

# Ignored Papers, Invented Quotations: A History of Fetal Alcohol Syndrome

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## Keywords

Embryopathy · Fetopathy · Fetal alcohol syndrome · Fetal alcohol spectrum disorders · Teratology · Eugenics · History

## Abstract

Given the high rate of alcoholism throughout history, its effects on the fetus may have existed for millennia. But, the claim that Greeks and Romans were aware of fetal alcohol syndrome rests on incorrect citations. From 1725, maternal alcohol consumption was associated with retarded fetal growth and neurological anomalies. From 1809, scientists followed Lamarck's theory that the disorders parents acquire during their lifetime are passed on to their offspring. Fetal effects were thought to be inherited mainly from the father. During the 19th century, parental alcoholism became associated with malformations. In 1915, Ballantyne distinguished genetic influence via germ cells from toxin's effect on the embryo. Fetal alcohol syndrome was characterized by Rouquette [Influence de la toxicomanie alcoolique parentale sur le développement physique et psychique des jeunes enfants] in 1957 and Lemoine et al. [Ouest Medical. 1968;21:476–482] in 1968 as consisting of 4 features: (A) facial anomalies (narrow forehead, retracted upper lip, and cupped ears), (B) severe growth retardation (prenatal and postnatal), (C) malformations (limbs, cardiac, and visceral), and (D) central nervous system anomalies (hyperexcitability and mental retardation). But, their studies, written in French, remained disregarded. In 1973, Jones et al. [Lancet. 1973;302:999–1001] reported "the first association between maternal alcoholism and aberrant morphogenesis in the offspring." The history of

fetal alcohol syndrome reveals shortcomings in citation practice. Alleged quotations remained unverified, non-English publications neglected, and short quotations taken out of context. Prejudiced by religious and abstinence groups, reports on alcohol damage to the unborn were fraught with emotions, moralizing, social implications, and presentism, the interpretation of past events with present knowledge.

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## Introduction

Fermented beverages have accompanied mankind since the Neolithic age. Using gas chromatography-mass spectrometry, McGovern et al. [1] found a fermented mixture of rice, honey, and fruit in pottery jars from the 7th millennium BCE in the Henan province of China. Beverages with >5% alcohol were consumed throughout human history, and distilled spirits with >20% alcohol were known to Egyptians and Babylonians around 2,000 BCE [2, 3]. Aztecs consumed pulque, the fermented juice of the agave plant. Fetal alcohol syndrome was described by Lemoine et al. [4] in 1968. In addition to the full-blown syndrome, fetal alcohol "spectrum disorders" include partial fetal alcohol syndrome and alcohol-related neurodevelopmental disorders, which are not part of this article. Fetal alcohol syndrome is a leading cause of mental retardation. Its historic sources were critically analyzed by Abel [5, 6] and James Sanders [7] and the more recent history by Jones and Streissguth [8] and Lemoine [9, 10]. This study aims to explain why prenatal alcohol damage

was understood so late and why so many publications contain contradictions. In this study, alcohol always means ethanol.

### Reports from Antiquity

Given today's prevalence of 0.5% in developed countries [11, 12], fetal alcohol syndrome may have existed for millennia. Many authors could not refrain from "proving" this hypothesis with historic citations [13–18]. Even Biblical sources have been cited to prove that Hebrews acknowledged the danger for the fetus [13, 14]. Judges 13:3–4 is usually quoted because an angel advised Samson's mother "thou shalt conceive, and bear a son. Now therefore beware, I pray thee, and drink not wine nor strong drink." As Abel pointed out [5], the advice did not refer to every pregnant woman, as the text continued "for the child shall be a Nazarite (consecrated to the Lord) unto God from the womb." Abel also demonstrated [6] that the claim that fetal alcohol syndrome was known to Greeks and Romans was borrowed from Robert Burton's "*Anatomy of Melancholy*" of 1621. Under the pseudonym "Democritus Junior," the Anglican priest published an encyclopedic monograph which sold well, went through 8 editions up to 1676, and was still being reprinted in the 19th century [19]. Although his "citations" sound convincing, they were often incorrect, taken out of context, or simply fabricated. A few examples are as follows.

