shown that thymectomy in adult mice, combined with total body irradiation, can result in homograft tolerance of a high degree(16). This finding suggests that the thymus gland may resume its perceptor function in adult life under circumstances in which there is temporary suppression of the lymphopoietic system.

Summary. Five patients with terminal renal failure have been treated with renal homografts. Total body irradiation and cytotoxic drugs were used to prevent rejection. In addition, the thymus and spleen were surgically removed prior to the homotransplantation. Four of the 5 patients are alive with good renal function after 105 to 198 days. The role of thymectomy and splenectomy in conditioning patients for the receipt of homografts is highly speculative at present. However, the early success rate in this group of patients exceeds that generally attained with renal homografts, and appears to justify further clinical evaluation of this approach under carefully controlled experimental conditions. The data are insufficient to allow a recommendation for the general use of these adjuvant procedures.

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Received May 2, 1963. P.S.E.B.M., 1963, v113.

Arterial Angiotensin Levels in Edematous Patients.* (28535)

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The relationship between the renal renin content, the granularity of the juxtaglomerular cells and the width of the adrenal zona glomerulosa in rats has been reviewed by Tobian(1) and by Hartroft *et al.*(2). Our findings of a direct stimulatory effect of valine-5 angiotensin II aspartic β-amide on aldosterone, both in normal subjects and in patients with arterial hypertension(3-6), have been confirmed by many other groups(7-11).

Bock *et al.* demonstrated the sodium retaining effect of angiotensin when infused into normal subjects(12). Subsequently, Nijenson (13), Peart *et al.*(14) and Genest *et al.*(3,4, 6) showed its natriuretic effect, when infused into hypertensive patients. Laragh also brought evidence of the same natriuretic effect in some patients with cirrhosis of the liver and ascites(15).

Merrill *et al.* reported an increase in "renin content" of renal venous blood from patients with congestive heart failure(16). Tobian *et al.* recently demonstrated a high degree of correlation between the ascites in rats rendered nephrotic by administration of aminonucleoside and the granularity of the juxtaglomerular cells(17).

Our findings of normal arterial angiotensin blood levels in 75% of patients with essential

* This work has been supported through grants from the Ministries of Health, (Federal-Provincial Plan), Medical Research Council of Canada, Nat. Inst. Health, U.S.A., Life Insurance Medical Research Fund, Rosemont, Pa., and Ciba Co., Montreal.

hypertension, in 65% of patients with hypertension associated with renal artery stenosis and in almost all patients with malignant hypertension or with primary aldosteronism, strongly suggest that excessive amounts of circulating angiotensin are not the cause of the increased blood pressure levels in most hypertensive patients(18).

The overall evidence points to a probable major role of angiotensin in the regulation of sodium, through its stimulation of aldosterone secretion and also probably through some direct effect on tubular transport of sodium(6, 19). Work was therefore undertaken to determine the arterial angiotensin blood levels in patients with various types of edema, usually accompanied by hyperaldosteronism.

Methods and subjects. A new procedure was utilized for angiotensin determination in arterial blood. This procedure has been briefly described by Boucher *et al.*(20) and has the advantage of being shorter than the former one devised by the same group(21), without any loss in specificity and sensitivity. Mean recovery of added angiotensin to blood or plasma, by this procedure, is 83% (range: 70-116%) in 12 different experiments. The major steps of this procedure are: 1) arterial blood is drawn under vacuum and rapidly cooled (5-0°C) through a siliconized copper coil immersed in crushed ice to prevent angiotensinase activity; 2) after centrifugation at 5-0°C, the citrated plasma is directly placed at the same temperature on a Dowex 50W-X2 (NH_4+) resin column (10 × 1 cm); 3) the fraction containing angiotensin is eluted at 5-0°C, with 0.1 N diethyl amine followed by 0.2 N ammonium hydroxide; 4) further purification of angiotensin is obtained by ascending paper chromatography on Whatman #2 using a system of n-butanol:acetic acid:water (45:10:50, v/v; Rf angiotensin: 0.27); 5) amounts of angiotensin are determined by a rat pressor assay using a highly purified valine-5 angiotensin II, aspartic β-amide standard.†

Results are expressed in nanograms per 100 ml of plasma (1 nanogram = 0.001 μg). Normal values vary between 0 and 35 nanograms percent of plasma with a mean of 6.3 ± 2 (S.E. of means). Seventy percent of normal subjects studied (20 healthy normotensive inmates of the Montreal jail) have no detectable arterial angiotensin level.

