The negative effect of smoking habit on human reproduction and intrauterine development are well known. The possible role of genetic factors on susceptibility or resistance to these effects, however, has been scarcely considered.

Previous studies indicate that genetic variability of cytosolic low molecular weight phosphotyrosine phosphatase (cLMWPTP or ACP1), an enzyme involved in signal transduction of insulin and other growth factors, may influence human fertility, intrauterine growth and congenital malformation. The data shown in the present note suggest that the negative effect of smoking habit on intrauterine growth is dependent on the maternal ACP1 genotype.

Subjects and Methods

In 364 healthy puerperae from the population of Penne and in 155 diabetic puerperae from the population of Rome we have determined ACP1 genotype. We have also considered 349 consecutive newborn infants previously studied by our group in the population of Rome. In this study ACP1 genotype was determined in newborn infants only. We have subdivided these newborn infants into two categories: *A/*A and other ACP1 genotypes. Only in the first class in fact, is the mother certainly a carrier of the ACP1*A allele and among them the great majority have *A/*A or *A/*B genotype (see later).

Three-way contingency table analysis has been performed using a log-linear model according to Sokal and Rohlf. Other statistical analyses have been performed according to SPSS programs. Percentile, quartile and median classes of birthweight have been assigned taking into account duration of gestation by using the tabular reference standard of Italian population.

Results

Newborn infants of *A/*A and *A/*B (low activity ACP1 genotypes) mothers who smoked have a birthweight about 300 g below that of other infants (those born of non-smoking mothers or from smoking mothers with *B/*B; *A/*C or *B/*C [medium-high activity] genotypes) (Table 1). In puerperae who smoked there is also a significant positive linear correlation between the birthweight of the infant and ACP1 activity (data not shown). No significant association has been observed among duration of gestation, smoking and maternal ACP1 genotype (data not shown).

An increase in the proportion of infants with a birthweight below the 50th percentile among healthy and diabetic puerperae with a smoking habit as compared to those not smoking is observed in women with low-activity ACP1 genotypes (*A/*A and *A/*B) only (Table 2). Such an increase is statistically significant in healthy women only (P < 0.02) but the pattern of interaction is concordant in normal and diabetic pregnancy.

In newborn infants from normal pregnancies in the population of Rome ACP1*A/*A genotype of the infant and smoking habit in the mother have a cumulative negative effect on birthweight corrected for gestational age (P = 0.025) (data not shown).

Discussion

Cytosolic low molecular weight acid phosphatase is controlled by a locus on chromosome 2 which shows three common codominant alleles: ACP1*A, ACP1*B, ACP1*C. ACP1 activity shows great quantitative differences among genotypes: Spencer et al. found the following activities (µmol p-nitrophenol produced in 30' per g of Hb at 37°): ACP1*A/*A = 122.4; ACP1*A/*B = 153.9; ACP1*B/*B = 188.3; ACP1*A/*C = 183.8; and ACP1*B/*C = 212.3. The *C/*C genotype is very rare. ACP1
is present in all tissues. Two different functions have been proposed for ACP1: phosphotyrosine phosphatase (PTPase) and flavin-mononucleotide (FMN) phosphatase activity. The enzyme is able to hydrolyze phosphotyrosine containing synthetic peptides of insulin receptor and of Band-3-Protein (B3P). Low ACP1 activity may favour glucose metabolism through an increase of insulin action and through an increase of phosphorylation of B3P which in turn activates aldolase, phosphofructokinase and glyceraldehyde-3-phosphate dehydrogenase. As FMN phosphatase low ACP1 activity may increase flavo-enzymes activity and in turn energy metabolism. Given the strong differences in enzymatic activity among ACP1 genotypes, the enzyme could have an important role in the physiological variability of a large spectrum of cellular functions.

