *et al*, 1994).

However, Mair *et al* (1979) provided a careful pathological and neuropsychological description of

two Korsakoff patients, whose autopsies showed lesions in the mammillary bodies and the midline and anterior portion of the thalamus but *not* in the medial dorsal nuclei. They suggested that these lesions might 'disconnect' a critical circuit running between the temporal lobes and the frontal cortex, and Warrington & Weiskrantz (1982) put forward a hypothesis concerning the functional significance of this circuit. Mayes *et al* (1988) presented findings in two further patients, who had had careful neuropsychological and autopsy investigations, which closely replicated the findings in the Mair *et al* (1979) study. Von Cramon *et al* (1985) reviewed findings in a personal series of six cases of thalamic infarction (of whom four were amnesic and two were not), together with a further five cases from the literature. These authors found that the region of the thalamus always implicated in the amnesic cases (and not implicated in the non-amnesic patients) lay in the anterior thalamus, involving the mammillo-thalamic tract, ventral to the medial dorsal nucleus (cf. Graff-Radford *et al*, 1990). More recently, Squire *et al* (1989*a*) and Dusoir *et al* (1990) have described two patients whose anterograde amnesia appears to have resulted from traumatic lesions to the mammillary bodies, consistent with the view that a circuit involving the mammillary bodies, the mammillo-thalamic tract and the anterior thalamus is crucial for memory formation. Findings generally consistent with these observations have also been reported by Castaigne *et al* (1981), Mori *et al* (1986) and Gentilini *et al* (1987).

Markowitsch (1984) has argued that lesions within the thalamic nuclei (or hippocampi) do not always give rise to amnesia and, when they do, there is usually concomitant involvement of other nuclei. It follows from von Cramon *et al*'s (1985) findings that there are critical regions within the thalami that must be implicated for amnesia to occur; and Markowitsch (1984) acknowledged that there may be 'nodal points' in the neural substrate of memory (c.f. Zola-Morgan *et al*, 1986). Markowitsch (1984) emphasised that the thalamic nuclei and hippocampi do not themselves represent discrete "functional entities", but are embedded in complex neural circuits and "neuronal assemblies". Consistent with this, Mishkin (1978, 1982) argued from animal experiments that there are two limbic circuits in which combined lesions are required to produce severe amnesia: the hippocampal (medial limbic) and amygdaloid (basolateral limbic) circuits, (but see Meunier *et al*, 1993; Murray *et al*, 1993). The anterior and dorsomedial thalamus and the medial temporal lobes are the anatomical locations ('nodal points') where these two circuits converge, and are, therefore, particularly vulnerable to the effect of discrete structural lesions (Speedie & Heilman, 1982; Markowitsch, 1984; von Cramon *et al*, 1985; Valenstein *et al*, 1987; Graff-Radford *et al*, 1990). On the other hand, Zola-Morgan *et al* (1989*a*,*b*) have produced evidence from primate studies arguing against the role of the amygdaloid circuit, and indicating that parallel projections from the perirhinal cortex may be more important (compare Meunier *et al*, 1993; Murray *et al*, 1993). A careful MRI study of an amnesic patient with a left thalamic infarction has recently been interpreted in these terms (Parkin *et al*, 1994), although the involvement of both the mammillo-thalamic tract and the dorsomedial nucleus in their patient leaves equivocal the relative importance of these two structures.

In summary, the balance of the more recent evidence appears to suggest that it is a circuit comprising the hippocampus, entorhinal and perirhinal cortex, the mammillary bodies, mammillo-thalamic tract, and the anterior (rather than the medial dorsal) nucleus of the thalamus, which is particularly critical in memory formation.

Neurochemistry of the Korsakoff syndrome

Thiamine

In an elegant series of experiments, Alexander (1940) and Alexander *et al* (1938) demonstrated that: (a) the lesions of Wernicke's encephalopathy could be produced in pigeons following thiamine deprivation; (b) these lesions were not produced by deprivation of all other vitamins, when doses of thiamine were adequate; and (c) the histology and topography of these lesions were identical to those obtained in a series of 16 Wernicke patients. Subsequently, Jolliffe *et al* (1941) reported clinical evidence of thiamine deficiency in 27 Wernicke patients, of whom 12 survivors manifested the Korsakoff syndrome. The latter group showed an incomplete and inconsistent response to thiamine therapy, although Bowman *et al* (1939) had earlier shown that disorientation and confabulation often show a favourable response to thiamine therapy in very early Korsakoff cases. Similarly, Campbell & Russell (1941) felt that thiamine deficiency was 'strongly incriminated' in a series of 21 cases of Wernicke's encephalopathy, and these authors also noted the common association with Korsakoff's syndrome in survivors. Subsequently, De Wardener & Lennox (1947) reported their observations in malnourished prisoners-of-war. The onset of symptoms, which included mental changes in 78% of cases and loss of recent memory in 61%, generally occurred 6–14 weeks after captivity; this is the same time as symptoms of beriberi develop (also

caused by thiamine depletion), but before the symptoms of other vitamin deficiencies. Moreover, the symptoms showed a very favourable response to thiamine treatment by injection, when this was available, but resulted in a very high mortality when thiamine was unavailable.