Fifteen edematous patients were studied. In 10 instances, the edema was secondary to congestive heart failure (in 4 of these, the failure was due to hypertensive cardiovascular disease), in 2, it was due to the nephrotic syndrome and in 3 others, to cirrhosis of the liver with ascites. In most patients, the first blood sample was taken at time of admission in the hospital and before onset of any treatment. Nine patients in the congestive heart failure group were studied also after total or partial relief of edema by administration of various natriuretic agents.

Edema was evaluated for gross clinical purposes, as follows:

\+ slight pitting edema of the ankles and pre-tibial regions,

\++ more marked pitting edema of the ankles and legs up to the knee region,

\+++ marked edema of the entire lower limbs with presence of pre-sacral edema,

\++++ anasarca.

A description of each patient studied is given in Tables I and II.

Results. The mean pre-treatment value of the group of edematous patients is 210 nanograms percent of plasma with a wide scatter of individual results (Fig. 1).

A—Edema secondary to congestive heart failure (Cases 1 to 10). Nine out of 10 patients had an arterial angoitensin level above normal range. Patients 1 to 9 were studied both before and after total (Cases 1 to 6) or partial (Cases 7 to 9) relief of edema. In 4 patients, angiotensin disappeared completely from the blood after relief of edema.

Mean arterial angiotensin levels in these 9 patients before administration of natriuretic agents, was 243 nanograms percent of plasma, whereas it fell to 86 nanograms percent after total or partial relief of edema. The only 2 patients presenting an increase in arterial angiotensin level (one of which does not appear

† This standard was kindly provided to us through the courtesy of Dr. Robert Schwyzer and Dr. Walter Murphy, Ciba Co., Basle and Montreal.

to be significant) after relief of edema, are patients with congestive heart failure secondary to hypertensive cardiovascular disease.

B—Edema secondary to the nephrotic syndrome (Cases 11 and 12). Case 11 is that of a 27-year-old woman presenting a nephrotic syndrome secondary to disseminated lupus erythematosus. Her edema was resistant to administration of several natriuretic agents alone or in combination and in high dosages.

TABLE I. Arterial Angiotensinemia in Congestive Heart Failure and Clinical Data.

Case No.	Age	Sample No.	B.P.	Edema	Wt	Angiotensin, % plasma	Remarks
1.	33	1	130/60	+++	49.0 K	142	Right cardiac failure.
		2	120/80	0	39.5 K	0	6 days later after digitalization and low salt diet.
2.	73	1	180/80	+++	77.7 K	82	Arteriosclerotic heart disease and hypertension. Hepatomegaly (5 cm).
		2	210/100	0	72.7 K	190	7 days later after digitalization and hydrochlorothiazide.
3.	54	1	160/100	+++	70.9 K	186	Hypertension — hepatomegaly (6 cm) — pulmonary rales over bases.
		2	160/110	0	61.4 K	0	10 days later after digitalization and thiazide diuretic. Low salt diet.
4.	78	1	140/80	+++	66.0 K	260	Hepatomegaly (5 cm)—pulmonary rales over bases.
		2	190/90	0	56.8 K#	74	6 days later after digitalization and chlorothiazide, 500 B.I.D.—pulmonary rales over bases—low salt diet.
5.	65	1	190/120	+++	86.4 K	510	Hypertension — chronic pyelonephritis — pulmonary rales over bases — hepatomegaly (6 cm) — Meralluride 80 mg I.M. the day before.
		2	145/95	0	80.4 K	260	6 days later after chlorothiazide 500 mg I.D.
6.	63	1	210/110	+++	70.0 K	12	Hypertension and chronic renal insufficiency (blood urea: 60 mg %). Pulmonary rales over bases—hepatomegaly (3 cm). Patient digitalized.
		2	150/80	0	63.0 K	32	One month later after 1.2 g Na diet.
7.	58	1	155/80	++++	77.0 K	856	Hepatomegaly (6 cm)— pulmonary rales over most of lung area. Ascites ++ —patient digitalized.
		2	125/75	++	68.9 K	220	6 days later after 1 g Na diet—less numerous pulmonary rales—no ascites.
8.	61	1	140/70	+++	68.0 K#	94	Pulmonary rale over lower half of lung area. Ascites +++ — hepatomegaly (5 cm). Was receiving hydrodiuril chlorothiazide 500 mg B.I.D.
		2	140/80	++	63.0 K	0	18 days later—less numerous pulmonary rales — ascites paracentesis 1600 cc 15 days before. Acetazolamide 250 mg B.I.D.—low salt diet.
9.	53	1	120/80	+++	62.8 K	52	Pulmonary rales over most of lung area— ascites ++ — hepatomegaly (5 cm).
		2	120/80	++	58.3 K	0	2 wk later: has received aldactone ? ; thiazide ? until 4 days before sample. One g Na diet.
10.	34	1	120/80	++++	50.9 K	176	Pulmonary rales over lower half of lung area — ascites ++ — hepatomegaly (6 cm)—low salt diet—digitalized—acetazolamide 250 g B.I.D.—Meralluride 80 mg I.M.

