Iodine intake as a possible cause of discontinuous decline in sperm counts: A re-evaluation of historical and geographic variation in semen quality

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bulletin

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In 1992, Carlsen et al. reported that sperm counts have gradually fallen over the last 50 years in presumably fertile men. The results have stirred much debate, with the issue having recently been reviewed by Crissman et al. As the cause of the worldwide decline in sperm counts, environmental oestrogens were suspected, namely the 'oestrogen hypothesis'. The decline might be related to endocrine disruptors which have become widespread in several decades. The suggested mechanism behind the oestrogen hypothesis is that the suppression of FSH levels caused by perinatal exposure to oestrogen could re-
duce sperm counts in adulthood by perma-
ently altering the number of Sertoli cells.

However, it is difficult to explain the dif-
ference of several decades in timing of sperm
counts in adulthood by permanently altering the number of Sertoli cells.

It is known that sperm counts are related
to hypothyroidism, which is a major child-
hood disease in iodine-deficient regions. This
disease has been prevented by introducing io-
dine supplements. Is there a cause-and-effect
relationship between sperm counts and iodine
supplements? Previous studies have shown
that the deficiency in thyroid hormone in-
creased Sertoli cell numbers and sperm pro-
duction. Crissman et al. found that a neo-
natal iodine deficiency increased testis weight
due to increased Sertoli cell proliferation, and
this significantly increased spermatogenic
function in rats, and proposed that the sperm
count decline has been, at least partially, due
to optimization of the human iodine and thy-
roid status.

In this paper we hypothesized that sperm
counts have been affected by the introduction
of iodine supplements, which have largely
eliminated hypothyroidism. This hypothesis
was examined from two different points of
view. First, we reviewed the relationship be-
tween sperm counts and the incidence of thy-
roid disease using the data that Jørgensen et
al. collected from four cities in Europe. Sec-
ond, we reanalyzed selected data, collected
mainly in the United States by Carlsen et al.
and Swan et al., since only a small number of
reports are available for meta-analysis in any
other countries.

The relationship between sperm counts
and thyroid disease incidence was studied us-
ing Jørgensen's data, which satisfies the cri-
teria of Carlsen et al. It was analyzed with
a linear regression weighted by the number of
subjects.

To reanalyze the historical change in
sperm counts over time, we selected 43 sets of
data, which were published between 1934 and
1996 in the U.S., from the original 101 studies
reported by Carlson et al. and Swan et al. They
are listed in Table 1. Semen analyses were
performed manually in all studies. There were
more than 10 subjects per set. All available data was adapted to the criteria of
Swan et al. Thus, a total of 9,229 fertile or
presumably fertile men were included in this
analysis.

Iodine supplementation started in 1924 in
the United States. The time at which sperm
counts fell was determined by dividing the
data into two groups for every year it was
published. When a decline was believed to oc-
cur, for example in 1964, the data was divided
into one group for studies published in 1934-
1963 and another group for those done in 1964
- 1996. Then the differences were analyzed
with the Mann-Whitney U-test.

We determined that the year with the
smallest p value was possibly the time when
sperm counts began to decline. Mean sperm
counts before and after this year were calcu-
lated by weighting the number of subjects in-
cluded in each individual publication.

All statistical analyses were performed
using a JMP statistical software package (ver-

Figure 1 shows the linear regression
analysis of the mean sperm counts against
the incidence of thyroid disease from data col-
lected in the European countries of Denmark,
Table 1. Historical values of mean sperm counts in the United States. Mean sperm count values indicated in millions per mL. Data were cited from Carlsen et al. (1992) and Swan et al. (2000).

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>Mean sperm count</th>
<th>No. of specimens</th>
<th>Author</th>
<th>Ref No.</th>
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<td>1934</td>
<td>119.0</td>
<td>15</td>
<td>Belding</td>
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<tr>
<td>1938</td>
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<td>(25)</td>
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<td>22</td>
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<td>(26)</td>
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<td>1943</td>
<td>66.9</td>
<td>25</td>
<td>Weisman</td>
<td>(64)</td>
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<td>MacLoed and Heim</td>
<td>(36)</td>
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<td>1949</td>
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<td>49</td>
<td>Farris</td>
<td>(15)</td>
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<td>1950</td>
<td>100.7</td>
<td>100</td>
<td>Falk and Kauffman</td>
<td>(13)</td>
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<tr>
<td>1951</td>
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<td>1000</td>
<td>MacLoed and Gold</td>
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<td>1956</td>
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<td>21</td>
<td>Lampe and Masters</td>
<td>(32)</td>
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<td>1963</td>
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<td>100</td>
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<td>13</td>
<td>Freund and Davis</td>
<td>(17)</td>
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<td>79</td>
<td>Santomauro et al.</td>
<td>(50)</td>
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<td>Nelson et al.</td>
<td>(42)</td>
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<td>Naghima-E-Rehan et al.</td>
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<td>Rogers et al.</td>
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<td>(14)</td>
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<td>Dougherty et al.</td>
<td>(11)</td>
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<tr>
<td>1982</td>
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<td>Hamill et al.</td>
<td>(21)</td>
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<td>Tjoa et al.</td>
<td>(59)</td>
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<td>1984</td>
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<td>(23)</td>
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<td>1986</td>
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<td>1988</td>
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<td>(34)</td>
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<td>1996</td>
<td>38.0</td>
<td>31</td>
<td>Weyandt et al.</td>
<td>(67)</td>
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</table>

France, the United Kingdom and Finland by Jorgensen et al. The mean sperm counts were weighted by the number of subjects. A good linear relationship is seen between them, with the respective parameters of $R^2 = 0.868$ and $p = 0.003$. The regression coefficient was estimated to be $20.2 \times 10^6 / \text{ml}$ per 1 percent of thyroid disease incidence.

