Late effects of pulmonary radiotherapy in early childhood upon lung function. MARY ELLEN B. WOHL, NORMAN JAFFE, DEMETRIUS G. TRAGGIS, and N. THORNE GRISCOM. *Harvard Med. Sch., Children's Hosp. Med. Ctr., and The Children's Cancer Research Found., Boston, Mass.* (Intr. by Joel J. Alpert).

We studied the effects of therapeutic pulmonary irradiation in early childhood on lung mechanics and CO diffusing capacity (D_{CO}) in ten children aged 11 to 19 years. Before the age of 50 months they had received bilateral irradiation to the lungs for treatment of metastatic Wilm's tumor. Radiographic evidence of pleural thickening and/or interstitial fibrosis was minimal except in 3 patients with moderately severe changes. Thoraco-lumbar scoliosis was present, but minimal. Total lung capicity (TLC) was 78% (range 68–87%) and vital capacity (VC) 72% (range 64–85%) of predicted values. However, 4 patients who had repeated pulmonary irradiation or surgical resection had TLC and VC averaging 66 and 55% of predicted, respectively. In the whole group D_{CO} was 65% of predicted (range 49–85%). D_{CO}/observed TLC was normal, suggesting that the reduction of D_{CO} was related to that of lung volume. Flow volume curves were used to measure maximal expiratory flow rates at 25% VC because at low lung volumes flow rates depend on resistance of peripheral airways and elastic recoil of the lung. All patients had normal flow rates in relation to body size. Elastic recoil of the lung, measured in 3 patients was high normal. These findings suggest that small airways are of normal size. It cannot be stated with certainty whether the diminished lung volumes are related to altered growth of lung parenchyma or to interstitial fibrosis.

Alpha$_1$ antitrypsin (AT) deficiency with both cirrhosis and chronic obstructive lung disease in two sibs. JOHN F. T. GLASGOW, ALBERT HERCZ, HENRY LEVISON, MATTHEW J. LYNCH, and ANDREW SASS-KORTSAK. *Univ. of Toronto, and Hosp. for Sick Children, Toronto, Ont., Canada.*

Three sibs (J.C. ♀, E.C. ♀, G.C. ♂) were studied. All had absent serum alpha$_1$ globulin peaks. Results of anti-protease and immunochemical studies.

	No.	μg Enzyme Inhibited/μl serum (M ± 2S.D.)			AT, Immunochem.
		Trypsin	Elastase	Chymotrypsin	mg/100 ml (M ± 2S.D.)
G.C., E.C.		0.46; 0.34	0.25; 0.18	0.29; 0.28	18.0; 9.0
Parents		0.78; 0.71	0.37; 0.39	0.75; 0.65	185; 186
Normal children	30	1.13 ± 0.22	0.66 ± 0.14	0.99 ± 0.31	280 ± 94
Normal adults	53	1.07 ± 0.30	0.56 ± 0.18	0.86 ± 0.32	263 ± 118
Diseased controls	27	1.14 ± 0.46	0.64 ± 0.30	1.13 ± 0.66	353 ± 221

J.C. and G.C. had neonatal obstructive jaundice with hepatosplenomegaly. *J.C.* developed progressive liver failure and portal hypertension, recurrent pulmonary infections from the age of 3 mos., emphysema at 10 yrs. and died at 11 yrs. Liver biopsy at 3 mos. and autopsy revealed a perilobular type of cirrhosis with progressive reduction of interlobular bile ducts and typical panacinar emphysema. *G.C.*'s liver biopsy (3 mos.) was similar to J.C.'s. His liver disease improved. Presently, at 12 yrs., liver function tests are normal but his liver is hard. From 7 years of age he had had a nocturnal cough and episodes of "wheezy bronchitis". The maximum mid-expiratory flow rate is 1.71 l/sec. (58% of normal), airway resistance 7.82 cm. H_2O/l/sec. (normal 3.51). *E.C.* at 14 yrs. of age is clinically normal with normal liver and lung function. This is the first report of both liver and lung involvement with alpha$_1$ AT deficiency.