(1) Burton claimed the Roman author Gellius [20] had written, "if a drunken man get a child, it will never likely have a good braine," while Gellius criticized wet nurses as "dishonest, unchaste, or drunken." (2) Burton quoted the Greek author Plutarch [21] as having written "one drunkard begets another," but in fact he had stated "that love was like drunkenness." (3) Burton claimed that Aristotle (322 BCE) wrote [22] "foolish, drunken or haire-braine women, for the most part bring forth children like unto themselves, *morosos* and *languidos*," but this citation cannot be verified either.

The 17th century quotations are frequently incorrect, especially when clerics were trying to support their moral claims. What is remarkable, however, is that Burton's "quotations" have persisted in the medical literature for 400 years. Undoubtedly, Greeks and Romans believed that at the time of conception, both mother and father should be sober, as Plato (427–347 BCE) emphasized in "*The laws*" [23]: [674 b]: "judges while on duty, should taste no wine at all nor should anyone do

so by night – be he man or woman – when proposing to procreate children." [775c-d]: "Drinking to excess is a practice that is nowhere seemly and certainly it is not so for those who take marriage seriously that the child that is begotten may be sprung from the loins of sober parents; moreover, it is not right that procreation should be the work of bodies dissolved by excess of wine, but rather that the embryo should be compacted firmly, steadily, and quietly in the womb; when drunk, a man is clumsy and bad at sowing seed, and is thus likely to beget unstable and untrusty offspring, crooked in form and character."

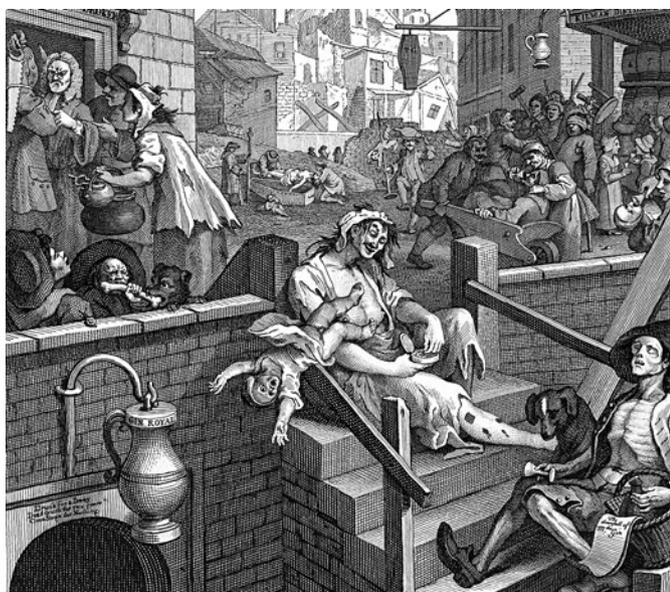
The Romans did not claim that alcohol itself was toxic for the fetus. They held maternal imagination responsible, as did Soranus around 200 CE [24]: "In order that the offspring may not be rendered misshapen, women must be sober during coitus because in drunkenness the soul becomes the victim of strange phantasies."

### 16th and 17th Centuries: "Very Wholesome"

Renaissance authors did not consider alcohol unwholesome during pregnancy. Roesslin [25] ordered in 1513: "And for drink, let her use good ripe wine mixed with water." Fernel [26] was aware of fetal addiction in 1554: "Maternal blood, the fetuses' first aliment, influences his temperament and constitution. He will need what she is used to. Thus an alcoholic mother will bring forth an alcoholic fetus, a mother habituated to drugs, a drug-addict." French pioneers of obstetrics treated vomiting and the morning sickness of pregnant women with wine. In 1620, Guillemeau [27] recommended drinking "wine diluted with water," and Mauriceau [28] specified in 1668: "She should drink old wine, better red than white, which is warmed and diluted with fresh fountain water." The Nurse's Guide of 1729 encouraged mothers and wet nurses to drink beer or ale [29]: "The drinking of Malt-Drink (*cervisia*) produces a great deal of milk, and is very wholesome."