In retrospect, the common factor in both the alcoholic and the non-alcoholic Korsakoff patients, who have developed the syndrome in the absence of any other brain pathology, is almost certainly a thiamine deficiency. However, it is sometimes claimed that a *combination* of thiamine deficiency and the direct neurotoxic action of alcohol is required to produce a *persistent* memory loss (unresponsive to treatment) in the Korsakoff syndrome (Freund, 1973; Butters & Cermak, 1980). Although it is probable that the non-alcoholic cases tend to show a better response to thiamine therapy, it should be noted that (a) Korsakoff's own series included 15 non-alcoholic cases; (b) one of De Wardener & Lennox's (1947) and three out of eight of Cruikshank's (1950) prisoners-of-war showed persistent mental symptoms despite treatment; and (c) in many other series adequate follow-up details are not provided, and consequently cognitive outcome is unknown. It seems likely that the response to treatment is determined by the age of the patient (Tallaksen *et al*, 1993), the abruptness of the onset of the disorder, and the rapidity with which treatment is instituted, and it is plausible that treatment is instituted more rapidly in the non-alcohol cases. Moreover, McEntee (1993) has pointed out that alcohol reduces both the absorption of thiamine and the activity of the enzyme which converts it to its active form.

It has been suggested that nicotinic acid deficiency may contribute to the development of the disorder in some cases (Jolliffe *et al*, 1941; Lishman, 1981; Ishii & Nishihara, 1981), although this suggestion is difficult to evaluate in view of the fact that all the B group vitamins have generally been depleted (and replaced) together. However, recent scares concerning anaphylaxis following Parentrovite administration may mean that inadequate replacement of the other B vitamins will become more common (cf. Serdaru *et al*, 1988).

A genetic factor has been postulated to explain why only a minority of heavy drinkers develop the syndrome, which is far less common than the hepatic or gastrointestinal complications of alcohol abuse. Transketolase is an enzyme which requires thiamine pyrophosphate (TPP) as a co-factor, and Blass & Gibson (1977) postulated that a hereditary abnormality of transketolase metabolism predisposed some alcoholics to the Korsakoff syndrome. However, their study was based on only four cases, and subsequently, Leigh *et al* (1981) reported wide variability in transketolase activity among Korsakoff patients and other alcoholics. Nixon *et al* (1984) reported that one particular pattern in the isoenzymes of human erythrocytic transketolase was associated with the presence of Wernicke-Korsakoff syndrome. However, the affinity (Km) for the interaction of this particular transketolase variant with TPP did not differ between patients and controls, leaving it unclear why these patients should be particularly vulnerable to the effects of thiamine depletion (Nixon *et al*, 1984). More recently, Jung *et al* (1993) demonstrated that transketolase activity in the fibroblasts of three Korsakoff patients was reduced by 45%, but their transketolase showed normal immunochemical characteristics. Consistent with this, McCool *et al* (1993) have identified the transketolase gene, finding that no particular allelic variants could account for the biochemical properties of the enzyme, when cultures from two Wernicke-Korsakoff patients with extremely low affinity (Km) for the TPP co-enzyme were compared with cultures from two non-alcoholic controls with extremely high affinity. Hence, McCool *et al* (1993) argued that (extragenic) differences in post-translational processing and modification of the transketolase polypeptide, rather than allelic variation, might underlie variable susceptibility to the development of the syndrome among alcoholics.

Witt (1985) has provided an excellent review of the possible ways by which thiamine depletion might predispose to the characteristic pathological lesions of the Wernicke-Korsakoff syndrome, although the precise mechanism involved is not known. TPP, the active form of thiamine, appears to be involved in DNA synthesis as well as three enzymatic reactions which are essential for glucose metabolism and neurotransmitter production; and the metabolic heterogeneity of different brain regions might explain why some areas are more vulnerable to thiamine depletion than others. Six neurotransmitter systems are affected by thiamine depletion, either by reduction of TPP-dependent enzyme activity, or by direct structural damage, and four of these neurotransmitters, acetylcholine, glutamate, aspartate, and gamma-amino butyric acid (GABA) are directly related to glucose metabolism (Fig. 1).

Acetylcholine

Particular interest lies in the possible contribution of cholinergic depletion to the memory disorder of the Korsakoff syndrome, in view of the evidence that cholinergic blockade in healthy subjects may induce memory impairment (Kopelman & Corn, 1988), and

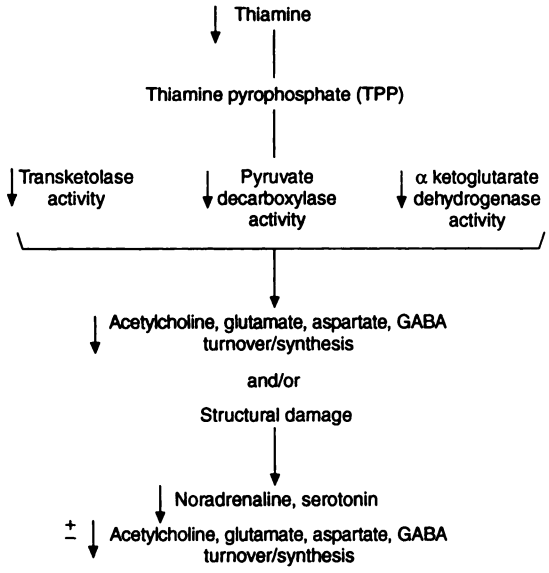

Fig. 1 Thiamine and neurotransmitter production (based on Witt, 1985).

that acetylcholine is depleted in Alzheimer's disease (Rossor *et al*, 1984; Kopelman, 1986*a*). TPP depletion would be expected to produce diminished levels of acetyl-CoA or high-energy phosphates (ATP, ADP, AMP), thereby resulting in depleted acetylcholine synthesis (Schenker *et al*, 1980; Witt, 1985). Although the data concerning acetylcholine levels following thiamine deficiency remain controversial, a consistent finding is that acetylcholine turnover is indeed reduced following dietary thiamine deficiency (Barclay *et al*, 1981), and there is some evidence that inhibition of (TPP-dependent) pyruvate decarboxylase causes a measurable impairment of acetylcholine synthesis (Gibson *et al*, 1975).

