The Alzheimer Pandemic: Is Paracetamol to Blame?

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Abstract: *Historical Background*: The clinical recognition of a form of dementia closely resembling Alzheimer's disease dates from around 1800. The role of analgesics derived from coal-tar in the spread of the pandemic is traced in terms of the introduction of phenacetin (PN) in 1887; its nephrotoxicity; the observation of lesions characteristic of the disease by Fischer and Alzheimer; the discovery of paracetamol (PA) as the major metabolite of PN; the linking of kidney injury and dementia with high PN usage; and the failure of PN replacement by PA to halt and reverse the exponential, inexorable rise in the incidence of Alzheimer-type dementia. Fischer observed his first case before Alzheimer; it is proposed to rename the syndrome Fischer-Alzheimer disease (F-AD).

Disease development: PA-metabolising enzymes are localised in the synaptic areas of the frontal cortex and hippocampus, where F-AD lesions arise. The initiating chemical lesions in liver poisoning comprise covalent binding of a highly reactive product of PA metabolism to proteins; similar events are believed to occur in brain, where alterations in the antigenic profiles of cerebral proteins activate the microglia. ß-Amyloid forms, and, like PA itself, induces nitric oxide synthase. Peroxynitrite modifies cerebral proteins by nitrating tyrosine residues, further challenging the microglia and exacerbating the amyloid cascade. Spontaneous reinnervation, N-acetyl cysteine administration and tyrosine supplementation may attenuate the early stages of F-AD development.

Conclusion: F-AD is primarily a man-made condition with PA as its principal risk factor.

Keywords: Alzheimer, Fischer, microglia, paracetamol, peroxynitrite, phenacetin, presenile dementia, tyrosine.

INTRODUCTION

Early in the 19th century a condition closely similar to F-AD was described as chronic dementia by Pinel [1] and Esquirol [2], but it did not begin to attract wider attention as a distinct form of mental illness until around 100yr later [3-9]. Each new forecast of patient numbers anticipates a remorseless rise [10-14]. Several European countries have responded by initiating national dementia strategies. In 2010 35 million cases existed world-wide; estimates for 2030 and 2050 are 66 and 115 million respectively. In the same year the global expense of maintaining patients with dementia was assessed at US$600 billion, and is expected to soar in proportion as numbers of dementia cases augment [14]. Meanwhile the primary emphasis in research into F-AD has moved away from aetiology.

Apart from the problem of dementia and paresis accompanying terminal syphilis [15], before 1907 presenile dementia was insufficiently common to be widely recognised as a distinct medical condition [3, 4, 7]. Although various factors, including genetic predisposition [10,16-20], may place individuals at risk, until recently the combination of aging and increasing life expectancy was deceptively viewed as making the major contribution to the growing incidence of dementia worldwide [10-12, 14, 17, 20-23]. Setting the average interval between diagnosis and mortality at five yr [17], dementia-associated deaths between 2010 and 2030 [14] can be expected to exceed 200 million.

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In this analysis the pre-analgesic recognition of F-AD is traced back to the start of the 19th century. The introduction of PN in 1887 and its prompt adoption in Europe and the United States are related to the abrupt emergence of F-AD in industrialised countries two decades later and to the consequences of its international replacement by PA. In 1971 Murray and his colleagues linked dementia in a small number of kidney dialysis patients with the presence postmortem of miliary plaques and neurofibrillary tangles and lifetime consumption of kg quantities of PN. Also in this neglected study [24] impairments of cognitive function and memory were observed in a second group of PN abusers. PA, the major [25, 26] and persistent [25] metabolite of PN, has been suggested as another causative factor [27, 28].

Comprehension of the metabolism of PA permits a better understanding of the progression and a potential prophylactic treatment of the disease. The role of short-lived free radicals is central to its initiation and progression. The first chemical events in the development of F-AD are identified and related to interference with synaptic function and immune-mediated structural disturbance. Isoenzymes of cytochrome P450 are present in both liver and brain. Although the chemistry is identical, the different responses of the two organs, acute and chronic, to the analgesic reflect the substantial difference in enzymic activity between the two.

Cerebral proteins antigenically altered by reaction with unstable free radicals activate the microglia, initiating an inflammatory reaction and leading to the production of ß-amyloid. Nitric oxide synthase is induced by both PA and ß-amyloid. Reaction of peroxynitrite with tyrosine modifies the antigenic profiles of cerebral proteins, thereby enhancing the inflammatory response and provoking the amyloid cascade.

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Endogenous repair mechanisms are identified. Inhibition of apoptosis and the provision of substrates for scavenging reactive metabolites and protein synthesis may attenuate the progress and, perhaps, in part reverse the early stages of the disease.

RECOGNITION OF F-AD IN THE 19TH CENTURY

Studies [1, 2] in three mental institutions in Paris between 1790 and 1835 revealed that a proportion of the patients diagnosed with incurable chronic dementia displayed many of the symptoms associated with F-AD [3-6, 8, 17]. These included financial irresponsibility, delusions of grandeur and possessions, total failure of short-term memory, inappropriate hilarity, turbulent and ungovernable movements, greatly diminished sensibility to family, objects and friends, absence of thought processes and abolition of the faculties of reasoning and judgement. Age at admission was generally between 40 and 80yr. Patients were incoherent, unable to write legibly and often suffered from paresis. The condition was commoner in men than in women [2]. The symptoms were irreversible and progressive; by contrast with certain other forms of insanity, patients with the condition did not return to the community [1, 2].