### 18th Century: "Pigmy Size"

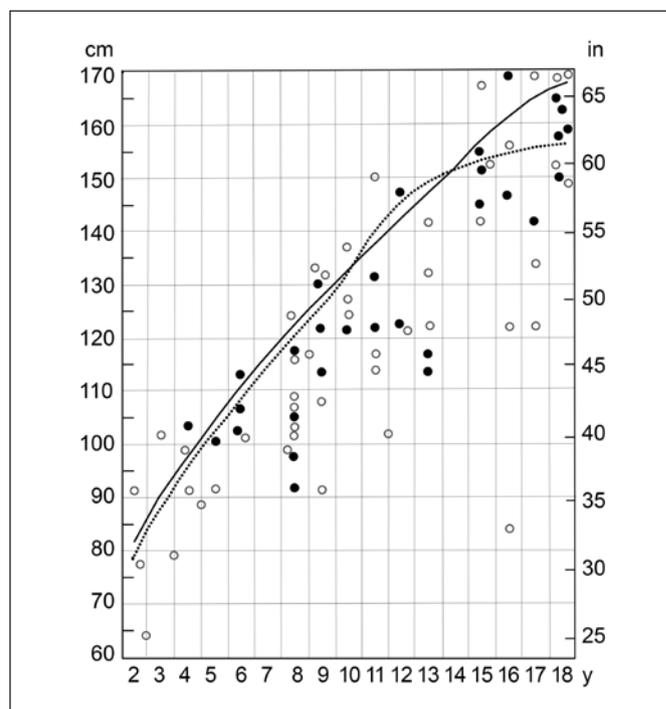
At the beginning of the 18th century, the British parliament lowered taxes and encouraged the sale of strong spirits. Gin consumption rose to epidemic proportions [30]. In January 1725, the Royal College of Physicians petitioned [31] to the House of Commons against the pernicious and growing use of spirits, which rendered "great



**Fig. 1.** “Gin Lane” (detail), copper engraving by William Hogarth, 1751 [71]. Hogarth was a lifelong benefactor and governor of the London Foundling Hospital since 1741. The illustration depicted the evils of drinking gin and aimed to support the British legislation “Gin Act,” passed in 1751.

numbers of both sexes diseas'd, not fit for business, poor, a burthen to themselves, and too often the cause of weak, feeble, and distemper'd children.” In the same year, the Middlesex Justices of Peace reported [32]: “Unhappy Mothers habituate themselves to these Distilled Liquors, whose Children are born weakly and sickly, and often look shrivel'd and old, as though they had number'd many Years.”

Alcoholism among the poor was drastically depicted by William Hogarth in 1751 (Fig. 1). The “Mother Gin Controversy” led to legislation that slowly reduced the consumption of distilled liquors [33]. In 1751, the Anglican priest Stephen Hales repeated the Justices' claim [34]: “Nay, the unhappy influence of these liquors reaches even to the children that are yet unborn. Of this we have too frequent instances, where the unhappy mothers habituate themselves to these distilled liquors, whose children, when first born, are often either of a diminutive, pigmy size, or look withered and old, as if they had numbered many years, when they have not, as yet, alas! attained to the evening of the first day.” Morris [35] evaluated the tables of christenings and burials within London from 1601 to 1750. He linked the drinking of spirituous liquors to “sterility of the females and renders such as are born meagre and sickly, and unable to pass through the first stages of life.”



**Fig. 2.** Body length of 76 Massachusetts children classified as “idiots,” the progenitors of whom were ascertained as alcoholics (closed circles) or nonalcoholics (open circles). Data from Howe [39], 1848. Comparison with normal Boston school children, 1877: straight line, boys; dotted line, girls [72].

### 19th Century: “Hereditary Alcoholism”

The temperance movement originated in the 1820s in many countries, led by churches and dominated by males. But, physicians played down alcohol dangers for women, as did Bouchut in his “Mothers Guide” [36]: “The nurses may drink wine in small quantity (one bottle a day, with water), beer, and cider, as they are used to.” From 1809, most scientists acknowledged Lamarck’s theory that physical characteristics and diseases that parents acquired during their lifetime are passed on to their offspring, as did Glasgow physician MacNish [37] in 1828: “From the general defect of vital power in the system, the children of drunkards are neither numerous nor healthy. They are usually puny and emaciated, and more than ordinarily liable to inherit all the diseases of their parents. Their intellect is also, in most cases, below the general standard.”