An alternative possible link between Korsakoff's syndrome and the cholinergic system has been mooted by Arendt *et al* (1983), who reported a 47% reduction of the neuron count in the nucleus basalis of three Korsakoff brains at autopsy, thereby implicating involvement of the ascending cholinergic projections. This led Butters (1985) to propose that Korsakoff's syndrome primarily involves a cholinergic (basal forebrain), rather than a diencephalic, pathology. Studies of basal forebrain lesions in traumatic and vascular cases seem to confirm that this region contributes to memory processes (Damasio *et al*, 1985*a*,*b*; Salazar *et al*, 1986; Irle & Markowitsch, 1987; Phillips *et al*, 1987; von Cramon & Schuri, 1992). However, psychopharmacological studies of cholinergic blockade in healthy subjects indicate that cholinergic depletion produces an anterograde amnesia, similar to that seen in the Korsakoff syndrome, but not any retrograde loss (Kopelman & Corn, 1988; Kopelman, 1992). More particularly, Mayes *et al* (1988), in a detailed autopsy study of two Korsakoff patients, failed to find more than minimal changes within the basal forebrain.

Glutamate/GABA

Glutamate appears to the main excitatory neurotransmitter to the pyramidal neurons of the hippocampus, and GABA is the inhibitory neurotransmitter within those neurons (Shepherd, 1988). In addition, Bowen *et al* (1992) have suggested that glutaminergic transmission may be the chief factor that normally sustains the activity of cortico-cortical neurons. Glutamate activates the N-methyl-D-aspartate (NMDA) receptor complexes in the hippocampi, which are widely thought to play a critical role in memory processes (Lynch & Baudry, 1988). Although there is evidence of hippocampal hypometabolism in the Korsakoff syndrome (Fazio *et al*, 1992), and that glutaminergic depletion may contribute to the memory deficit in Alzheimer's disease (Ellison *et al*, 1986; Hyman *et al*, 1987; Bowen, 1990), this neurotransmitter system has not, as yet, been implicated in the Korsakoff syndrome.

Noradrenaline and serotonin

In a series of papers, McEntee and Mair have implicated the noradrenergic system in the memory disorder of the Korsakoff syndrome (McEntee & Mair, 1978, 1979; McEntee *et al*, 1984). Their argument has been based upon the findings of: (a) reduced 3 methoxy 4-hydroxy phenylglycol (MHPG) levels in the cerebrospinal fluid (CSF) of Korsakoff patients; (b) a strong correlation between MHPG levels and an index of memory impairment; and (c) a small but statistically significant improvement in memory test performance on administering clonidine to these patients. Similarly, O'Donnell *et al* (1986) reported that one week's oral administration of methylphenidate (an adrenergic agonist) produced a statistically significant improvement in six Korsakoff patients on a verbal recall task.

On the other hand, (a) Martin *et al* (1984) failed to replicate the finding of reduced MHPG; (b) the MHPG – memory test correlation was obtained in a sample of only nine patients and was not reported in the enlarged series; and (c) O'Carroll *et al* (1993) have recently failed to replicate the findings in a clonidine trial, not obtaining any significant improvements in 18 Korsakoff patients across a number of

cognitive tests. Animal studies implicate the adrenergic system in mechanisms mediating attention and arousal, rather than memory (Robbins, 1984; Sahgal, 1984). Mair & McEntee (1983, 1986) themselves have acknowledged that the noradrenergic system may operate by a general effect upon attentional and arousal mechanisms. Although it is very plausible that an attentional deficit may explain some of the characteristic personality and behavioural disorders seen in the Korsakoff syndrome (e.g. apathy), it seems unlikely that it would account for the 'core' memory disorder, especially in view of the relative preservation of primary or working memory (see below).

A new development was reported by Martin *et al* (1989) who found an improvement in free recall performance in five patients with an alcoholic Korsakoff syndrome, following administration of fluvoxamine, a serotonin reuptake inhibitor. They argued that these improvements in memory correlated significantly with reductions in the levels of 5-hydroxy-indole-acetic acid (5HIAA). This finding is broadly consistent with an earlier study in alcohol-treated volunteers by Weingartner *et al* (1983*a*). However, at least three studies have failed to find significant gain on cognitive tasks following the administration of 5-HT reuptake inhibitors to Alzheimer patients (Cutler *et al*, 1985; Dehlin *et al*, 1985; Lawlor *et al*, 1988), and the finding requires replication in Korsakoff patients.

Neuro-imaging studies

Structural imaging

Clinical and autopsy studies of the Wernicke-Korsakoff syndrome have been complemented by *in vivo* computerised tomography (CT) or MRI investigations, the most important of which have been part of larger studies of non-Korsakoff alcoholic patients.