In the 1790s a survey of 200 patients at the Asylum Bicêtre in Paris revealed 18 with an unspecified form of dementia [1]. Between 1826 and 1833 the total number of patients admitted to the Hôpital Charenton was 1557. Of these 113 had incurable chronic dementia, representing around 7% of the number of confined patients [2]. In 1831 the population of Paris was 785,000 [29], of whom around 1% were institutionalised.

Diagnostic practice, nomenclature and disease classification will have varied widely from one country to the next. In the 1830s figures for the proportions in mental institutions of the populations of several European countries and New York ranged from one in 550 in Norway to one in 3800 in Italy; in France generally the ratio was 1 in 1750 [2]. The frequency of chronic dementia in the general populations is impossible to assess with any accuracy from these inadequate data, but it may be inferred that at this time the numbers of patients with symptoms resembling those of F-AD were small. The combined estimate of 160,000-260,000 cases of idiopathic F-AD in Europe and the United States at the beginning of the 20th century may be reasonably accurate [23].

The rarity of F-AD in the 19th century is further illustrated by the absence of descriptions of the collective symptoms of chronic dementia [1, 2] from most contemporary works on mental disease [30-39]. Other clinicians noticed certain features in common with F-AD in patients classified as demented, notably delusions, failures of memory and judgement and an inability to comprehend new ideas [40-43]. An association with paralysis was observed [40, 42]. However, one authority working in the Scottish lowlands concluded from a detailed histological survey of the cerebral pathology of 331 patients, including a group of sufferers from senile insanity, that miliary scleroses, as plaques were originally termed [16] did not exist, ascribing, in the company of others, their occurrence to artifacts or postmortem changes [35]. The impact of genetic predisposition on incidence is not great [18, 19], and may, for example, be manifested through different expression of cytochrome P450 isoenzymes at synaptic junctions in the cortex and hippocampus [44].

Apart from the perceptive observations of Pinel [1] and Esquirol [2], both of whom also recognised senility as a separate age-related entity, up to the beginning of the last century mental impairment associated with aging was commonly regarded as a consequence of gradual cerebral deterioration and distinct from dementia. The process was essentially considered as a slow enfeeblement of mental faculties, usually beginning spontaneously in the seventh and eighth decades [30, 31, 41, 43]. Similarly, an asymptomatic latent period precedes the appearance of F-AD [17, 22, 45, 46], the clinical features of which have been described by one authority as malignant [20, 22].

F-AD IN THE 20TH CENTURY; CLINICAL RECOGNITION AND AUGMENTING PREVALENCE

Some of the earliest instances of dementia with lesions listed in Table **1** are likely to have arisen idiopathically. In 1901, 14yr after PN went on sale, Fischer noticed an unusually premature case of dementia. Frau Josefa V was 56yr old and died in 1903 [3, 5, 9]. Twelve days after Fischer's diagnosis Alzheimer independently observed a similar presentation in Frau Auguste D, who died in 1906 aged 56 [4, 6, 7, 8]. Both investigators associated the presence of plaques and tangles, demonstrated by means of a novel silver stain [58], in their patients with a distinct and unknown form of dementia [3, 4, 6-8]. When Alzheimer presented his single case in 1906, the absence of questions from the discussion [4, 8] suggests that the anecdotal nature of his presentation aroused no concern.

Twenty yr after the introduction of PN the number of cases of F-AD reported from Prague [3,5], Munich [6, 52, 56], Frankfurt [53], Freiburg [53], Michigan [54] and Massachusetts [57] began to multiply abruptly; 114 more instances were diagnosed between 1907 and 1911 (Table **1**), an annual rise of almost forty-fold. In 1910 Fischer described a total of 56 individuals with dementia, all with plaques [5, 9]. Issues of diagnosis and priority between Prague and Munich were in part confused by different nomenclature [5, 55]. Subjects exhibited confusion and profound disturbance of memory [4-6, 16, 52, 54, 55, 57]. An illness first characterised in modest numbers was beginning to afflict hundreds, and was later to affect millions. In 2005 a new case was diagnosed worldwide every seven seconds [13].

F-AD: HISTOLOGICAL RECOGNITION AND DISTURBANCE OF CEREBRAL FUNCTION

The elucidation of the structure and function of the brain became a focal point of international scientific enquiry during the second half of the 19th century. Parallel interest in pathology [35, 43] was stimulated in part by the degenerative changes in the brain seen terminally in syphilis [15], the cause of which was not identified until 1905 [59]. By 1902 the Medico-Psychological Association of Great Britain and Ireland, founded in 1841, had over 600 members [60]. The Association organised meetings across the United Kingdom and with its European counterparts. International contacts