Although the thyroid disease in Figure 1 included hypothyroidism and hyperthyroidism, Vanderpump et al. reported that the incidence of hypothyroidism was 5-fold higher than that of hyperthyroidism. Hollowell et al. also estimated that the prevalence of hypothyroidism (4.6%) was higher than that of hyperthyroidism (1.3%). Thus, the most common thyroid disease is hypothyroidism. Moreover, sex and age are major factors for thyroid diseases. In Figure 1, although there is no description of the details of thyroid diseases, the eligibility criteria in this investigation are 20 to 45 years of age and male sex. Thus, we suggest that the etiological variety of thyroid diseases might not differ significantly among countries in this study. Sertoli cells are rich in thyroid hormone receptors in neonatal testes.
Iodine as cause of decline in sperm counts

A deficiency in thyroid hormone retards the maturation of Sertoli cells and prolongs the proliferation period during which the number of Sertoli cells increases. The number of Sertoli cells determines the number of spermatogenic clonal units. Thus thyroid disease incidence may increase the sperm-producing capacity of the testicles.

The mean sperm counts are plotted against the publication years in Figure 2. Each circle was weighted according to the number of subjects. The smallest \( p \) value was obtained when the critical line was drawn at the years between 1965 and 1969 (Figure 2). Before and after this period, the data was analyzed for differences with the Mann-Whitney \( U \)-test \( (p = 0.0005) \). On drawing the critical line at the years between 1964 and 1969 or between 1951 and 1972, \( p \) values were found to be less than 0.001 or 0.01, respectively. Hence it was concluded that the sperm counts were significantly altered between 1965 and 1969 in the United States. The respective mean sperm counts were estimated to be \( 111 \times 10^6/\text{ml} \) and \( 70 \times 10^6/\text{ml} \) before and after these dates. Paulsen et al.\(^{44} \) and Fisch et al.\(^{16} \) also reported similar results in their longitudinal studies, indicating no alteration or a slight increase in sperm counts in the United States after 1970.

Figure 2. Mean sperm counts in 43 publications are represented by circles whose area is proportional to the number of subjects. The \( p \) values calculated with the Mann-Whitney \( U \)-test are represented by squares, which indicate the timing of the decline in sperm counts. The most significant fall was detected between the two vertical lines (1965-1969) \( (p = 0.0005) \). Horizontal lines indicate the mean sperm counts of each group, weighted by number of subjects \( (111 \text{ and } 70 \times 10^6/\text{ml}) \). The arrow indicates the presumed period of sperm count decline caused by the introduction of iodine supplements in the United States (1958-1973). Data were cited from Carlsen et al. (1992) and Swan et al. (2000).
This conclusion supports the hypothesis that iodine supplementation to eliminate hypothyroidism decreases sperm counts. Hypothyroidism, an endemic goiter caused by a deficiency of iodine, was a common disease in children in iodine-deficient regions, such as the Dakotas, Minnesota, and the Great Lakes basin in the United States. Iodized salt was first introduced in Michigan in 1924 to prevent endemic goiter and a salt iodization policy was established in the rest of the United States within 15 years\(^{43}\).

The mean age of sperm donors was calculated as 31 years in publications by Carlsen et al.\(^{6}\). The time of sample collection always predated publication, often by several years. In Swan et al.\(^{57}\), the mean time span between publication and sample collection was estimated to be 3 years. Therefore, 34 years was the time span between the donors’ birth and sperm donation on the average. For example, sperm counts reported in 1958 would logically be attributed to donors who were born in 1924, when iodized salt was just introduced in the United States. Sperm counts reported in 1973 would logically come from donors who were born in 1939, when iodized salt was widely being used all over the United States. Thus, if iodine intake caused sperm counts to decline, the decrease would be exhibited between 1958 and 1973 in publications from the United States.

In France iodized salt was introduced in 1952\(^{60}\). Sperm count decline was indicated in men born after the 1950s in a birth-cohort study\(^{9}\). Mean sperm counts decreased in Paris between 1973 and 1992 from 89 x 10^6/ml to 60 x 10^6/ml in male donors averaging 34 years of age\(^{10}\). Therefore, it would indirectly seem that sperm counts decreased in men born between 1939 and 1958. In Toulouse, France, however, no alteration was exhibited in sperm counts between 1977 and 1992 for donors whose mean age was 34 years\(^{5}\). Toulouse faces the Mediterranean Sea. The intake of seafood containing a large amount of iodine may have prevented iodine deficiency and thus caused no alteration of sperm counts in Toulouse.

There has been a three-fold increase in the amount of iodine in the British diet between 1952 and 1982 from 80 μg/day to 255 μg/day\(^{10,66}\). Intake of 150 μg/day was recommended for children by the Department of Health and Social Security in the United Kingdom. A birth-cohort study in Scotland indicated that 98 x 10^6/ml was the median sperm count of donors born in the 1950s, though 78 x 10^6/ml was that of donors born in the 1970s\(^{57}\).

There is no endemic goiter in Japan because of the tradition of eating seafood. Sperm counts in Japan have shown no change in the last 25 years\(^{88}\).

We suggest that iodine intake has been a factor in the decline in sperm counts in the United States and some European countries. Although environmental endocrine disrupters are suspected of affecting male gonadal development during the fetal period, obvious evidence for sperm count decline still has not been demonstrated at the concentrations to which humans are exposed in daily life\(^{52}\). It should be noted that Crissman et al. reported recently that higher round spermatids and heavier testis weights were exhibited by 133-day old adult rats fed a low iodine diet only in the neonatal period and then fed a control diet afterward\(^{58}\). This study mimicked the situation of men who are born in an iodine-deficient region and who receive an iodine supplement after their neonatal period.

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