Three CT scan studies have employed planimetric or computerised measures of ventricular enlargement, and either rating scales or computerised measurements of sulcal, interhemispheric and Sylvian fissure widening. Carlen *et al* (1981) found that alcoholic subjects ($n = 93$) showed significantly greater ventricular enlargement and sulcal widening than a non-alcoholic control group, but that differences between a Wernicke-Korsakoff group ($n = 25$) and other alcoholics were minimal and non-significant. Within the Korsakoff group, there was a significant correlation between sulcal widening and an overall index of cognitive impairment, but other radiological/cognitive correlations were not impressive. In a small study of seven alcoholic Korsakoff patients, seven non-Korsakoff alcoholics, and seven healthy controls, Shimamura *et al* (1988) reported significant enlargement of the third ventricle and widening of the Sylvian fissures and the left frontal sulci in Korsakoff patients, relative to healthy controls. In general, non-Korsakoff alcoholic subjects had measures approximately midway between the control and the Korsakoff groups. Within the Korsakoff group, a computerised measure of frontal sulcal enlargement was reported to show a statistically significant median rank correlation ($R = -0.43$) with 12 memory measures.

In a much more thorough study of 38 alcoholic Korsakoff patients, 100 non-Korsakoff alcoholics and 50 control subjects, Jacobson & Lishman (1987, 1990) found that Korsakoff patients as a group had wider third ventricles, larger lateral ventricles, and wider interhemispheric fissures than non-Korsakoff alcoholics or healthy controls. However, sulcal and Sylvian fissure widths did not differ between Korsakoff patients and other alcoholics. A computerised measure of enlargement of the anterior interhemispheric fissure correlated with general intellectual decline (indicated by the differences between estimated premorbid IQ, based on a reading test, and current IQ). On the other hand, the degree of third ventricular enlargement (which presumably reflects thalamic and hypothalamic pathology) was related to the severity of memory impairment (indicated by the difference between current IQ and a memory quotient). A comparison of subgroups of patients with (a) a small anterior interhemispheric fissure and a large third ventricle, or (b) a larger anterior interhemispheric fissure and a small third ventricle, produced differences in the degree of intellectual decline and memory impairment, significant at a 0.06 level (Jacobson & Lishman, 1987).

Two case reports have indicated areas of CT scan hypodensity in the thalamus of Wernicke-Korsakoff patients (McDowell & Le Blanc, 1984; Mensing *et al*, 1984). Similarly, Shimamura *et al* (1988) reported a significant reduction in mean thalamic density in Korsakoff patients, relative to healthy controls, and a significant median rank correlation between density and twelve memory measures within the Korsakoff group ($R = 0.34$). However, density measurements are very prone to a number of important sources of artefact, which require careful control (Jacobson *et al*, 1985). After controlling for these in his much larger study, Jacobson (1987; Jacobson & Lishman, 1990) found that left and right thalamic density measurements were indeed significantly reduced in male Korsakoff patients, relative to non-Korsakoff alcoholics ($P < 0.05$), but that there were only weak, non-significant correlations with measures of memory

impairment. Furthermore, after controlling for artefacts, there were no significant differences between Korsakoff patients, non-Korsakoff alcoholics and healthy controls in terms of frontal density.

Christie *et al* (1988) conducted an MRI study and confirmed the presence of cortical atrophy in Korsakoff patients, but these authors obtained only one significant correlation between measures of cortical atrophy and memory test scores. Squire *et al* (1990) conducted an MRI study in four alcoholic Korsakoff patients, finding abnormally small mammillary nuclei, barely detectable by magnetic resonance, whereas the temporal lobes, hippocampi, and parahippocampal gyri were of normal size. These findings in the Korsakoff patients contrasted with the MRI results in another group of amnesic patients, who were considered to have probable temporal lobe pathology. Finally, Jernigan *et al* (1991) have reported widespread reductions in grey matter volumes in Korsakoff patients, particularly in the anterior portion of the diencephalon, but also in medial temporal and orbito-frontal cortex.

Functional imaging

Hata *et al* (1987) used xenon-contrast computed tomography to make three-dimensional measurements of local cerebral blood flow in seven Wernicke-Korsakoff patients (at a very early stage in their disorder), ten non-Korsakoff alcoholics, and 17 healthy controls. They claimed that the most prominent reductions of local cerebral blood flow in the Korsakoff patients were found in the hypothalamus and basal forebrain, although close inspection of their data indicates that the findings were equivocal, as only two healthy controls had measurements in these regions. Subsequently, Hunter *et al* (1989) used single photon emission computerised tomography (SPECT) in Korsakoff and Alzheimer patients, finding that the Korsakoff group showed a general trend towards reduced tracer uptake throughout the cortex, except for the posterior temporal cortex, where regional cerebral blood flow was preserved. The impaired flow showed significant rank correlations with clinical (CAMCOG) measures of orientation and recent memory (Roth *et al*, 1986). Fazio *et al* (1992) studied 11 patients with 'pure amnesia', including two Korsakoff patients, using fluorodeoxy-glucose (FDG) positron emission tomography (PET), finding significant bilateral reductions in metabolism in interconnected limbic-hippocampal regions, including the thalamic nuclei, as well as the frontal basal cortex. This metabolic impairment did not correspond closely to alterations in structural anatomy, and appears to have arisen irrespective of underlying aetiology. Finally, Martin *et al* (1992) have recently examined a mixed group of ten Korsakoff and alcoholic dementia patients, finding metabolic disruption within anterior brain regions and right posterior white matter, with hyperactivity in cerebellar-cortical connections on FDG PET.