Reactive oxygen species have been identified as mediators of pathological manifestations after exposure to cigarette smoke. Reactive oxygen species are also important mediators of signal transduction involving protein-tyrosine phosphorylation. Environmental agents that cause oxidative stress may therefore alter the course of cellular response through modification of signal cascade. ACP1 stability and activity are strongly influenced by oxidative substances and the effect of such substances are dependent on the ACP1 genotype. Low activity genotypes (*A/*A and *A/*B) could be more susceptible to oxidative damage from cigarette smoking thus explaining the association of these genotypes with decreased growth rate.

The data from three independent samples point to a protective role of maternal ACP1 genotypes with medium-high activity (*B/*B; *A/*C and *B/*C) against growth retardation caused by smoking. It should be noted, however, that the three sets of data are not homogeneous, i.e. they are not an exact replication in other populations of the observations shown in Tables 1 and 2. Further studies confirming the present association are needed before drawing definite conclusions.

The possibility that women with a smoking habit, carrying *A/*A or *A/*B genotypes may have an increased probability of carrying to term a fetus with growth retardation as compared to women with high activity ACP1 genotypes is not supported by our set of data.

### Table 1

<table>
<thead>
<tr>
<th>ACP1 Genotype</th>
<th>Not Smoking</th>
<th>Smoking</th>
<th>Difference in Mean</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SE No.</td>
<td>Mean SE No.</td>
<td>Mean SE 95% CI</td>
<td></td>
</tr>
<tr>
<td>*A/*A and *A/*B</td>
<td>(a) 3390 37.6 151</td>
<td>(b) 3070 138.8 15</td>
<td>320 126.8 (70–571) 0.013</td>
<td></td>
</tr>
<tr>
<td>Other ACP1 genotypes</td>
<td>(c) 3349 32.3 181</td>
<td>(d) 3459 93.2 17</td>
<td>–111 109.3 (–326, 105) 0.312</td>
<td></td>
</tr>
</tbody>
</table>

Variance analysis (one-way)
(a) versus (b) versus (c) versus (d) P < 0.05.

Pairs of groups significantly different at the 0.05 level (Duncan multiple range test)
(b) versus (a); (b) versus (c); (b) versus (d).

T-Test for differences between:
(a) and (b) P < 0.02.
(b) and (c) P < 0.05.
(b) and (d) P < 0.025.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Non-smoking mother</th>
<th>Smoking mother</th>
<th>Odds ratio (smoking versus not smoking)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of infants below</td>
<td>% of infants below</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>the median</td>
<td>No.</td>
<td>the median</td>
</tr>
<tr>
<td>Healthy mothers with *A/*A and *A/*B genotypes</td>
<td>38.6% 145</td>
<td>73.3% 15</td>
<td>4.37 1.20–17.23</td>
</tr>
<tr>
<td>Diabetic mothers with *A/*A and *A/*B genotypes</td>
<td>10.3% 39</td>
<td>26.1% 23</td>
<td>3.09 0.65–15.44</td>
</tr>
<tr>
<td>Healthy mothers with other ACP1 genotypes</td>
<td>46.2% 171</td>
<td>33.3% 17</td>
<td>0.64 0.20–1.98</td>
</tr>
<tr>
<td>Diabetic mothers with other ACP1 genotypes</td>
<td>27.7% 65</td>
<td>32.1% 28</td>
<td>1.24 0.42–3.58</td>
</tr>
</tbody>
</table>

Three-way contingency analysis by a log-linear model
X = birthweight (below/above the median).
Y = smoking (yes/no).
Z = sample (healthy/diabetic).

Mothers with *A/*A and *A/*B genotypes
xyz interaction NS.
xy association P < 0.01.

Mothers with other ACP1 genotypes
xyz interaction NS.
xy association NS.
If confirmed, the present observation might open perspectives in other fields of human pathology. Genetic variability of signal transduction might have a role also in the relationship between smoking and susceptibility to cancer. Moreover, since an important part of the negative effect of smoke on birthweight is due to its action at the placental vascular level, a possible effect of ACP1 genetic variability in the susceptibility or protection to vascular damage in smokers seems another promising area for future investigations.

References