II). Likewise, the individual clearances of p-aminohippurate fell within normal limits apart from the lowest (324 ml/min.) and the highest (1110 ml/min.). The mean renal plasma flow was 595 ml/min.

Plasma sodium values were normal except for 3 patients. In view of a normal filtration rate the load of sodium presented to the tubule can be considered essentially normal. The actual urinary excretion of sodium, however, was practically negligible in 5 patients (1 to 2 micro equivalents/min.), while the others excreted sodium in amounts which could be considered normal. It is evident, therefore, that the inability to excrete sodium in cirrhosis is not a function of the filtration rate.

The degree of abnormality of the liver function tests was not related to the rate at which the patient was accumulating fluid. Moreover, in the same patient spontaneous diuresis may occur prior to any significant change in the liver function tests, as was subsequently observed in patients WS and WT. This confirms the well known clinical observation that the degree of liver damage measured by the usual tests does not necessarily parallel salt retention.

Comment. The data presented demonstrate that in cirrhosis of the liver profound salt retention can occur in the presence of a normal glomerular filtration rate. It is not doubted that for a given patient the capacity to eliminate sodium will be greater at higher than at lower rates of filtration(14) but this does not imply that a low filtration rate is the cause of sodium retention. The present data indicate that sodium retention in cirrhosis of the liver is due to excessive tubular reabsorption since a normal sodium load is presented to the tubule. This observation is in accord with the findings of Goodyer and his group(5). In addition, they were able to demonstrate that patients with cirrhosis still failed to eliminate sodium in the normal fashion even though the sodium load was increased by the intravenous infusion of 5% saline.

Summary. Glomerular filtration and renal plasma flow were found to be normal in eleven patients with cirrhosis of the liver who were accumulating edema fluid indicating that the retention of sodium is due to increased tubular reabsorption.

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Compensatory Hypertrophy of the Intact Adrenal of Fetal Rats Subjected to Unilateral Adrenalectomy.* (18359)

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There are several lines of evidence that the mammalian adrenal begins to function prior to birth. The suprarenal cortex of the human fetus becomes markedly enlarged(1). Obviously this is only circumstantial evidence, and, as has been pointed out(2), the physiological significance of this hypertrophy is not understood. It has been demonstrated that pregnancy prolongs the life of adrenalectomized dogs(3,4). The removal of the adrenals of pregnant rats causes an increase in the weight of the adrenals of the fetuses (5,6). The removal of the hypophysis of fetal rats by decapitation inhibits the growth of the adrenal(7,8), as does also the destruction of the hypophysis of fetal mice by ir-

* Aided by grants from (1) the Committee on Human Reproduction, National Research Council, acting on behalf of the National Committee on Maternal Health and (2) The Ciba Pharmaceutical Products, Inc.

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radiation(9). This effect has been prevented experimentally by introducing adrenocorticotrophin under the skin of headless fetuses(10, 11). In fetal rats in which the adrenals had been destroyed by applying cautery through the translucent uterine wall, Tobin reported a decrease in the number of acidophilic cells of the hypophysis and an absence of effects upon the reproductive tract(12). The implantation of a pellet of androgen beneath the skin of the fetal rat increased the volume of the fetal adrenal(13). On the other hand, there is some evidence that the adrenals of fetal rats do not produce an androgenic hormone. In adrenalectomized fetuses, those changes in the seminal vesicles which can be induced by castrating fetuses were not observed(14).

It is generally accepted that the removal of one adrenal after birth causes a compensatory hypertrophy of the remaining gland(15-18). Thus it was decided to subject fetal rats to unilateral adrenalectomy, to autopsy them before birth and to make a quantitative study of the remaining adrenal. Hypertrophy of this remaining organ would suggest that the adrenal begins to function before birth in that it is already able to respond to an experimentally introduced stimulus.

Procedure. The rats used were of the Sprague-Dawley strain. The estimated age of the fetuses was dated from the time of witnessed copulation. The litter was used as the experimental unit. At approximately 19 days and 11 hours after copulation, a mother was etherized and a fetus was presented for surgery by removing it from the uterus without interrupting the placental circulation(19,20). Using a binocular dissecting microscope, iridectomy scissors and jeweler's forceps, an oblique lumbar incision was extended into the abdominal cavity of the fetus and the left adrenal was removed. After suturing the abdominal incision, the fetus was placed in the maternal peritoneal cavity and the etherization of the mother was discontinued. At the end of the experimental period the fetus was obtained by sacrificing the mother at about 21 days and 15 hours after copulation (at about one hour preceding the estimated time of earliest parturition)(20). The operated fetus and a littermate control of the same sex were weighed, killed and eviscerated in order to expose their adrenals. The eviscerated bodies were fixed in Bouin's solution. After fixation the adrenal of both fetuses was dissected, removed, dehydrated, imbedded in paraffin and sectioned in series at 10 micra. The sections were stained with hematoxylin and eosin. Throughout this entire procedure, the glands of a litter were subjected, as closely as possible, to the same conditions. The volume of an adrenal was determined from the stained serial sections by the paper-weight method of Hammar(21). Every sixth section was projected at a magnification of 50 diameters and drawn. Then the formula of Boyden(22) was adapted and used.

Observations. The volumetric data are presented in Table I. Not shown is the fact

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TABLE I. Volume of the Right Adrenal.