Neuropsychology of the alcoholic Korsakoff syndrome

General cognitive and frontal lobe deficits

As mentioned above, Jacobson & Lishman (1987) showed a variable degree of impairment on a standard IQ test. Their findings suggested a continuum between those patients who showed a disproportionate impairment of anterograde memory and those patients with a fairly severe, general cognitive decline, suggestive of 'alcoholic dementia', even though those alcohol patients with clear clinical evidence of generalised dementia had been excluded from their study. This calls into question the definition of the alcoholic Korsakoff syndrome as a disproportionate memory impairment, relative to other cognitive functions, given above. However, Jacobson & Lishman (1987) employed the original version of the Wechsler Memory Scale (WMS; Wechsler, 1945) as their measure of anterograde memory. As others have pointed out (Warrington, 1982; Weiskrantz, 1985; Brandt & Butters, 1986), the WMS is confounded by the inclusion of digit span and mental control as determinants of the memory quotient, and most Korsakoff patients perform within normal limits on those subtests. The revised Wechsler Memory Scale (WMS-R) avoids this problem, and tends to give substantially lower quotients to Korsakoff and other amnesic patients than the previous scale (Butters *et al*, 1988). It seems quite likely that, had Jacobson & Lishman been able to use the WMS-R (which was not available at the time of their study) or some other, relatively 'pure' measure of anterograde memory, their patients would indeed have shown a disproportionate impairment of anterograde memory, although this remains to be demonstrated. In that case, it would remain true that the degree of generalised cognitive impairment varies widely between individual Korsakoff patients, as Jacobson & Lishman (1987) indicated, but the neuropsychological findings would be consistent with the clinical definition of the disorder (i.e. disproportionate memory impairment).

More specifically, there is evidence that Korsakoff patients show deficits on tasks requiring visuoperceptive and visuospatial capacities, including the digit-symbol substitution test, hidden or embedded

figures tests, and various concept formation tests requiring sorting and discrimination of complex visual stimuli (Oscar-Berman, 1973; Kapur & Butters, 1977; Butters & Cermak, 1980; Brandt & Butters, 1986). These visuoperceptual deficits are also found in chronic alcoholics who are not clinically amnesic, and probably arise from atrophy in cortical association areas (Brandt & Butters, 1986). Jacobson *et al* (1990) found that Korsakoff patients are impaired, relative to other alcoholics and healthy controls, on an automated digit–symbol test, and that female Korsakoff patients were also impaired at a spatial orientation task.

There is also considerable evidence of frontal lobe or 'executive' dysfunction in Korsakoff patients (Shimamura *et al*, 1988; Leng & Parkin, 1988; Janowsky *et al*, 1989; Kopelman, 1989, 1991*a*; Jacobson *et al*, 1990; Shoqeirat *et al*, 1990; Joyce & Robbins, 1991), consistent with the neuro-imaging and autopsy findings of frontal lobe atrophy. For example, Janowsky *et al* (1989) found impairment on the Wisconsin Card-Sorting test and on the initiation and perseveration subscales of the Dementia Rating Scale (Mattis, 1976). Leng & Parkin (1988) also found impairment on the Wisconsin Card-Sorting test, but not a cognitive estimates test. Jacobson *et al* (1990) found impairment on a verbal fluency task for categories and on a computerised category sorting test. Kopelman (1989, 1991*a*) found significant impairments on the FAS verbal fluency, the Nelson version of card-sorting, and on a cognitive estimates test. As discussed below, various aspects of the memory deficits found in Korsakoff patients have been attributed to frontal dysfunction (e.g Moscovitch, 1982; Squire, 1982; Schacter *et al*, 1984; Mayes *et al*, 1985; Janowsky *et al*, 1989; Shimamura *et al*, 1990; Kopelman, 1991*a*).

Memory deficits

There are many studies of the pattern of impaired and preserved memory function in the alcoholic Korsakoff syndrome, using concepts of memory such as those illustrated in Fig. 2 (for review see Squire, 1987; Kopelman, 1987*a*; Mayes, 1988; Baddeley, 1990; Squire & Butters, 1992).

Working memory

Beyond the immediate sensory memory stores (holding information for a matter of milliseconds), primary or working memory refers to the capacity to hold small quantities of information for brief periods of time (up to about 30 seconds) without