Chronic pulmonary disease associated with an unusual genetic type of α_1-antitrypsin deficiency in childhood. A. MYRON JOHNSON, DANIEL GOTTOVI, THOMAS B. BARNETT, and GERALD W. FERNALD (Intr. by W. Paul Glezen). *Univ. of North Carolina Sch. of Med., Chapel Hill, N. C.*

Chronic pulmonary disease (CPD) occurs in most individuals with the common α_1-antitrypsin (α_1AT) deficiency phenotype, PiZZ, and less frequently in heterozygotes (PiMZ; normal = PiMM). A few other variants are associated with lesser degrees of deficiency, but their roles in pathogenesis of disease are unclear. For example, the incidence of CPD in PiSS and PiSZ individuals is not known, although Fagerhol has reported that these phenotypes may predispose to CPD. His two patients had asthma and chronic bronchitis rather than emphysema *per se*.

An 8-yr-old boy with severe asthmatic attacks and chronic inflammatory lung disease was found to have a serum α_1AT level of 85 mg/100 ml (31% of nl. mean) and trypsin inhibitory capacity of 0.55 mg/ml. Genetic typing by immunofixation and by antigen-antibody crossed electrophoresis indicated that he was PiSZ. Sweat chlorides and serum IgG are normal; IgA and IgM are borderline. The patient's father is PiMZ; his mother and sister are PiMS. Both parents have mild obstructive changes in their pulmonary dynamics, but are clinically well. The sister is apparently normal.

The clinical progression and prognosis with α_1AT variants other than PiMM, MZ, and ZZ are unknown. The relative frequencies of these phenotypes make genetic typing and long-term followup important in order to clarify these questions and to ascertain the need for genetic and medical counselling.

Effect of bradykinin on the pulmonary vascular resistance in the term fetus. DONALD V. EITZMAN, RAYMOND D. GILBERT, JACK R. HESSLER, and SIDNEY CASSIN. *Univ. Fla. Coll. Med., Gainesville, Fla.*

It is possible to separately measure two areas of resistance in the pulmonary circulation: proximal resistance (R_P), or the resistance from a point at which pulmonary arterial pressure is measured to the vessels acting as Starling resistors, and distal resistance (R_D), or the resistance from the Starling resistor vessels to a point at which pulmonary venous pressure is measured. A model has been set up in the near term fetal goat utilizing a Starling resistor concept of the pulmonary circulation and requires that the circulation to a portion of the left lung be isolated and perfused at a constant flow. Resistance in the different segments are calculated from figures derived in the experimental procedure previously reported in the Fed. Pro. 29:775–6, 1970. Previous work has demonstrated that the drop in resistance which occurs with expansion of the lung and with increased PaO_2 occurs in both R_P and R_D. During hypoxia in the newborn both R_P and R_D increase. In the unventilated lung bradykinin infusion into the pulmonary artery (60–240 η.g./min.) produced a significant decrease in the R_P to 52% of control values, no change in R_D, and a decrease in the pressure tending to close the Starling resistor vessels (P_S). In the ventilated lung, there was a significant decrease in the R_P (64% of control values) with no changes in either R_D or

P_s. These data indicate that bradykinin has an immediate and direct effect on the pulmonary vasculature and significantly reduces its resistance to flow. This effect is mediated through the resistance vessels proximal to the area of the Starling resistor.

Initiation of respiration by direct electrical stimulation of the fetal brain stem. VICTOR CHERNICK, ADOLPH SKLENOVSKY, VICTOR HAVLICEK, and REYNALDO D. PAGTAKHAN. *Univ. of Manitoba, and Children's Hosp., Winnipeg, Manitoba, Canada.*

The mechanisms which ensure fetal apnea and the initiation of respiration at birth are poorly understood. Direct study of the fetal respiratory center has not been previously undertaken. We have mapped the inspiratory center of the exteriorized fetal sheep near term using stereotaxic placement of a stimulating electrode in the region of the medulla. Ventilatory efforts were monitored by connecting the trachea to a liquid plethysmograph. The results were compared to a similar mapping of the respiratory center of the newborn lamb. The fetal respiratory center was quite diffuse, extending from the obex to the lower pons and 2.5 mm on either side of the midline. In contrast, the respiratory center of the newborn lamb was more localized, extending only 6 mm rostral to the obex. In the unanesthetized fetus the threshold current required to initiate respiration was 0.15 ± .06 ma. Stimulation of a similar area in the unanesthetized newborn lamb caused apnea at 0.33 ma. Pentobarbital increased the threshold current in the fetus to as high as 1.96 ± .40 ma. In contrast pentobarbital decreased the apneic threshold in the newborn lamb to .21 ± .03 ma. It is concluded that the respiratory center is not actively inhibited during the latter period of gestation and therefore cannot account for respiratory inactivity in utero. The nature of the respiratory response to electrical stimulation of the brain stem and the influence of pentobarbital appears to depend on the presence or absence of rhythmic respiration.