The Select Committee of the British House of Commons queried in 1834 [38]: “Is there any difference in the appearance of such children?” The physician Robert Dods answered: “Sometimes not appreciable, at others quite distinct; the infant has frequently not merely a want

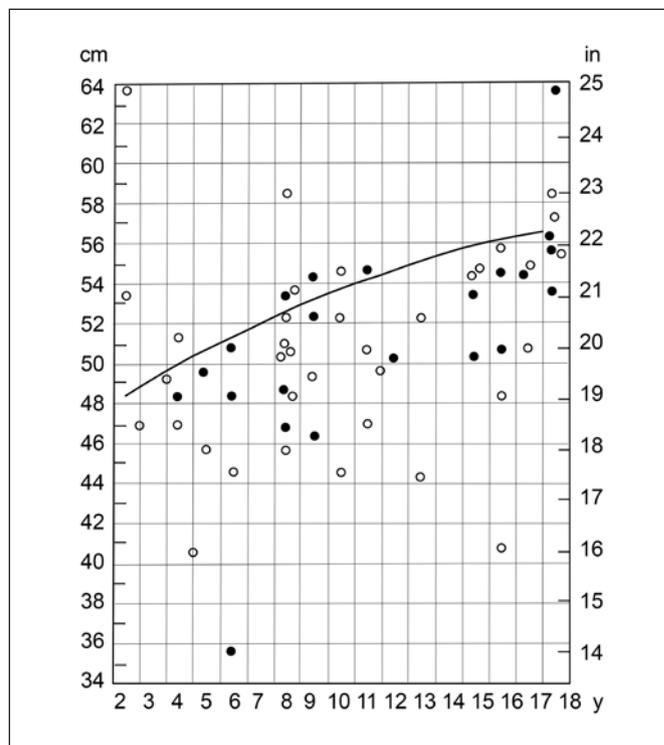
of healthy aspect, of plump, round outline, but a starved, shrivelled, and imperfect look.”

Mandated by the legislature, Howe [39] studied the “condition of 574 human beings considered as idiots” in Massachusetts, half of them in almshouses. From 1846 to 1850, he wrote several reports to the government, with a wealth of information in extensive tables: “Of the 359 idiots, the condition of whose progenitors was ascertained, 99 were the children of drunkards; the children of such persons are feeble in body and weak in mind.” The author did not discern maternal from paternal inebriety, nor prenatal from postnatal growth retardation. He understood the association of parental alcoholism, short stature, microcephaly, and idiocy (Fig. 2, 3), but his explanation conformed to the eugenic doctrine of the time.

In 1874 in the Paris Salpêtrière Hospital, Hippolyte Martin recorded the family histories of 83 epileptic patients born to alcoholic parents [40]: 169 of the 327 offspring died in early childhood and a third of the survivors suffered seizures. Haddon [41] of Manchester wrote in 1876: “Children (of intemperate women) born at the full time are generally weak and puny, and likely to fall at an early age victims to disease;... it is possible that a large proportion of our excessive infant mortality may be due to the malnutrition of the embryo, caused by the use of alcohol.” In Liverpool, Sullivan [42] analyzed the reproductive history of the women’s prison inmates in 1899: “Drunken mothers (21 cases) had 125 children, of whom 55% died under 2 years. Sober mothers (28 cases) had 138 children, of whom 24% died under 2 years.”

### 20th Century: “Teratogen”

In 1899, Nicloux [43] found that alcohol passed readily through the human placenta yielding a fetal blood concentration almost equal to that in maternal blood. In 1915, Ballantyne [44] of Edinburgh, founder of antenatal medicine and the journal *Teratologia*, clearly distinguished the genetic influence via germ cells from a toxin’s influence on the embryo: “The hereditary aspects of the subject neglect the more immediately practical ones when the child of a mother who is given to alcoholism is living within her womb.” Two years later Ballantyne [45] added: “It may in the future be shown that alcohol has the power of picking out certain tissues, or even organs, in the fetus and embryo, and of attacking certain constituents of the germ cell and there may come a necessity to give to these particular changes a specific and defining term.”



**Fig. 3.** Head circumference of 58 Massachusetts children classified as “idiots,” the progenitors of whom were ascertained as alcoholics (closed circles) or nonalcoholics (open circles). Data from Howe [39] 1848. Straight line: median head circumference of normal Washington school children, 1897 [73].

