Malformations have been produced in rodents by maternal treatment with lathyrogens after ingestion of a 50:50 Lathyris odoratus sweet pea diet and in rats, rabbits, and ferrets treated with chemical lathyrogenic agents (Abramovich and De Voto, '68; Steffek, '69; Steffek et al., '71). In these species one of the most frequently observed gross congenital malformations produced with these compounds was cleft palate. The present study was undertaken to extend these earlier investigations and to determine the teratogenic potential of two of the compounds in baboons (Papio sp.).

MATERIALS AND METHODS

Female baboons were maintained in individual cages according to the method described by Hendrickx et al. ('71). Timed pregnancies were determined by single matings of approximately 8 hours on the third or fourth day preceding deturgescence (day 16 or 17 of the menstrual cycle); the day of mating was then considered day 0 of pregnancy. Two lathyrogens, β-aminopropionitrile (BAPN) and aminoacetonitrile (AAN), were given parenterally or orally (concealed in an apple or banana) during the time of palate formation and closure, which occurs on approximately days 40–50 of pregnancy in the baboon (Bollert and Hendrickx, '70). All fetuses, including a set of twins, were removed on day 100 by cesarean section and examined for gross congenital malformations. Specimens were then fixed in 10% buffered formalin or FAA (5 parts formalin, 5 parts glacial acetic acid, and 90 parts 80% ethyl alcohol) and decalcified, and coronal serial sections were cut at 10 μ through the orofacial area. The sections were subsequently processed and stained with hematoxylin and eosin or the one-step trichrome stain of Gomori ('50).

RESULTS

The results are summarized in table 1. Three pregnant baboons were given BAPN. The first was given 200 mg/kg/day intramuscularly on days 38–50, which resulted in fetal resorption, determined by the presence of an intact placenta and membranes but no fetus on day 63 of gestation. The second animal received 300 mg/kg/day orally on days 37–48 of gestation, which again resulted in fetal resorption as determined by the recovery of an intact endometrial sac containing a placenta, and intact membranes, but no fetus on day 54 of gestation. The third baboon, given 500 mg/kg/day intravenously on days 43–48 of pregnancy, produced a macerated fetus with spina bifida which was recovered by cesarean section after threatened abortion on day 74 of gestation (fig. 1).
AAN was given orally or intramuscularly to three animals, in doses of 20, 60, and 70 mg/kg/day on days 38–50, 38–48, and 38–41, respectively. Two aborted and one had a fetal resorption.

Oral doses of AAN, 75 mg/kg/day on days 43–48, produced a fetus with digital defects, and a set of twins with abnormal curvature of the limbs and cleft palate (fig. 2). Doses of 20 and 40 mg/kg/day on days 38–50, and 60 and 130 mg/kg/day on days 40–48, 45–48, or 46–48 resulted in five normal offspring.

Midline clefts extended through the entire length of the soft palate and the posterior portion of the hard palate in both fetuses (fig. 4). In each fetus the nasal septum and nasal cavities were flanked by the hard and soft palate, respectively. In normal baboon fetuses of similar age the palate has closed and extends posteriorly to the pharynx.

A coronal section of a normal palate at the anterior level of the palate shows the corpus of the vomer bone, the paired palatal processes of the maxillas, and the horizontal process of the palatine bone (fig. 5). The nasal septum and middle inferior concha are well developed, the tongue is flattened, and there is only a slight arching of the roof of the mouth. Coronal sections of the cleft palate specimens at levels anterior to the overt cleft show some anatomical alterations distinct from the control specimen. Figure 6 illustrates a deviation of the nasal septum, a greater degree of arching of the roof of the mouth, and a curling of the tongue into a "U-shaped" configuration. In addition, the palatal processes are not fused to the same extent as in the control.

More posteriorly the palatal shelves are extremely thinned out at the midline point of contact (fig. 7). The overlying palatal epithelium still remains intact and the tongue remains curled. A section midway

