subsequent birth of normal children occur frequently enough to be frustrating for those involved in the evaluation of malformed children and counseling of the parents.

The fetal hydantoin syndrome, while a recognizable pattern of malformation in some patients, is not such a well defined entity as, for example, achondroplasia or Down syndrome is. It is not uncommon for one to see a child with several features of the "fetal hydantoin syndrome" in the absence of a history of exposure to a hydantoin. The infant reported by Bartoshesky et al could have been malformed due to a genetic mutation (autosomal recessive, X-linked recessive, or new dominant mutation) or chromosomal imbalance. No mention of chromosome studies was made in the report.

Although it is possible that the infant had an unusually severe manifestation of the fetal hydantoin syndrome, the report implies that the diagnosis was proven beyond a reasonable doubt. It is misleading and potentially dangerous to investigate a family inadequately and attribute "new findings" to a "known or suspected teratogen."

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**In Reply.—**

We would agree with both writers that there were certain features of the child described in our report that were not typical of the so-called fetal hydantoin syndrome, particularly the birth weight. It is certainly true that single case reports do nothing more than suggest possible associations between malformations and in utero exposure, but much information has been accumulated associating clefts and congenital heart malformations with phenytoin.

The baby described had a normal male karyotype. Attempts were made to do karyotyping on tissue obtained at autopsy but were unsuccessful. As both writers suggest, the possibility of mutagenic effect from the diphenylhydantoin or some other agent cannot be ruled out.

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**Expanding Phenotype of Fetal Hydantoin Syndrome**

**To the Editor.—**

We read with interest the article by Bartoshesky et al on ophthalmic and lethal cardiac malformations in the newborn exposed to diphenylhydantoin in utero. The article makes an important point about previously undescribed clinical features of fetal hydantoin syndrome and emphasizes the generalized effect of diphenylhydantoin as a teratogen. To elaborate further on this point, we wish to share our clinical observations in two patients with fetal hydantoin syndrome.

One patient, a male (Figure), showed subcutaneous vascular abnormalities (cystic hygromas, telangiectasias, and capillary phlebectasias) on the anterior neck and both axillae, in addition to developmental delay, esotropia, epicanthal folds, high palate, triphalangeal thumbs, hypoplastic nails, inguinal hernia, and seven arches on the fingertips. He was the most severely affected of three siblings (all born after 1975) with the stigmata of fetal hydantoin syndrome. The exposure in utero was 200 mg/day of Dilantin throughout the entire gestation.

The other patient, a female, was exposed to 300 mg/day of Dilantin and 50 mg/day of phenobarbital. At birth three teeth were present as well as high palate, elongated philtrum, epicanthal folds, hypoplastic fingernails, and ten arches on the fingertips. Subsequently, failure to

**Figure.** Face and subcutaneous lesions in patient with fetal hydantoin syndrome.
thrive, impaired renal function, and *Proteus* urinary tract infection were diagnosed. When the infant was 6 weeks old, a cystoscopy revealed a blind-ending left ureter and right ureteropelvic junction (UPJ) obstruction with grade 3 reflux. Right pyeloplasty corrected the UPJ obstruction which proved to be of the fibrous type. At operation the left kidney was absent and the right kidney was large with multiple small cortical cysts. Biopsy results showed proximal tubular damage suggestive of hydropnephrosis. There was no dysplasia. When the infant was 10 months old, reimplantation of the right ureter corrected the reflux. There has been no urinary tract infection or evidence of obstruction since, but the patient has been treated for polyuria, polydipsia, enuresis, increased diaphoresis, and transient elevations of blood pressure. A repeat open renal biopsy when the patient was 6 years old showed mesangial hypertrophy and moderate focal chronic interstitial nephritis consistent with postreflux nephropathy and/or chronic pyelonephritis. Short stature, microcephaly, mild mental retardation, and mitral valve prolapse became apparent late in childhood.

In these patients no other teratogen was found to account for the aberrant phenotypes, and the karyotypes with the trypsin Giemsa banding method were normal.

In recent years several clinical features such as retinoschisis, neuroblastoma with hemorrhagic diathesis, and melanotic neuroectodermal tumors have been reported in children exposed to diphenylhydantoin in utero. These abnormalities together with the ones reported by Bartoshesky et al., and the cystic hygromas, the mitral valve prolapse, the unilateral renal agenesis and the contralateral UPJ obstruction of a multicystic kidney in the reported patients seem to indicate that the phenotype of fetal hydantoin syndrome is expanding as we learn more about it. Another important point is that the patients in most of the reports are <6 years old, which implies that Dilantin continues to be used as an anticonvulsant during pregnancy despite its known (since 1975) teratogenic effect. This may indicate that the drug as teratogen is taken lightly by some professionals and this leads to a recurrence of a condition which is, by definition, preventable.

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**Adult Respiratory Distress Syndrome in an Infant**

To the Editor.—

The review of adult respiratory distress syndrome (ARDS) in children by Lyrene and Truog summarizes their experience in 15 children ranging in age from 15 months to 14 years. We wish to emphasize that this syndrome may occur in very young infants.

We have cared for a previously well 6-week-old infant who had the clinical presentation, course, and ventilatory data compatible with ARDS. The infant was found dusky and gasping in her crib and was noted at a local hospital to be tachypneic and in marked respiratory distress (PaO2 was 29 mm Hg on room air). A chest radiogram showed no abnormalities. After she was intubated and ventilated by bag and mask, her PaO2 improved to 65 mm Hg on 45% FIO2. During transfer to our hospital, she developed left lung atelectasis secondary to right mainstem intubation. The endotracheal tube was repositioned, but she continued to have a PaO2 <60 mm Hg on 100% FIO2 and a positive end-expiratory pressure (PEEP) of 4 to 6 cm H2O. We then increased the PEEP to 10 cm H2O and her PaO2 ranged from 70 to 120 mm Hg on 100% FIO2. Immediate complications of the increased pressure were bilateral pneumothoraces and subsequent pneumomediastinum and pneumoperitonium. These were controlled with bilateral chest tubes and repeated abdominal paracenteses. Higher values of PEEP were not attempted because of a massive air leak into the peritoneal cavity. Chest radiograms revealed diffuse, hazy infiltrates bilaterally. The infant was successfully weaned from the ventilator on the seventh day without apparent respiratory or neurologic sequelae. Infiltrates on the chest radiogram cleared. Bacterial and viral cultures were negative. Sleep studies revealed no evidence of apnea. The etiology of this infant’s asphyxial episode and subsequent acute respiratory insufficiency was not determined.

Our data are consistent with those previously published for children and adults with ARDS and ventilation employing high PEEP. The initial alveolar-arterial oxygen tension difference (A-aDo2) was 44 mm Hg on room air. A chest radiogram showed no evidence of apnea. The etiology of this infant’s asphyxial episode and subsequent acute respiratory insufficiency was not determined.

The pediatric reviews of ARDS have detailed patients as young as 5 months. Our experience with this patient suggests that ARDS may occur in very young infants. We believe that it is important for physicians caring for infants with respiratory failure to consider this diagnosis because of the potentially life-saving advantage of ventilation with high PEEP values.

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LETTERS TO THE EDITOR 329

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