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## Acetaminophen: A major danger to world health

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Up to 1900 Alzheimer-type dementia (ATD) was a rare condition of unknown etiology. During the last century it gradually became a huge threat to public health. Over the next two decades 200-250 million patients will die with ATD. The illness is widely assumed to be a consequence of increases in life expectancy, but the assertion is unproven. Phenacetin, the metabolic precursor of acetaminophen, was introduced in 1887. In 1901 Fischer found his first case of ATD; by 1910 he had 55 more. In 1971 the nephrotoxicity of phenacetin was linked in dementia patients with characteristic ATD lesions and high lifetime intakes of the analgesic. ATD is basically an inflammatory state of the brain initiated by chronic phenacetin/acetaminophen usage. The condition arises from immune responses to two different chemical modifications of cerebral protein. First, acetaminophen is metabolised to an unstable benzoquinoneimine which reacts with sulphhydryl groups to form acetaminophen-protein adducts. Following immune attack,  $\beta$ -amyloid clumps formed by proteases acting on amyloid precursor protein induce nitric oxide synthase. The resulting increase in peroxynitrite flux nitrates tyrosine residues. Second, proteins bearing nitro groups undergo immune attack. The amyloid cascade progresses independently of further analgesic intake. Anticipated rises in ATD incidence in developing countries belatedly match the dramatic expansion of acetaminophen manufacture in and export from China and India. In overdose acetaminophen causes liver failure, but ATD results from medically-acceptable intake over periods of time. Neither analgesic was ever tested to modern standards. The safety of acetaminophen is in urgent need of thorough investigation.

### Biography

G Robert N Jones graduated from Cambridge in Natural Sciences in 1954. He entered cancer research in 1959 and was awarded a PhD in Pathology by the University of London. In 1974 he recognised that its unique vulnerability singles the malignant mitochondrion out as the ideal cellular target for chemotherapy. His book *In the Darker Shadow of Science: The Subjugation of Cancer* (2010) describes the successful search for a widely-applicable cancer therapy based on promethazine as its active principle. In 2001, he concluded that Alzheimer's disease is caused chiefly by acetaminophen; this year he published a detailed review of the evidence.

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