Acid mucopolysaccharides in cardiac intracavitary tumors. REUBEN MATALON and RENÉ A. ARCILLA. *Univ. of Chicago, Chicago, Ill.*

Three left atrial myxomas and one myxosarcoma were analysed and studied in tissue culture. The myxomas contained 0.2% mucopolysaccharide (wet weight) which on fractionation yielded hyaluronic acid 22%, chondroitin sulfate 30%, chondroitin 47%, and dermatan sulfate <1%. On incubation of the explants there was rapid growth of cells and gelling of the culture medium. The latter has never been observed in the culture of various human tissues including those of cardiac origin. Electronmicroscopy showed abundant collagen fibers, which may be responsible for the gel formation. Hyaluronic acid was the major component of the culture medium.

Analysis of the myxosarcoma revealed high molecular weight hyaluronic acid as the only polysaccharide. These striking differences in composition might be specific for the two types of tumors.

Sera from two patients with myxomas and one patient with myxosarcoma revealed a five-fold increase of mucopolysaccharide. Following the surgical removal of the tumors the serum mucopolysaccharide returned to normal in all three patients.

PULMONARY

Airway closure in normal subjects and patients with cystic fibrosis. ANTHONY MANSELL, ARTHUR C. BRYAN, and HENRY LEVISON. *Univ. of Toronto, Research Inst., Hosp. for Sick Children, Toronto, Ont., Canada.*

Lung units close as lung volume is reduced and the volume at which closure occurs (CV) can be detected as a discontinuity of the alveolar plateau in the single breath nitrogen washout (Anthonisen, N. R.: Resp. Physiol. 8, 58–65, 1969–70). We have used this technique to define the closing volumes of 23 normal children, ranging from 8–18 years and 136–179 cm height, and those of 16 patients with cystic fibrosis, 7–27 years and 125–176 cm, with the following results:

	Normals	Cystic Fibrosis
Closing volume as percent of vital capacity	8.5% ± S.D.4.3	24.2% ± S.D.16.0
Closing volume as percent of total lung capacity	28.9% ± S.D.5.0	48.0% ± S.D.15.8
Functional residual capacity—closing volume (FRC-CV)	0.88L ± S.D.0.31	0.07L ± S.D.0.40

All differences are highly significant ($P > 0.01$). Six of the 16 patients with cystic fibrosis had a closing volume greater than the functional residual capacity, indicating gas trapping during normal tidal breathing. Closing at high lung volume is a major factor in producing the gas exchange failure in these cases. For this reason this method appears to be a sensitive indicator of gas exchange abnormality in certain pulmonary diseases in childhood.

Pulmonary ischemia and surfactant in the neonatal lung. RONALD S. BLOOM, CHERILL M. PARMENTIER, COLBY R. PARKS, DAVID E. WOODRUM, and W. ALAN HODSON (Intr. by Ralph J. Wedgwood). *Univ. of Washington Hosp., Seattle, Wash.*

Hyaline membrane disease is associated with a functional and possibly a quantitative deficiency in surfactant. It has been suggested that this is caused by hypoperfusion of the lungs. This work demonstrates that when the left pulmonary artery is occluded in the fetal state and the animal is permitted to breathe, there is no change in surfactant. Nine fetal lambs varying in gestational age from 132–147 days were partially delivered by Caesarian section. With the umbilical circulation intact, a thoracotomy was performed under local anesthesia and the left main pulmonary artery ligated. The chest was closed and 45 minutes post ligation, the umbilical cord was clamped and the animal was allowed to breathe. The lambs were sacrificed and the lungs removed 8 hours (mean) after ligation, Heart rate, blood pressure, pH, PCO_2 and PO_2 were monitored through a carotid catheter to evaluate the lamb's condition throughout the experiment. DNA, total and compositional phospholipid analysis were performed on both the right and left lung of each animal. There was no significant difference between the non-ligated and ligated lungs in the total amount of phospholipid/mg DNA, phosphatidylcholine/mg DNA, DNA/gm wet wt. and pressure volume characteristics. These results indicate that in the fetal lamb short term pulmonary ischemia within the last 10% of gestation, does not affect pulmonary surfactant.

$\dot{V}A/\dot{Q}$ relationships and lung volume in hyaline membrane disease. PETER A. M. AULD and CARLOS A. TORI. *Cornell Univ. Med. Ctr., N. Y., N. Y.*