But, political developments did not look favorably on teratology. World War I interrupted basic research in Europe, and prohibition laws of 1919 reduced drinking as a significant social problem in the USA. Nazi Germany made eugenics a state doctrine and declared alcoholism a flawed character trait rather than a disease. The “Law for the Prevention of Hereditarily Diseased Offspring,” passed in 1933 [46], forced the “eugenic” sterilization of alcoholics. World War II halted high-quality research. By 1967, alcohol teratogenicity was forgotten or ignored to such an extent that intravenous ethanol was introduced to suppress premature labor [47], a treatment that persisted in the USA until 1978 [48].

At the Bicêtre hospice in 1952, Desclaux and coworkers [49] studied electroencephalograms of mentally retarded children aged 7–18 years. They found altered traces (delta rhythm) in children of alcoholic parents, but not in other forms of retardation or in normal controls. At the Paul Parquet nursery in Neuilly (near Paris), Jacqueline Rouquette [50] studied 100 children of alcoholic parents in 1957 [10, 50]. She discerned alcoholism of the father (*n*

= 42), the mother ( $n = 28$ ), and both parents ( $n = 30$ ) and detected birth weights below 2,500 g, severe mental retardation, and stunted postnatal growth particularly in infants born to alcoholic mothers. In addition, Rouquette [50] described “the alcoholic infant’s portrait the head is often small the nose is turned up, its root flat the upper lip is short and retracted, a frontal angioma persists during the first months the infant is irritable, its movements jerky and awkward (postnatal) growth is severely retarded.” Among her 100 “alcoholic infants,” remarkably many had congenital malformations: harelip ( $n = 3$ ), other face malformations ( $n = 2$ ), hydrocephalus ( $n = 3$ ), and cardiac malformations ( $n = 4$ ). In Nantes, 400-km distant, Paul Lemoine [51] saw alcohol embryo-fetopathies at the University Hospital and suspected ethanol as a teratogen for the human embryo. He reported 15 cases to the Medical-Surgical Society in March 1964 and more completely to the Pediatric Society in April 1967 [10, 51] and published a study on 127 cases in 1968 [4]. To Lemoine’s 61 cases, added 66 others examined by Borteyru [52] in the social health dispensaries. Lemoine characterized the syndrome to consist of 4 features: (A) facial anomalies (narrow forehead, retracted upper lip, and cupped ears), (B) severe growth retardation (prenatal and postnatal), (C) malformations (limbs, cardiac, and visceral), and (D) central nervous system anomalies (hyperexcitability and mental retardation). His explanation focused on chronic maternal alcoholism: “Being immersed for nine months in an alcoholic bath easily explained the anomalies seen in the children.” But his study, written in French and originating far from Paris, remained disregarded.

At the King County (Harborview) Hospital in Seattle, pediatric resident Christy Ulleland and colleagues [53] observed 12 babies from 1968 to 1969 and reported on them in May 1970 at the American Pediatric Society in Atlantic City, NJ, USA: “Infants of alcoholic mothers are at high risk for pre- and postnatal growth and developmental failure,” and in 1972 [54]. In February 1973, Ulleland’s children were shown to David Smith, professor of pediatrics and specialist in dysmorphology, and his postdoctoral fellow Kenneth Jones [8]. On June 9, 1973, Jones published (with Smith and Ulleland as co-authors [53]) “Pattern of Malformation in Offspring of Chronic Alcoholic Mothers” in the *Lancet* [55], claiming “this seems to be the first reported association between maternal alcoholism and aberrant morphogenesis in the offspring.” Within a few years, alcohol embryofetopathy was confirmed in large cohorts in Germany [56], the USA [57], Britain [58], and many other countries.

## Misrepresentation and Sloppy Quotation

Jones [8] remembered in 2010: “Soon after the initial publications describing fetal alcohol syndrome, a study of Dr. Paul Lemoine of Nantes, France, was identified. One of us (K.L.J.) wrote to Dr. Lemoine, and he wrote back saying that he had published a study in 1968 in which he identified features very similar to what we had described in *Lancet*.” Lemoine [10] remembered the sequence of events differently: “Smith in Seattle, after reading the abstract on my work in the Archives, published 8 cases with the same conclusions. He wrote me asking for my complete text. This is an amusing fact: the 127 cases of a modest pediatrician from Brittany did not create any interest, whereas 8 American cases became immediately convincing ... in the whole world.”