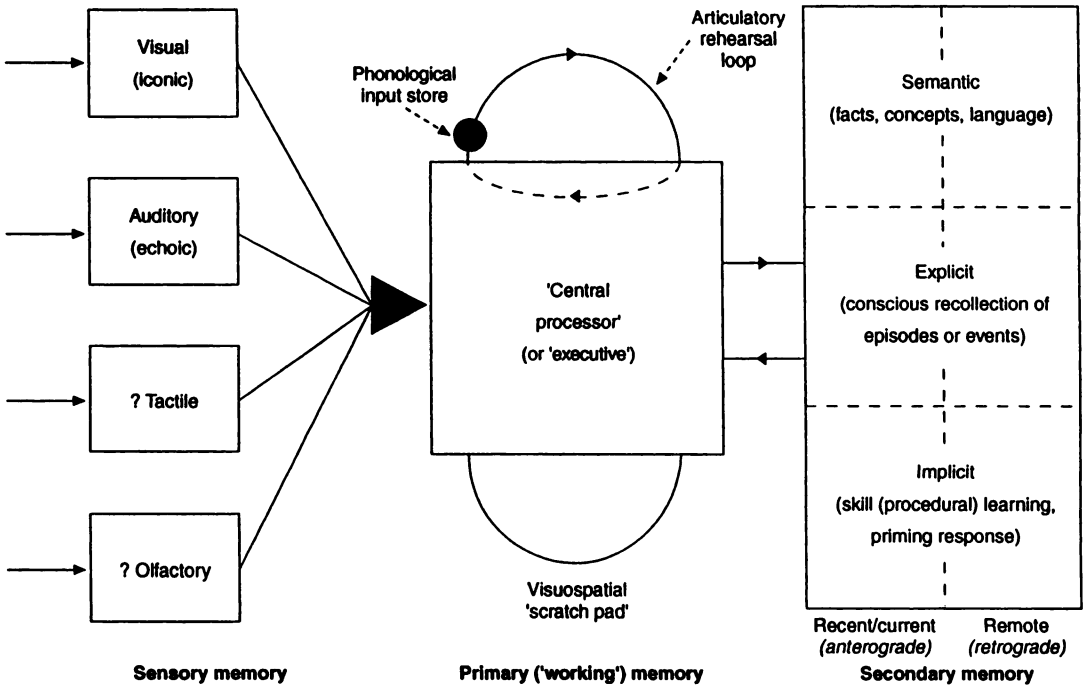

Fig. 2 Current concepts in memory research.

active rehearsal (James, 1890; Baddeley, 1990). It is usually measured by performance on span tasks, the 'recency' component of free recall, or measures of 'short-term' forgetting (Baddeley, 1986, 1990). There are many investigations showing that performance on span tests (verbal and non-verbal) is preserved in the Korsakoff syndrome (e.g. Zangwill, 1946; Baddeley & Warrington, 1970; Kopelman, 1985, 1991*b*). Performance on short-term forgetting tasks is much more variable, with some studies showing preserved ability (Baddeley & Warrington, 1970) and some showing severe impairment (Butters & Cermak, 1980). However, the consensus now appears to be that there is a variable pattern of performance by Korsakoff patients on both verbal and non-verbal tasks (Kopelman, 1985, 1991*b*; Mayes *et al*, 1988; Leng & Parkin, 1989). Leng & Parkin (1989) suggested that this variability in performance correlated with the degree of frontal lobe dysfunction, whereas Kopelman (1991*b*, 1992) argued that the impairments on verbal and non-verbal short-term forgetting tasks were correlated with left-hemisphere and right-hemisphere cortical atrophy respectively, as measured on CT scans.

Explicit memory

Secondary memory (Fig. 2) refers to the capacity to hold much larger quantities of information for periods beyond a few seconds (James, 1890; Baddeley, 1990). It is usually assumed that some specific 'encoding' process or underlying physiological mechanism of 'consolidation' is required to store information in secondary memory (Milner, 1966; Butters & Cermak, 1980), and that appropriate retrieval cues may greatly facilitate its recall (Tulving & Thomson, 1973; Roediger & Blaxton, 1987). The 'explicit' component of secondary memory refers to those memories of which we are, or can be made, consciously aware (Shimamura, 1986; Schacter, 1987; Tulving & Schacter, 1990), and, by definition, 'explicit memory' is severely impaired in Korsakoff patients. It is plausible that this deficit results from an underlying dysfunction in the process of physiological 'consolidation', and this may have neurochemical and electrophysiological correlates (Meudell & Mayes, 1982; Kopelman, 1986*a*, 1987*a*).

However, various psychological deficits have also been postulated, including an impairment in the encoding of semantic (or 'meaningful') information (Cutting, 1978*b*; Butters & Cermak, 1980) or in the encoding of contextual information (Huppert & Piercy, 1976, 1978*a*; Hirst, 1982; Mayes *et al*, 1985; Mayes, 1992; Parkin, 1992). While there does indeed appear to be some degree of deficit in the processing or encoding of some types of semantic information, it seems unlikely that this accounts for the severity of the memory disorder in the Korsakoff syndrome (McDowell, 1981). Similarly, although Korsakoff patients show a disproportionate deficit in the encoding of such aspects of context as temporal order, spatial location, modality of presentation, and source of information (e.g. Huppert & Piercy, 1976, 1978*a*; Schacter *et al*, 1984; Meudell *et al*, 1985; Kopelman, 1989; Shoqeirat & Mayes, 1991; Mayes *et al*, 1991), such deficits may be incidental to the memory impairment for 'target' information, being evident in some patients but not others (Schacter *et al*, 1984; Shimamura & Squire, 1987; MacAndrew & Jones, 1993). Moreover, although Korsakoff patients' performances on contextual memory tests often show statistically significant correlations with their scores on 'target' memory tasks, the degree of shared variance is usually relatively low (Kopelman, 1989; Pickering *et al*, 1989; Shoqeirat & Mayes, 1991). It may well be the case that contextual information is particularly difficult to learn, but that it does not represent the core component of the amnesic disorder (Baddeley, 1990; Kopelman, 1992).

The 'long-term' forgetting of explicit memories refers to the rate of decline in retrieving 'target' information which had previously been learned to an adequate level (Huppert & Piercy, 1976, 1978*b*; Kopelman, 1992). In empirical studies, this involves 'matching' the initial learning of amnesic patients to that of healthy controls, usually by prolonged exposure of the stimulus material to the amnesic group. Using such a technique, several studies have shown that rates of long-term forgetting are normal, once target information has been learned to an adequate level for as long as ten minutes (Huppert & Piercy, 1978*b*; Squire, 1981; Kopelman, 1985; Martone *et al*, 1986). Two possible qualifications to this finding are: (a) that all these studies have involved recognition memory, as 'matching' is extremely difficult to achieve on recall tasks; and (b) that it is plausible that there are differences in forgetting rates over intervals shorter than ten minutes (Kopelman, 1992).