Table 1. F-AD Cases; Reports and Denial of Lesions

Year	Event	Location
1887*	Observation of cortical plaques (4)	Russia [47]
1892	Observation of plaques and tangles (1)	France [48]
1898	Ditto (2)	Vienna [16]
1900	Existence of miliary scleroses (plaques) denied	Scotland [35]
1901	Fischer diagnoses Frau Josefa V	Prague [3, 9]
	Alzheimer diagnoses Frau Auguste D	Frankfurt [4, 7, 8]
	Observation of plaques (1)	Leipzig [49]
1903	Death of Frau V	Prague [3, 9]
1906	Observation of plaques and tangles (1)	France [50]
	Observation of plaques (2)	Tokyo [51]
	Death of Frau D	Frankfurt [4, 6-8]
	Alzheimer describes lesions in Frau D (1)	Tübingen [4, 6-8]
1907	Observation of plaques and tangles in Frau V and others (12)	Prague [3]
	Alzheimer publishes findings on lesions in Frau D	Frankfurt [4]
1908	Observation of plaques and tangles (1)	Munich [52]
1909	Ditto (6)	Frankfurt, Freiburg [53]
1910	Ditto (44)	Prague [5, 9]
	Ditto (2)**	Munich [6]
	Ditto (8)	Michigan [54]
1911	Ditto (1)	Washington [55]
	Ditto (24)	Munich [56]
	Ditto (16)	Massachusetts [57]
1971	High PN usage linked with nephrotoxicity, dementia, and F-AD lesions (6)	Glasgow [24]
2001	PA implicated as a cause of F-AD	London [27]

Numbers of subjects with lesions are given in parentheses.
*The results were communicated orally in 1886.
**Two single cases were described elsewhere [4, 52].

between similar organisations in Europe were actively maintained. Towards the end of the century the journal of the Association, the *Journal of Mental Science* founded in 1853, the *Journal of Nervous and Mental Diseases* founded in the United States in 1857, and the *Neurologisches Centralblatt* founded in Germany in 1882 printed reports of congresses held abroad, book reviews and abstracts of publications from foreign journals on all aspects of brain and mind.

Despite this level of activity, the characteristic histological lesions of F-AD only began to be described in patients with dementia in the late 1880s, illustrating the rarity of the condition at the time. Between 1886 and 1906 the number of dementia cases reported with plaques with or without tangles as described by Fischer [3, 9] and Alzheimer [4, 7, 8] amounted to only 13 (Table **1**). Significantly, the first reports of F-AD were largely confined to German-speaking areas of Europe and to the United States (Table **1**), regions where sales of PN were actively promoted [61-64]. Before the advent of the Bielschowsky silver stain [58] in 1902 the presence of lesions was revealed by various staining procedures including carmine red [16,48-50], haematoxylin [3], eosin [3, 16, 50], polychrome methylene blue [3], toluidine blue [6, 53] and van Gieson [3, 6, 16, 49].

Symptoms of dementia appear when plaque populations reach critical densities [65]. In contrast with the pre-analgesic era [2], more recently dementia has been commoner in women than in men [5, 10, 12, 17, 21, 24, 66-68]. In the largest of the early reports [5] the proportion of men to women was 5:9; the average age of men at death was 74.5+/-8.1yr (range, 55-84yr), and of women, 75.8+/-9.4yr (range, 58-103yr). Greater female longevity would be expected to offset the disparity in incidence [23]; on the other hand F-AD shortens lifespan [14, 17, 22].

Correlations have been found between cortical plaque counts and quantitative measures of deterioration of intellect and personality [65]. However, synapse disappearance [20] fitted more closely with cognitive impairment than lesion density [69], and is considered more injurious to cerebral function than neuronal destruction [70]. Peroxynitrite generated by nitric oxide synthase, an enzyme induced in the liver by PA [71], chemically modifies proteins in synaptic membranes [72]. Depending, for example, on the extent of

analgesic consumption, disease progression may be expected if in the early stages of F-AD neuronal regeneration [3, 73-76] proves insufficient to keep pace with synapse loss [70].

DEMENTIA, AGING AND LIFE EXPECTANCY

The widespread belief that the rise in numbers of F-AD patients [11, 14, 20, 23] is basically due to increases in elderly populations [10, 11, 17, 20, 23, 77] fails to take observations of juvenile [19,78] and presenile [3, 4, 6, 8, 17, 19, 24] dementia into account. Moreover, even though the elderly are primarily affected [10, 11, 17, 20], the mismatch between the slow progressive increase in longevity within industrialised societies during the last century [79] and the exponential growth of dementia witnessed onward from around the middle of the 20th century has been set aside [10-13]. Dementia is not an inevitable consequence of the aging process. For example, an investigation of a group of subjects over 85yr found 45% with the condition [68]. In another group aged over 90yr the incidence of dementia was 25% [20]. In Holland no plaques or other significant degenerative changes were found in a woman of 115yr [80].

The earlier view that the rising incidence of F-AD is linked with increasing life expectancy calls for closer examination. In the instance of Scotland, in 1901 life expectancy was 46.8yr [81] and the population was 4,480,000 [79]. In the Scottish lowlands miliary scleroses (plaques) in the brain were virtually unknown [35]. In Czechoslovakia expectancy was similar [79], but numerous instances of F-AD were being diagnosed in Prague [3, 5]. By 2002 Scottish men and women were living to an average age of 76.3yr [81] and the population had risen to 5,055,000 [79]; 57,300 individuals were living with dementia, of whom 55% were classified as F-AD cases [82].

In Russia life expectancy fell precipitously between 1987 and 1994, dropping by 9yr for men and 2yr for women. The increase in mortality was largely confined to young and middle-aged men, and began to reverse after 1994. A similar but less marked pattern was seen in the 70-80yr cohort [83]. On the other hand the incidence of dementia, of which 40-90% was classified as F-AD, kept rising exponentially [84]. Although the frequency of the disease in the elderly rises sharply with age [10, 11, 17, 20, 77], the figures are also consistent with longer exposure to PA as requirements for pain relief become greater with advancing age.

