Journal of Allergy & Therapy
ISSN: 2155-6121

Jones GR, J Allergy Ther 2014, 5:2
DOI: 10.4172/2155-6121.1000172

Commentary Open Access

The Role of Acetaminophen in the Development of Dementia

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Rec date: Mar 11, 2014, **Acc date:** Apr 26, 2014, **Pub date:** May 07, 2014

Commentary

In a little over a century Alzheimer-type dementia (ATD) has grown in importance from a rare and poorly understood condition into a scourge of international dimensions, one which leads to premature mental incapacitation and the deaths of millions every year. The exponential manner in which the number of sufferers has been increasing in many parts of the world [1] rightly concerns political leaders [2]. Searches for a major risk factor for ATD have been disappointingly unsuccessful [3], although in 1971 [4] phenacetin was unambiguously implicated in its etiology. The link between ATD and the coal tar analgesics phenacetin [4] and acetaminophen, its chief metabolite [5], continues to be disregarded.

ATD, an inflammatory condition of the brain [6], is caused by specific alterations in the antigenic profiles of cerebral proteins. The process occurs in two stages. Initially acetaminophen is metabolised in the cortex and hippocampus, where analgesic-protein adducts are formed. The second step involves nitration of tyrosine residues in cerebral proteins. Immune attack occurs at sites where antigenically-altered proteins are found. Once the characteristic lesions of ATD are established, disease progression continues independently of analgesic intake [5].

The longer the time taken for an adverse effect of a drug to manifest itself, the longer the intervening period before recognition of the connection is likely to be. Since 1887 populations have been increasingly exposed to phenacetin [5] and its metabolite. The nephrotoxicity of phenacetin develops within months and was described in 1888 [7]; the observation was confirmed in 1890 [8]. ATD was characterised [6,9] fourteen years after the introduction of the analgesic [10]. Not until 84 years after the introduction of phenacetin [5,10] was the connection between extensive medication with the analgesic and ATD made in kidney dialysis patients [4]; before then no feasible cause had been identified [3,5]. The replacement of phenacetin by acetaminophen between 1953 and 1980 [5] failed to halt the continuing rise in ATD incidence [1]; the inescapable conclusion is that both analgesics are cerebrotoxic. The connection between acetaminophen and ATD was made 114 years after the introduction of phenacetin [11].

Firm evidence that the exponential rises in ATD incidence in countries across the world [1] are primarily a consequence of growing life expectancy is lacking. In England and Wales age-standardised mortality for any mention of ATD increased from 1985 to 2004 by eightfold for men and twelvefold for women. Over the same period life expectancy for the two groups rose by 5.2 and 3.8 years respectively [12]. Dramatic rises in ATD incidence have lagged behind similar increases in acetaminophen output in both China and India, who between them continue to dominate world production and export [5].

Beginning in 1962, increasingly stringent regulatory mechanisms for new pharmaceutical products were gradually introduced in the United Kingdom. All established drugs were presumed safe. Despite newspaper reports of deaths from phenacetin in 1969, the Medicines Control Agency waited until 1974 before withdrawing the analgesic while providing no reason [13]. Both the existence of regulatory agencies and confidence in their presumed effectiveness has universally created a false sense of security. The paucity of safety signals has been used to justify inertia, but since 2001 evidence of the acetaminophen/ATD link [5,11] has been challenging the traditional culture of complacency and inaction [13]. Neither phenacetin nor acetaminophen has ever been subjected to anything beyond primitive testing [5,10]; up to the year 2000 other hazards beyond the known and accepted toxicity of the latter were not suspected [3]. The prevalent assumption of safety is no longer tenable; rigorous scrutiny and appropriate testing are urgently called for.

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