Implicit memory

Implicit memory refers to learning of which the subject is not consciously aware (Shimamura, 1986; Schacter, 1987; Tulving & Schacter, 1990). It encompasses simple conditioning tasks, the acquisition and retention of perceptuo-motor skills ('procedural memory'), and 'priming', which refers to the facilitation of a particular response to a cue by an earlier stimulus. The cue may be either the same as the

earlier stimulus ('repetition priming'), a fragment of the earlier stimulus, (e.g. 'word-completion priming'), or semantically related to the stimulus ('semantic priming'). There are many studies which demonstrate that Korsakoff patients show preserved capacity on simple conditioning and procedural memory tasks (Brooks & Baddeley, 1976; Weizkrantz & Warrington, 1979; Martone *et al*, 1984) as well as at various priming tasks (Warrington & Weiskrantz, 1970; Graf *et al*, 1984; Shimamura & Squire, 1984; Schacter & Graf, 1986; Tulving & Schacter, 1990). Such findings are generally interpreted as demonstrating the existence of an 'implicit' memory system, preserved in amnesia and mediated by cortical structures (priming) and/or subcortical structures (procedural memory), distinct from the impaired 'explicit' memory system, mediated by limbic–diencephalic structures. Korsakoff patients also show preserved affective or evaluative memory responses (Johnson *et al*, 1985; Frith *et al*, 1992), possibly mediated by Mishkin's (1982) amygdaloid circuit, as opposed to the hippocampal/anterior thalamic circuit implicated in explicit memory (see above). The findings of preserved implicit memory processes in the Korsakoff syndrome may well have implications for the design of rehabilitation and retraining programmes (Glisky *et al*, 1986; Baddeley & Wilson, 1994).

Semantic memory

Semantic memory is a conglomerate term referring to knowledge of language, concepts, and well-rehearsed facts (e.g. 'Paris is the capital of France'), independent of the recall of any particular episode or incident specific in time and place (Tulving, 1972). Many researchers believe that, with increasing rehearsal, explicit memories of particular episodes gradually become assimilated within the knowledge-based semantic memory system (Cermak, 1984; Weiskrantz, 1985), implying a continuum between 'explicit' and 'semantic' memory. However, there is also neuropsychological evidence of their dissociation, some patients showing a disproportionate loss of personal or autobiographical memories (case 3 above; Dalla Barba *et al*, 1990; O'Connor *et al*, 1992; Ogden, 1993; Evans *et al*, 1993), while others manifest a relatively specific loss of semantic memory, as in patients with 'semantic dementia' secondary to atrophy or pathology in the 'dominant' temporal lobe (De Renzi *et al*, 1987; Snowden *et al*, 1989; Hodges *et al*, 1992). In general, Korsakoff patients show relative preservation of performance on semantic memory tests compared with Alzheimer or other dementia patients (Weingartner *et al*, 1983*b*; Perani *et al*, 1993). However, Korsakoff patients are impaired at speeded tasks such as verbal fluency (Shoqeirat *et al*, 1990; Kopelman, 1991*a*); and amnesic patients often fail to learn the definitions of words which have come into the language since the onset of their amnesia (Gabrielli *et al*, 1988) or the names of the current Prime Minister or other public figures (Kopelman, 1986*b*).

Retrograde amnesia

Each of these components of memory potentially has a retrograde as well as an anterograde component (Fig. 2), but this has been studied in detail only with respect to explicit memory. There is clearly an extensive retrograde memory loss in the Korsakoff syndrome, extending back several decades, as Korsakoff (1889) himself noted. Modern neuropsychological studies have confirmed that this retrograde memory loss extends back at least 25–30 years (Albert *et al*, 1979; Cohen & Squire, 1981; Kopelman, 1989; Squire *et al*, 1989*b*; Parkin *et al*, 1990). This extensive retrograde loss includes memory for remote public or 'semantic' information, facts about a patient's own life ('personal semantic memory'), and autobiographical memory for incidents or events from the patient's past (Kopelman, 1989). All these aspects of retrograde memory show a temporal gradient, with relative sparing of the most distant memories, and the gradient is significantly steeper than that seen in dementing disorders such as Alzheimer's disease (Kopelman, 1989). The relative sparing of early memories may result from their greater salience and rehearsal, such that they have become assimilated within semantic memory (Cermak, 1984; Weiskrantz, 1985). Consequently, there are two possible reasons why Korsakoff patients have a steeper temporal gradient than dementing patients: (a) semantic memory is relatively preserved in Korsakoff's patients, allowing better retrieval of early memories than in dementing patients; and (b) a progressive anterograde impairment during the Korsakoff patients' periods of heavy drinking may have made the loss of recent memories particularly severe.

Although confabulation may occur in retrieving remote or autobiographical memories, it is relatively rare except for fleeting intrusion errors (Victor *et al*, 1971; Berlyne, 1972; Kopelman, 1987*b*), which may well represent a normal response to a weak or failing memory (Kopelman, 1987*b*). In those relatively rare cases where spontaneous and florid confabulation persists beyond the initial confusional (Wernicke) stage, it may result from either a disorganised and disinhibited retrieval of memories and their

associations (Baddeley & Wilson, 1986; Kopelman, 1987*b*) or from a deficit in 'reality monitoring' (Dalla Barba, 1993). In either event, there is substantial evidence that frontal lobe dysfunction (possibly resulting from damage to orbital medial pathways) may underlie 'spontaneous confabulation' (Luria, 1976; Stuss *et al*, 1978; Kapur & Coughlan, 1980; Baddeley & Wilson, 1986; Kopelman, 1987*b*), and that frontal lobe atrophy and dysfunction are characteristic in the Korsakoff syndrome.