GLOBAL SPREAD OF F-AD

Historically, the problem of dementia has been most acute in industrialised societies [10, 13, 20] where F-AD originated (Table **1**). Up to the 1980s dementia was virtually unknown in developing countries [85-87]. In a large Nigerian hospital between 1957 and 1990 not a single authenticated case of F-AD was observed out of 350,000 individuals aged 65 and over [86]. Comparisons between identical ethnic groups revealed relatively high incidences of dementia and F-AD in the United States [88] but low frequencies in Nigeria [89]. The difference between the two communities is consistent with the greater preponderance of a risk factor present in the United States environment.

In four studies of Chinese populations published between 1984 and 1988 only 0.46-1.86% of the elderly displayed dementia, among whom 0.07-0.66% had a diagnosis of F-AD. Shortly afterwards a study in Beijing revealed that 3% of a group of 3,888 subjects aged 65 and over had F-AD; the proportion of affected individuals rose sharply with age [67]. In mainland China the incidence of senile dementia in this age group had risen to 5-7% by 2010, among whom 2.5-4.2% had clinically-diagnosed F-AD [90]. In India prior to 1985 examination with the electron microscope of the brains of a randomly selected group of subjects aged 60 and above failed to find any tangles, even though at the time 15% of Westerners in the same age range displayed lesions [87].

In recent years the situation in developing countries has been changing abruptly [13]. The gradual replacement of PN by PA [91, 92] has failed totally to halt the exponential increases worldwide in the frequency of dementia [10-14]. This crucial failure constitutes the strongest evidence of all that PA is currently the chief risk factor for F-AD. Numbers of patients with dementia in European countries are expected to rise within the range 84%-169% between 2001 and 2040, equivalent to a doubling every 44 and 28yr [13]. PA manufacture in Asia [93, 94] is rising much faster than the incidence of dementia [13]. In the decade leading up to 2006 domestic PA consumption in China increased annually by 15.8% [95], equivalent to a five yr doubling. In geographical areas comprising China and India [13] between the years 2001 and 2040, increases of around 325% in the prevalence of F-AD have been estimated. In the future the burgeoning usage of PA in developing countries [95, 96] may make a greater disproportionate contribution to the rising incidence of F-AD than anticipated [13].

PN AND PA: INTRODUCTION AND INITIAL REGIONAL USAGE

Relevant landmarks in the histories of these two analgesics and their usage are set out in Table **2**. The effective antipyretic and painkilling properties of PN were described in 1887 [97, 98] and 1888 [61, 99]. Marketing in Germany began in 1887 [97]. Schieffelin, a long-established importer and distributor of drugs based in New York [63], actively promoted sales in the United States [61, 62]. Despite only rudimentary toxicity testing [97] PN soon became a panacea [61, 62, 92]. Promotional pamphlets published in the United States claimed that patients with influenza and a number of other medical conditions benefitted from the drug [61, 62]; one edition included over 80 testimonials from doctors in Italy, Germany, Austria, the United States, France, Poland, England and Czechoslovakia [62]. By the end of 1892 a hundred reports of PN usage both as antipyretic and analgesic appeared in medical journals across the world, including fourteen countries in Europe [64]. The successful advocacy of PN in America [61, 62] is illustrated by the publication in clinical journals over the same period of fifteen papers from the United States describing various applications [64].

At first prescribed doses varied wildly. One report claimed that 500-750mg brought elevated temperatures down to normal within 4hr, warning that the daily dose

Table 2. PN and PA: Their Histories, Applications and Dangers

Year	Event	Location
1887	Antipyretic properties of PN discovered	Germany [97, 98]
	PN goes on sale	Germany [97]
1888	Analgesic properties of PN discovered	Germany [61, 99]
	Beneficial effect of PN on influenza reported	Germany [99], United States [61, 63]
	Use of PN becomes international [61-64]	
1889-90	Asiatic influenza pandemic [101]	
1890	Nephrotoxicity of PN reported	Germany [100]
1918-19	Spanish influenza pandemic [102]	
1949	Metabolism of PN investigated; analgesic properties of PA discovered	United States [25]
1953	PA marketed by Sterling Winthrop	United States [92]
1963	PA entered into the British pharmacopoeia	United Kingdom [91]
1971	PN implicated as a cause of F-AD	Scotland [24]
2001	PA implicated as a cause of F-AD	England [27]

should not exceed 8g [99]; another advised 2.9-7.8g every 24hr [97]. For headaches 1g was conservatively recommended, though some physicians advised 6g. Associated cyanosis was sometimes observed [61], and its nephrotoxicity was soon reported [100]. In May 1889 an outbreak of influenza originating in Bukhara, Uzbekistan, attained pandemic proportions; a quarter of a million people died [101]. Between 1918 and 1920 the Spanish influenza pandemic raged, claiming an estimated 50 million victims [102]. The properties of PN were soon exploited in the treatment of the virus [61, 63, 64, 99, 103-105]. Described as being `unrivalled as an analgesic' [105], PN cut the duration of acute illness short [62,103]. In Chicago, where the epidemic caused a sudden peak in mortality, `immense quantities' of PN were prescribed [62].