Groups	No. of fetuses	Age at operation, da : hr	Exper. period, hr	Body wt, g	Vol., $mm^3 \cdot 10^2$	Vol., $mm^3 \cdot 10^2$ / Body wt, g: Per group	Vol., $mm^3 \cdot 10^2$ / Body wt, g: E/C
Control*	6			4.54(3.89-5.20)	37.8(24.47-52.45)	8.3(5.60-10.20)	
Exper.†	7	19:11(19:9-19:13)	53(51-55)	4.23(3.66-4.86)	50.5(33.73-62.75)	11.9(9.21-14.79)	1.43(1.08-1.65)

* Seven observations in 6 fetuses (3 male and 3 female).
† Seven fetuses from 6 litters (3 male and 4 female).

that the "t test" was applied to those data from which the averages in the third vertical column from the right were obtained. In making this test, the first step was to determine the difference between the experimental and control values, litter by litter, by making a series of seven simple subtractions (23). The outcome suggests that these differences are "highly significant" (probability of $t = .001$).

Comparable sections of the glands were microscopically studied with the aid of a microcomparator, an instrument which brings one-half the field of each of two microscopes into view. When a section of adrenal of an experimental fetus (section E) was thus directly compared with that of a litter mate control (section C), it was usually found that the capsule in E was thinner than in C. This suggests that it had been "stretched" by the "pressure of growth" of the cortex. An outer zone of cortical cells, comparable in position to the zona glomerulosa of postnatal life, was usually thinnest in E. The cells of this zone were largest in E. This increase involved both the cytoplasm and the nucleus. An intermediate zone in C was characterized by vacuolated cells; this zone was widest in E and its cells were largest in E. In E this intermediate zone appeared to have increased in width at the expense of cells from both the outer and inner zones. In an inner zone, the thickness was approximately the same in E and C, but the cells were the largest and contained the most vacuoles in E.† The vascular sinusoids were most conspicuous in E, suggesting that the blood supply of the gland had been increased. This method of observation failed to reveal any apparent differences in mitotic activity between C and E. There were no marked differences between the section of a male adrenal and that of a female adrenal, in either C or E.

Discussion. The observations support most of those of Tobin(12), and extend them. He studied a remaining adrenal of each of 3 fetuses in which he had been unsuccessful in performing a bilateral adrenalectomy by means of cautery. He reported a 15 to 20% increase in $\frac{\text{volume}}{\text{body wt}}$ (cf. an increase of 43% in our series). My material fails to confirm his report of an increased thickness of the "glomerulosa zone."

The observations presented are in agreement with those of Swinyard and Bruner(17). In dogs unilaterally adrenalectomized after birth, they noted an increased size of the intact gland and attributed this to an increase in size of its cortical cells.

The hypertrophy observed is new evidence that the fetal adrenal is able to respond to an introduced stimulus. However, it fails to assist in answering the question as to whether the functioning of the adrenals of fetuses is a factor in prolonging the life of animals adrenalectomized during pregnancy. This effect was attributed to the fetal adrenal by Billman and Engel(4). Rogoff and Stewart(3) suggested that the maternal ovary and corpus luteum were factors since they failed to observe hypertrophy of the adrenals of newborn puppies from mothers adrenalectomized during the period of gestation. Recent studies have brought out evidence which supports the view that either the corpus luteum(24) or proges-

23. Treolar, A. E., Random Sampling Distributions, Burgess Publishing Co., Minneapolis, 94 p., 1942.

† The developing adrenal medulla, like that of the human fetus, is not distinctly circumscribed, but instead consists of cellular nests which give the impression of lying in the fetal cortex.

terone(25) will prolong the life of certain adrenalectomized mammals including the ferret and the cat. Regardless of what prolongs the life of adrenalectomized pregnant females, it has been shown that adrenalectomizing the mother results in hypertrophy of the adrenals of fetuses(5,6). It has also been found that the injection of adrenal cortical extracts into the mother will prevent these effects(6). These observations raise a question as to whether the same factors responsible for hypertrophy of fetal adrenals after adrenalectomizing the mother play a part in the compensatory hypertrophy noted in the unilaterally adrenalectomized fetuses of this present series. It is reasonable to assume that one factor in both these instances is the action of an adrenocorticotrophin. A number of recent observations point to the view that adrenocorticotrophin is produced by the hypophysis of the mammalian fetus(7-12). Against this view is a recent report that in immature rats subjected to injections of epinephrine or to cold the hypophysis does not release ACTH until the 8th day and 16th day, respectively, after birth(26). This report poses a question as to whether the effective adrenocorticotrophin might have come from the maternal hypophysis, the fetal hypophysis or, conceivably, the placenta. Also one has to consider the possibility of the direct effect of reduced quantities of adrenal cortical hormones upon the fetal adrenal. From the observations noted in this series, it is not possible to settle the matter.

Conclusion. Subjection of the fetal rat to unilateral adrenalectomy causes a compensatory hypertrophy of the intact adrenal. Manifestations of this include an increased volume of the gland and an increased size of cells of all cortical zones. Those cells at both borders of the intermediate zone show an increased vacuolation, suggesting that the zone had been widened by the metamorphosis of cells at these borders.

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Arteriovenous Shunts in the Human Lung.* (18360)

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The presence of arteriovenous (A-V) shunts bypassing the capillary circulation in the human lung has been suspected from studies on blood gas analyses(1), the passage of certain parasites through the lung(2), and the formation of telangectasis(2) and arteriovenous aneurysms(3-6) within the lung.

Although these shunts have not been observed in the human lung(7,8), Prinzmetal *et al.*(9) have shown that glass spheres many

* This study was supported in part by the Fluid Research Fund of the University of Rochester School of Medicine and Dentistry, and by the Eastman Kodak Company, Rochester, N. Y.

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