However, it is more typical for Korsakoff patients to show an impoverished, aspontaneous recollection of remote memories than florid confabulation. This aspontaneity is analogous to the 'non-fluent' pattern of retrieval described by Baddeley & Wilson (1986) and Della Sala *et al* (1993) in other patients with frontal lobe lesions (possibly involving the more dorso-lateral regions). Several studies have shown that the severity of the retrograde and anterograde memory impairments are poorly correlated in this group of patients (Shimamura & Squire, 1986; Kopelman, 1989, 1991*b*; Parkin, 1991). While performance on retrograde and anterograde memory tests showed only 21% shared variance in one study, there was a significant association between performance on frontal lobe tests and retrograde memory, such that a regression equation on the basis of three 'frontal' tests predicted 68.5% of the variance on retrograde memory tests (Kopelman, 1991*b*, 1992). This suggested that frontal lobe dysfunction, resulting from the known abnormalities in this region revealed in neuro-imaging and autopsy studies, may contribute to a failure in organising retrieval processes for remote and autobiographical memories in Korsakoff patients (Kopelman, 1992, 1993). Studies of patients with vascular lesions in the diencephalon, in whom retrograde memory was either relatively spared (Parkin & Hunkin, 1993; Parkin *et al*, 1994) or disrupted (Hodges & McCarthy, 1993) in the presence of intact or impaired 'frontal' test function, respectively, can be interpreted as broadly consistent with this hypothesis.

Table 1
Neuropsychology of Korsakoff's syndrome

Component	
Primary/working memory	Relatively intact (span tests, 'short-term' forgetting)
'Psychological' encoding	
semantic	Deficits probably insufficient to account for amnesia
contextual	Deficits incidental to amnesia rather than core feature?
'Physiological consolidation'	Difficult to assess in man
Retention/storage/forgetting	Intact if learning accomplished
Retrieval	Deficits secondary to encoding/consolidation (Meudell & Mayes, 1982)
Priming/procedural learning (skills)	Preserved
Retrograde amnesia	Extensive impairment (25 years or more) with 'temporal gradient'

Table 1 summarises the pattern of preserved and impaired memory processes in the Korsakoff syndrome.

Conclusions

At the end of the 19th century, Lawson and Korsakoff both described a syndrome, commonly but not always associated with alcohol abuse, in which memory was profoundly impaired while other cognitive functions remained intact. The modern definition of the syndrome, provided by Victor *et al* (1971), is in terms of an impairment of "memory and learning . . . out of all proportion to other cognitive functions", resulting from nutritional (thiamine) depletion. At an early stage, the association with the clinical features of Wernicke's encephalopathy was recognised, but it now appears that a history of Wernicke's syndrome is not invariably present, and that coma or an insidious onset are alternative initial manifestations of the disorder. Moreover, the characteristic neuropathology can sometimes be found at autopsy in alcoholic subjects who have never been diagnosed during life as having the Korsakoff syndrome.

The characteristic pathological features of the disorder are found in the paraventricular and periaqueductal grey matter. There is consensus that lesions in either the thalamus or the mammillary bodies, or both, are critical for the production of memory impairment. Controversy has concerned the relative importance of the thalamus and mammillary bodies, whether the anterior or dorso-medial thalamus is critical for memory disruption, and the way in which the diencephalon interacts with the hippocampi and basal forebrain in memory formation, but the most recent studies emphasise the importance of the circuit comprising the mammillary bodies, the mammillo-thalamic tract, and the anterior thalamus. Neuro-imaging studies have corroborated the finding in autopsy studies that cortical atrophy, particularly frontal atrophy, is also present in many cases.

A variety of causes of malnutrition or malabsorption have been reported to produce either the Wernicke or the Wernicke-Korsakoff syndrome. The belief that a history of alcohol abuse is required to produce a permanent memory impairment is not well substantiated, although 'pure' non-alcoholic

cases have proved hard to find in recent times. The common factor underlying the development of the Wernicke-Korsakoff syndrome is almost certainly thiamine depletion; but why some subjects should be especially vulnerable to thiamine depletion, and the precise manner by which it produces the characteristic Wernicke-Korsakoff lesions, are not understood. One possibility is that thiamine deficiency produces a reduction in acetylcholine turnover and synthesis, although depletions in the noradrenergic and serotonergic systems have also been mooted.

However, psychopharmacological studies concur with neuropsychological investigations in suggesting that lesions in partially independent brain structures and neurochemical systems may underlie anterograde and retrograde amnesia. There is now general agreement concerning the pattern of the memory deficit in the Korsakoff syndrome, involving a severe impairment of new learning and an extensive retrograde loss, with intact or well-preserved working memory, priming, procedural memory and the rate of 'long-term' forgetting. The present paper has suggested that, while structural lesions or neurochemical deficiencies involving the limbic-diencephalic circuits produce anterograde amnesia, some other factor, such as frontal lobe dysfunction, must account for the severe retrograde memory loss, which commonly extends back 25 years or more in this disorder.

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Michael D. Kopelman, PhD, Division of Psychiatry and Psychology, UMDS, Guy's and St Thomas's Hospitals, St Thomas's Campus, London SE1 7EH

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