PN: CONSUMPTION AND ADDICTION

After 1887 PN was marketed as a leading painkiller [61-64, 92] for almost a century. The analgesic has been reported to induce euphoria [61]; abuse of PN and other new synthetic drugs was recognised as early as 1894 [106]. In 1909 a mixture of PN with the addictive drug codeine phosphate was introduced [107]. From the beginning PN was open to commercial exploitation [61, 62, 66, 106, 108-113]. For example, in Australia a powder containing PN, codeine and aspirin was popularised in the mid-1960s by an advertising jingle [28, 110, 112, 113]. Women especially became addicted to analgesic mixtures containing PN [66, 112, 113], and comprised 60-85% of cases of terminal kidney failure [112]. An epidemic of kidney failure prompted its withdrawal in 1975 [28, 112, 113]; PN addiction became rare [77]. Excessive use had become problematic elsewhere [26, 106, 108, 109, 111, 114, 115]. In 1970 some 250,000 individuals in the United Kingdom alone were consuming at least five analgesic tablets daily without medical supervision; anxiety over side effects, including nephropathy, was expressed [111]. Female usage of analgesics, initially PN, tended to predominate [10, 24, 66, 112, 113], sometimes by as much as 2:1 [114].

In 1949 PA was found to be the chief metabolite of PN and primarily responsible for its analgesic action. The half-lives of the two compounds are 3hr and 40min respectively [25]. After PA was put on sale by Sterling Winthrop in 1953 PN was gradually withdrawn [92]. In the United Kingdom compound codeine, a popular preparation containing in addition PN and aspirin, was withdrawn in 1979. Both analgesics were in trusted use before the thalidomide catastrophe of 1957-61 [116]; as such they escaped the framework of safety legislation introduced in 1963 for new pharmaceutical products [117]. PA entered the British pharmacopoeia in the same year and became the most widely known and highly regarded of all painkillers. In 1976 no less than 260 products containing PA were on sale in the United States and the United Kingdom [91].

PA MANUFACTURE AND EXPORT

Price undercutting from Asia forced the closure in 2008 of the Rhodia plant in southern France [93], ending PA manufacture in Europe [94, 118]. Much of the world production of PA is currently based in China, whose exports have been mounting year on year by 13% [94]. Whereas between them China and India produced 50,000 tonnes of PA in the mid-1990s, output jumped to 80,000 tonnes by 2001. Production in 2008 was 115,000 tonnes; during the next two yr their joint share of the global market rose from 70% [93] to 80% [96]. Also in 2008 the United States company Covidien manufactured a further 30,000 tonnes [93, 118], conservatively making a world total of around 145,000 tonnes. In the first quarter of 2009 China exported 7,500 tonnes of PA to Asia, 1,900 tonnes to Africa, 3,200 tonnes to Europe, 2,700 tonnes to India and 1,100 tonnes to Nigeria [94]. Global output of the PA precursor 4-aminophenol rose by almost 30,000 tonnes between 2008

and 2010. Asian demand for PA is expected to strengthen appreciably over the next few years [96].

PN: NEPHROTOXICITY AND F-AD

Haematuria and nephritis were reported as side effects of PN [100] soon after its introduction. The frequent occurrence not only of nephritis [6-8, 54] but also of more serious forms of kidney injury [6, 52, 55] at postmortem among early F-AD cases, including Frau D [6,7], suggests over-medication with PN. One patient complained of severe headaches [6]. Alzheimer himself suffered kidney failure in the last few weeks of his short life; he too may have used PN to excess [8]. The recognition of senile dementia as a consequence of nephritis in an unspecified number of patients may have been an error of interpretation but not of clinical observation [37]. Chronic forms of nephritis were recorded in a series of 16 dementia patients who displayed plaques with or without tangles [57]. PN was given routinely for the purpose of sedation in two institutions [61, 62]; the practice may not have been uncommon [3-8, 50, 51, 53-56].

In the 1970s a correlation between dialysis and dementia was sometimes noticed in kidney patients [24, 119-121]. Lesions associated with F-AD were occasionally present in a minority of patients surveyed [122]. While this particular group [122] is likely to have undergone PN exposure [cf 24], the rarity of plaques and tangles in dialysis dementia noted later [123, 124] is consistent with the gradual disuse into which PN fell [92]. Acute cerebral ischaemia arising during dialysis can lead to cognitive dysfunction, and is considered to represent an intermediate stage in the development of vascular dementia [124-126].

ANALGESICS AS RISK FACTORS FOR F-AD: (1) EXPOSURE AND INDIVIDUAL CONSUMPTION

A comparison of the time frames of events listed in Tables **1** and **2** would suggest that the minimum time of exposure to PN required for F-AD expression is around 15yr; the figure for PA is expected to be comparable. A complexity of factors may affect the onset of symptoms, including the frequency and extent of analgesic consumption [24], the specificities and activities of isoenzymes of cytochrome P450, the stabilities of chemically-modified cerebral protein [127], nutrition, enzyme induction, individual susceptibilities and the duration of analgesic exposure. With regard to the popular use of PA for children, the question arises whether or not the analgesic, when given in childhood, might contribute to the development of neurodegenerative illness in adulthood [128].