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### TABLE 1

**Summary of experiments using BAPN and AAN in baboons (Papio sp.)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Days of treatment (gest. age)</th>
<th>Dose (mg/kg/day)</th>
<th>Route of administration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAPN</td>
<td>38–50</td>
<td>200</td>
<td>im</td>
<td>Fetal resorption</td>
</tr>
<tr>
<td>BAPN</td>
<td>37–48</td>
<td>300</td>
<td>oral</td>
<td>Fetal resorption</td>
</tr>
<tr>
<td>BAPN</td>
<td>43–48</td>
<td>500</td>
<td>iv</td>
<td>Fetal maceration, spina bifida</td>
</tr>
<tr>
<td>AAN</td>
<td>38–50</td>
<td>20</td>
<td>im</td>
<td>Abortion</td>
</tr>
<tr>
<td>AAN</td>
<td>38–48</td>
<td>60</td>
<td>oral</td>
<td>Fetal resorption</td>
</tr>
<tr>
<td>AAN</td>
<td>38–41</td>
<td>70</td>
<td>im</td>
<td>Abortion</td>
</tr>
<tr>
<td>AAN</td>
<td>43–48</td>
<td>75</td>
<td>oral</td>
<td>Abnormal flexure of digits on right foot</td>
</tr>
<tr>
<td>AAN</td>
<td>43–48</td>
<td>75</td>
<td>oral</td>
<td>Twins — both with cleft palate and abnormal curvature of arms and legs</td>
</tr>
<tr>
<td>AAN</td>
<td>38–50</td>
<td>20</td>
<td>im</td>
<td>Normal</td>
</tr>
<tr>
<td>AAN</td>
<td>38–50</td>
<td>40</td>
<td>im</td>
<td>Normal</td>
</tr>
<tr>
<td>AAN</td>
<td>40–48</td>
<td>60</td>
<td>oral</td>
<td>Normal</td>
</tr>
<tr>
<td>AAN</td>
<td>45–48</td>
<td>130</td>
<td>oral</td>
<td>Normal</td>
</tr>
<tr>
<td>AAN</td>
<td>46–48</td>
<td>130</td>
<td>oral</td>
<td>Normal</td>
</tr>
</tbody>
</table>
through the cleft shows the palatal shelves extending downward and the tongue lying between them (fig. 8). The oral and nasal cavities communicate freely, and the nasal septum and corpus of the vomer bone are unattached at their ventral ends.

**DISCUSSION**

Orofacial malformations have been reported previously in various primates. A mandrill with a median cleft lip and retarded development of the apical region of the nose was described by Hill and Sabater (‘70). A rhesus monkey with cleft lip and cleft palate was characterized grossly by Swindler and Merrill (‘71) and isolated cleft palate occurred in a marmoset (Kraus, ’68) and rhesus monkey (Kraus, personal communication). The cleft palates, however, observed in our study are to our knowledge the first reported in twin non-human primates after maternal treatment with a pharmacological agent. The incidence of twin births in baboons was four out of 730 deliveries in the baboon colony at Southwest Foundation, San Antonio, Texas, (Hendrickx et al., ’68) and two out of 837 deliveries at the Sukhumi colony in Russia (Lapin and Yakovleva, ’63, p. 228).

A cursory histological comparison of the orofacial area of the marmoset specimen described by Kraus (’68) and the baboon in our study shows one conspicuous similarity. In both specimens a pronounced indentation of the tongue was present. The palatal processes in both specimens were oriented ventromedially, although in the marmoset a greater degree of “cupping” of the palatal shelves around the tongue was seen. The midline deviation of the nasal septum present in the baboon was not observed in the marmoset.

Even though limb malformations were seen in three of the baboon fetuses, indicating the susceptibility of this species to the teratogenic action of AAN, we do not intend to propose a casual relation between cleft palate production and AAN treatment based on twin specimens obtained from only one treated animal. The concordance in these dizygotic twins for cleft palate is suggestive of a common environmental etiology. Further investigations in baboons are needed to confirm the potential of AAN as a cleft palate teratogen and to determine the most effective dose and time of administration.

**LITERATURE CITED**


PLATE 1

EXPLANATION OF FIGURES

1 A macerated fetus with spina bifida recovered by cesarean section on day 74 of gestation. This specimen was obtained from a pregnant baboon treated iv with 500 mg/kg/day BAPN on days 43–48.

2 Diamniotic, dichorionic twin baboons obtained from a pregnant baboon receiving 75 mg/kg/day AAN orally on days 43–48 and delivered by cesarean section on day 100 of gestation, each with limb malformations and cleft palate.
3 Baboon fetus showing a thickening and curvature of the long bones (right specimen of fig. 2). 75 mg/kg/day of AAN was administered orally days 43–48 of pregnancy.

4 Ventral surface of one of the twins with cleft palate with the tongue and mandible removed, (left specimen of fig. 2).
CLEFT PALATE IN BABOONS
A. J. Steffek and A. G. Hendrickx
5 Frontal section through the anterior palatal region of a normal 100-day baboon fetus.

6 Frontal section anterior to the cleft palate, showing the deviated nasal septum, arching of the roof of the mouth, and "U-shaped" configuration of the tongue.

7 A more posterior section just before the actual cleft, showing a "thinning-out" of the palate and persistence of the notch in the tongue.

8 A section midway through the cleft showing a ventromedial orientation of the palatal processes and the notching of the tongue.