Reviewing historical misrepresentations in science in 1998 [59], Shibley [59] found that the studies of Jones et al. [13, 55] had been cited a combined total of 1,736 times, while that of Lemoine et al. [4] had been cited only 156 times since its publication. This is not the forum to define which research deserves citation in historic contexts. But, the history of fetal alcohol syndrome does shed light on shortcomings of citation practice in medicine. Incorrect quotations were carelessly adopted and led to persisting erroneous assumptions. Non-English publications were neglected. Short quotations were taken out of context. The sequence of publications was inverted by Warner and Rosett [14]: “A neglected report by Lemoine et al. [4] concerning 127 offspring of alcoholic parents is the most striking confirmation of the observation of Jones et al. [13, 55].” Sloppy citations obviously did not ruin academic reputation in the 1970s.

## Pathogenetic Mechanism

From 1880, researchers tried to provoke embryonic malformations with ethanol in animal fetuses, as did Frédéric Combemale [60] at the Montpellier insane asylum in 1888, who intoxicated dogs; Charles Stockard at Cornell University from 1912, who treated guinea pigs [61]; and Raymond Pearl [62] at the Maine Agricultural Experiment Station, who inebriated chickens from 1913. Not knowing that embryotoxins are highly species specific, and chained to the doctrine of their time, their research focused on paternal effects. When indeed abnormal offspring were born, damage to the germ cells seemed proven, and the chance to understand the teratogen was missed.

Human fetal alcohol dehydrogenase has only 3–4% of adult activity per gram of liver tissue [63]. In 1971, Seppälä et al. [64] found that the newborn takes twice as long as the mother to eliminate alcohol. Errors in migration led to diminished brain growth and structural anomalies [65]. Molecular mechanisms remained unclear. In the developing brain, alcohol impairs gene expression of the guidance cue and receptor families required for axon growth [66].

## Epidemiology

Population-based studies established a worldwide prevalence of about 0.5% for fetal alcohol syndrome [11], ranging from a minimum of 0.1% in Australia to a maximum of 4.5% in South Africa [67]. Among 116 children in an isolated native Indian community in British Columbia, Robinson et al. [68] identified 14 children with the full-blown syndrome and another 8 with a partial syndrome. The frequency of “alcohol spectrum disorders” is 2–8 times higher and even more variable due to different definitions, measurements, and age of the study populations. In Europe, the per capita consumption is up to 10 L of pure alcohol per year, which translates to 22 g per person per day [69]. Together with the fact that >40% of pregnancies are unintended [70], a huge public health problem emerged.

## Conclusions

Given the high rate of alcoholism throughout history, fetal alcohol syndrome may have existed for millennia. Reliable reports, however, are available only from 1725 about retarded growth and neurological abnormalities. Why was the obvious, clear pattern detected so late? Infants with low birth weight frequently died soon after birth, and those with cardiac malformation died before mental retardation became manifest. Fetal growth retar-

dation was confused with prematurity or lumped together as “weaklings,” “puny,” or “shriveled.” Martin [16] hypothesized that maternal drinking could account for significant proportions of infant mortality in former centuries. Up to 1866, diseases characterized by mental retardation (Down’s, hypothyreosis, and postasphyxia) were not discerned. Assuming maternal alcoholism to be rare, fetal effects were interpreted as hereditary, resulting mainly from the father, and acting by degenerated germ cells. Why do so many articles on fetal alcohol syndrome contain false citations? Ballantyne [45] gave us an answer a century ago: “It would be preferable could the subject (alcohol and antenatal child welfare) be discussed in the cold, clear air of pure science, far removed from emotionalism and unhampered by ethical limitations and religious exhortations.” Prejudiced by religious and abstinence groups, reports on alcohol damage to the unborn are fraught with emotions, moralizing, psychology, and social implications. To these add the intrinsic problems of retrospective diagnosis and presentism, the interpretation of past events with present knowledge.

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The author has no conflicts of interest to declare.

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