Theoretically the hydrolysis of 1g of PN at the ether linkage yields 0.84g of PA; conversion to other metabolites is around 20-40% [26]. Information regarding the amount of PN required to induce the illness is scanty; the only available estimates range from 10-50kg [24]. On this basis [24-26] the corresponding amounts of PA required to establish F-AD range from 5kg to 33kg. Personality disorders were noted in two patients whose overall PN intake was 6kg each; presenile dementia was observed in a third who had consumed 12kg [24]. One subject unaccustomed to PA but with a modest history of PN ingestion (lifetime intake <0.5kg) noticed interference with memory in both the short- and the long-term on two separate occasions after consuming approximately 10g PA over two weeks [28]. The maximum daily amount of PA recommended for pain relief is 4g [129], equivalent to 1.46kg per yr. At this dosage an annual worldwide production of 145,000 tonnes [93, 94, 118] is sufficient to control the chronic pain of 100 million patients.

ANALGESICS AS RISK FACTORS FOR F-AD: (2) EPIDEMIOLOGY

In epidemiological studies in which all analgesics were grouped together no significant effect was reported on the onset or incidence of F-AD [130-133]. More recently the influence of non-steroid anti-inflammatory drugs (NSAIDs) has been recognised as being largely protective [18, 45, 46, 68, 134-139]. In siblings at high risk from F-AD the sustained use of NSAIDs alone was linked with delayed onset and reduced incidence of disease [135]. Users of high-dose aspirin had a lower prevalence of dementia; cognitive function was better preserved in this group [137]. A recent investigation of almost 50,000 subjects over periods in excess of 5yr found that some NSAIDs decreased the risk of dementia, but that others had the opposite effect [138]. Certain NSAIDs may delay the onset of symptoms [45, 135, 139], but once the condition begins to develop their effects may no longer be beneficial [139].

With one exception [130] the work of Murray and his colleagues [24] was not acknowledged by investigators who examined dementia in the context of PA usage. The vital link between PN as risk factor and PA as its metabolite would appear, therefore, to have been largely missed [45, 68, 136, 137]. In an assessment of PA and other psychotropic drugs in subjects aged over 85yr, the analgesic was taken by 51% of patients with dementia but by only 21% of those assessed as non-demented; the difference was significant ($p<0.001$) [68]. Consumption of PA has been considered among factors that might influence onset [45, 137]. Odds ratios of around 0.4 were observed for NSAIDs and aspirin, but no value was provided for PA [45]. The relative risk of developing dementia among users of PA for more than 2yr, although not considered statistically significant, was still 1.58 [136].

No effect of an unspecified PA regimen on the prevalence of dementia or on the deterioration of cognitive function in subjects aged 80 or over was found [137]. In other studies no distinction was drawn between chronic and occasional use of PA; information regarding intake was omitted [45, 136, 137]; and the study timespans were short [137] or ill-defined [45, 136]. One investigation recognised that individuals whose PA consumption was low were likely to have been misclassified as having undergone greater exposures [136]. In the absence of more precise knowledge of the extents of analgesic consumption and the durations of exposure, the reliability of these reports [45, 136, 137] is open to question.

The finding of lesions at postmortem in non-demented individuals [56, 57, 65, 140, 141] lends support to the surmise that late onset F-AD is probably linked with infrequent PA use. In instances where the lifetime PA intake has been small, increases in life expectancy [23] permit an age to be reached at which lesions are present yet the disease

is either at too early a stage of development to be diagnosed or may not be expressed at all [45, 46].

PN AND PA: METABOLISM

The vulnerabilities of kidney [101, 142] and liver [143-151] to toxic amounts of PN and PA respectively arise from partial conversion of the analgesics to reactive metabolites through the agency of cytochrome P450 [26, 147, 149, 152-155]. Although in man 60-80% of PN is converted to PA [26], any of the minor metabolic intermediates *3*-hydroxy-PN [142], PN-*3,4*-epoxide [152], N-hydroxy-PN or reactive derivatives produced therefrom [153] could account for its nephrotoxicity [100]. In man PA forms the substrate for a number of cytochrome P450 isoenzymes in the liver [149]. When given therapeutically the analgesic is excreted in the free form [142, 156] and as glucuronide [26, 142, 151, 156] and sulphate [142, 156] conjugates.

Further metabolic studies have been confined mostly to rodent liver. The lack of cytochrome P4501A2 and P4502E1 in double null mice affords protection against PA hepatotoxicity; it follows that the conversion of the analgesic to toxic intermediates requires the participation of both P450 isoenzymes and an active form of oxygen [147]. In rat liver PA toxicity is mediated by initial metabolic activation. Cytochrome P450 isoenzymes convert the analgesic to N-acetylbenzoquinone-*4*-imine [26, 44, 143-147, 153-155, 157], a minor but key metabolite which rapidly binds to protein-bound cysteine through a thioether bond. After administering hepatotoxic amounts of PA to mice [150], the presence of entire molecules of the analgesic covalently linked to protein [143-148] in pre-necrotic centrilobular regions of liver [144, 146, 151] provides evidence of imine formation.

In rat liver peroxynitrite, a highly reactive free radical able to nitrate the ring systems of aromatic and heterocyclic amino acids [158], is formed in the course of PA metabolism [71, 150, 151]. PA also induces nitric oxide synthase [71] in the liver. In hepatic protein the *3*-nitro- [146, 148, 151, 159] and *3,5*-dinitro- derivatives [159] of tyrosine and both *4*-nitro- and *6*-nitrotryptophane have been detected following the administration of PA in hepatotoxic quantities, though the extent of tryptophane nitration is substantially less than that of tyrosine [160]. PA toxicity correlates with both PA-adduct formation [161] and tyrosine nitration [148] in liver.

N-acetylbenzoquinone-*4*-imine can also acetylate amino groups but is more effective as an arylator [144, 152], and reacts with glutathione *in vivo* [144] and *in vitro* [154] to form a PA-conjugate. Levels of the peptide are depleted by toxic doses of PA [26, 147, 154, 161]; analgesic binding to protein is favoured when the availability of glutathione is restricted as a consequence of PA overdose [154, 161]. Inadequate dietary intakes of sulphur-containing amino-acids may accelerate the early development of F-AD.

CYTOCHROME P450

In detoxifying systems the relative proportions of the metabolites produced from PA will be governed by the specificities and activities of cytochrome P450 isoenzymes. In quantitative terms the contribution of cytochrome P450 in the brain to the overall detoxification of both PN and PA is probably very minor by comparison with metabolism elsewhere in the body. Low levels of P450 isoenzymes and the restriction of enzymic function to the production of very small amounts of reactive intermediates [44] would explain the resilience of the brain to an acute toxic overdose of PA by comparison with the pronounced susceptibility of liver [143-147, 149-151, 162].

In man inducible forms of cytochrome P450 are distributed unevenly within the brain. The location of mRNA associated with cytochrome P4502D is highest in the frontal cortex and hippocampus [44], regions where the characteristic lesions of F-AD arise [5]. Enzymic expression in close proximity to pre- and post-synaptic receptors suggests that cytochrome P450 isoenzymes may have a role in the creation of micro-environments [44]. If PA possesses the ability to induce P450 isoenzymes capable of metabolising the analgesic in human brain [cf 71], regular users may be at greater risk than patients whose consumption is infrequent.

PA AND F-AD: EARLY-STAGE CEREBRAL INJURY

The development of F-AD is preceded by a silent asymptomatic phase of long duration [17, 20, 45, 46] during which injury accumulates. Whereas acetylation and nitration are events which occur naturally, the non-physiological nature of PA-protein adducts singles arylation out as the chemical lesion likely to initiate F-AD. Although antigenic profiles of neuronal proteins are modified by tyrosine nitration [163], the greater size of the PA hapten indicates that the contribution of covalently-bound PA molecules to altering antigenicity will be profound. These chemical changes pitch the immune system into the initial phase in the development of cellular injury. Chemically-altered cerebral proteins are recognised as significant cellular targets in terms of disease progression. The response of the microglia to cellular components newly recognised as foreign substances regardless of where they occur creates an environment of increasingly hostility as chemical modifications augment. Over a period of time each pharmacological challenge makes its own minuscule, subtle contribution to cumulative injury in stepwise fashion.

Alterations in the chemistry of neuronal proteins give rise to other forms of damage. Adduct formation with enzymes [161] decreases or destroys catalytic function [72, 159, 164]. The peroxynitrite-dependent nitration of tyrosine residues is catalysed by the cytosolic copper-zinc form of superoxide dismutase [165]. Peroxynitrite inactivates a wide range of enzymes [158] including the manganese-dependent form of the enzyme in the brains of both man and experimental animals [164]. *6*-Nitrotryptophane has been detected in the hippocampus and cerebellum of the rat under normal physiological conditions [166]. Proteins [163, 167], enzymes and amino acids [158] are not the only targets of peroxynitrite and its congeners. DNA undergoes strand scission [163, 168]; other cellular components, including lipids [159, 163] and macromolecules [167] undergo oxidation. Amyloid precursor protein is converted into ß-amyloid [169, 170].

In F-AD microglia and astrocytes [163, 171], especially in the cerebral cortex and hippocampus [172], become activated. Interference with synaptic transmission precedes cognitive impairment [69] as well as synapse [20] and neuronal [4] disappearance. An ultrastructural study of synaptic regions in cortical biopsies from F-AD patients demonstrated loss of anastomoses [173]; peroxynitrite-induced damage to synaptosomal membranes has also been reported [72].

Losses of neurones resulting from ß-amyloid activation of microglia [163, 171, 172], the expression of inducible nitric oxide synthase [174, 175] and microglial phagocytosis [171] are mediated by peroxynitrite attack [163, 172, 176] and the subsequent nitration of tyrosine residues [146, 148, 151, 159, 164, 167, 168, 177]. Peroxynitrite produced by nitric oxide synthase-positive neurones resisting destruction in the hippocampus may augment the injury [178].

PA AND F-AD: LATE-STAGE CEREBRAL INJURY AND THE AMYLOID CASCADE

F-AD has been categorised as an inflammatory response [5, 134, 163, 171, 179] exacerbated by peroxynitrite [163]. Plaques and tangles are chronic irritants [171]. The extent of tyrosine nitration in the proteins of cerebrospinal fluid relates inversely to the level of cognitive function [127]. The mechanism of cell death invoked by peroxynitrite is considered to be apoptosis [179, 180].

Random events govern the onset of the amyloid cascade. By the time ß-amyloid deposition is widespread the contribution of PA-protein adducts to the progression of disease is no longer likely to be of significance. ß-amyloid raises peroxynitrite production by inducing nitric oxide synthase in the microglia [163, 174] and tangle-bearing neurones [175], thereby stimulating the microglial destruction of neurones [54, 171, 172].

Isolated ß-amyloid cores injected into the cerebral cortex [181, 182] and hippocampus [181] of rat brain brought about extensive neuronal losses in the vicinity. In the later stages of disease tyrosine nitration in the glia [168], cortex and hippocampus [159, 167, 177], neurofibrillary tangles [177] and cerebrospinal fluid [127, 159, 183] provide evidence of ongoing peroxynitrite activity. Collectively these events constitute an `autotoxic loop' [171] and furnish an explanation for the acceleration of terminal decline [184].

F-AD: REPAIR MECHANISMS

In addition to ß-amyloid production microglia engage in the phagocytosis of plaques [54, 171, 185, 186]. Evidence from cell culture suggests that plaque phagocytosis is under astrocyte control [186]. Activated microglia are found concentrated in areas of plaque ß-amyloid formation [172, 187]. Shrinkage of both diffuse and compact ß-amyloid plaques was detected in the cortex and hippocampus of APP/PSI mice in response to the RXR agonist bexarotene; reversal of cognitive, social and olfactory deficits occurred simultaneously [188].

A deeper understanding of the mechanisms of injury allows strategies which promote repair to be designed. In man N-acetyl cysteine has been used to prevent the early stages of liver necrosis [143] caused by PA in man by supplying a scavenging molecule intended to react preferentially with N-acetylbenzoquinone-*4*-imine [162] and to furnish cysteine for the synthesis of glutathione. Similar prophylaxis against PA-adduct formation may be provided for the brain prior to analgesic use.

Neuronal proteins bearing nitrotyrosine residues are unstable and undergo degradation [127]. In addition to tryptophane and tyrosine, phenylalanine and histidine are also liable to undergo peroxynitrite-mediated nitration [158]. Neurogeneration [3, 73-76] will be restricted when the availabilities of tyrosine and other essential amino acids are limited. A proteinaceous diet and nutritional supplementation with essential amino acids may slow the progress of disease in its early stages by facilitating protein resynthesis in the brain, and may even confer capacity for new memory.

In an early trial with neurotransmitter precursors, tyrosine, 5-hydroxytryptophane and carbidopa were given daily to ten patients. All had severe disease; six had multi-infarct dementia and seven had F-AD. Side effects necessitated lowering the dosages in some cases. Although it was found that 5-hydroxytryptophane and carbidopa competitively inhibited tyrosine uptake into the brain, improvements in clinical and psychological condition as well as in memory were noted in two patients [189]. In addition to participating in protein synthesis, free tyrosine of exogenous origin might act as a scavenger by providing an alternative substrate for reaction with peroxynitrite. However, as the disease advances such measures are likely to be overwhelmed by the persistence of ß-amyloid and the relentless generation of peroxynitrite [127].

CONCLUSIONS

Evidence that much of the dementia of today is man-made is too powerful to ignore. The unsatisfactory nature of the present situation calls for urgent action. If epidemiological data are to have relevance, critical factors calling for attention during planning include proper classification of analgesics, consideration of the amounts consumed, and duration of patient exposure. However, the passage of time and the rapidly increasing international use of PA may mean that studies along these lines cannot provide unambiguous answers to the question whether PA causes F-AD or not. A search for both chemical and pathological changes consistent with F-AD lesions in the brains of rodents or primates in response to PA feeding could short-circuit the need for long-term prospective investigations, which may now be ruled out on ethical grounds. The chain of events whereby F-AD develops is considered to begin with arylation of neuronal protein by the reactive PA metabolite N-acetylbenzoquinone-*4*-imine. Changes in protein antigenicity prompt a hostile response from the microglia. Neuronal function becomes impaired; ß-amyloid is formed and structural damage follows. ß-Amyloid induction of nitric oxide synthase, peroxynitrite production and the nitration of tyrosine residues emerge as key destructive features of the amyloid cascade. Ongoing microglial responses to tyrosine nitration ultimately establish the self-sustaining and irreversible inflammatory reaction that constitutes F-AD.

SEARCH STRATEGY, SELECTION CRITERIA AND RATIONALE

Medline was screened from 1949 to May 2013 with appropriate combinations of the words acetaminophen; acetophenetidin; Alzheimer; amyloid; apoptosis; cognitive impairment; dementia; neurogenesis; nitrohistidine; nitrophenylalanine; nitrotryptophane; nitrotyrosine; NO-synthase; peroxynitrite; phenacetin; plaque; superoxide; tangle; tau; and tyrosine. The archive of the Library of the Institute of Psychiatry (London) was searched for pertinent literature between 1800 and 1915. Bibliographies of relevant articles and reviews were also searched. Additional information and rare material were accessed or purchased at *www.abebooks.com* Commercial data were obtained using internet search engines with combinations of the words China; India; manufacture; paracetamol; and report. Except where translations were available, material in French, German and Italian was read in the original language. Deduction played a central role in the construction of this analysis. Priority in citation was accorded on the basis of discovery, originality, persuasiveness and relevance irrespective of the publication date.

AUTHORSHIP

This work is solely that of the author.

ABBREVIATIONS

F-AD = Fischer-Alzheimer's disease

NSAIDs = Non-steroid anti-inflammatory drugs

PA = Paracetamol

PN = Phenacetin

CONFLICT OF INTEREST

The author confirms that the content of this review has no conflict of interest. Expenses arising from production of the work have been borne exclusively by the author.

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