TABLE II. Arterial Angiotensinemia in Nephrotic Syndrome and Liver Cirrhosis and Clinical Data.

Case No.	Age	Sample No.	B.P.	Edema	Wt	Angiotensin per 100 cc plasma	Remarks
Nephrotic syndrome:							
11.	27	1	120/80	+++	50.8 K	216	Pulmonary rale over bases—ascites ++ — hepatomegaly — lupus erythematous disseminated.
		2	125/75	+++	51.6 K	344	8 days later: increased edema despite spironolactone 100 mg. Q.I.D. I.M.— hydrochlorothiazide 100 mg B.I.D.—△ cortisol 25 mg T.I.D.—500 mg Na diet.
12.	24	1	160/90	+		25	Edema of ankle since 2 days. Low salt diet for one year.
Liver cirrhosis with ascites:							
13.	56	1	110/70	+		0	Hepatomegaly (4 cm) — ascites ++ — chlorthalidon 100 mg I.D.
14.	56	1	150/80	++++		0	Pleural effusion — ascites ++++ — impending coma — hepatomegaly (8 cm).
15.	53	1	155/75	+++		490	Pulmonary rales over bases — ascites ++++ — Meralluride 80 mg I.M. every after days. Splenectomy and spleno-renal anastomosis, 17 days before.

Her arterial angiotensin level was much higher than normal (see a, nephrotic syndrome column, Fig. 1) and urinary aldosterone excretion on the day of the blood sample was 25 μg. One week later, her edema was more marked and the arterial angiotensinemia reached even higher levels (see b, same column, Fig. 1).

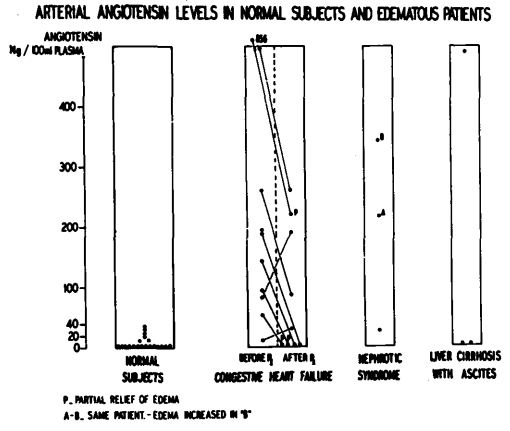

FIG. 1. Results of arterial angiotensin levels in 20 healthy normotensive subjects and 15 patients with generalized edema due to congestive heart failure, nephrotic syndrome or cirrhosis of the liver with ascites. Note the marked fall in angiotensin levels in 7 of 9 patients with congestive heart failure, after relief of edema. The increase in angiotensin level in one patient with congestive heart failure does not appear significant, since the 2 levels found before and after treatment are within the normal range.

Case 12 is that of a 24-year-old man with nephrotic syndrome secondary to membranous glomerulonephritis. At the time of the blood sampling, he presented only a very slight pitting edema (+) of the ankles. His arterial angiotensin level was within normal limits.

C—Edema secondary to cirrhosis of the liver with ascites (Cases 13 to 15). Two of these patients had no detectable angiotensin in their arterial blood and the third had an arterial angiotensin level of 400 nanograms percent of plasma.

Discussion. The present findings, though preliminary, suggest a relation between the renin-angiotensin system and clinical states characterized by generalized edema usually due to secondary hyperaldosteronism. This possibility occurred to us as a consequence of our previous work(18) and has also been proposed by Laragh(22) and by Davis and Urquhart(23). More detailed observations of such patients must be made under metabolic balance conditions for correlative study of arterial angoitensin levels, aldosterone secretion rate and excretion and sodium balance. Such studies would be especially necessary in patients with edema secondary to congestive heart failure because of the uncertainty con-

cerning the role of aldosterone in the pathogenesis of cardiac edema.

The concept put forward by Tobian(1), of the juxtaglomerular cells being stretch-receptors sensitive to fall in renal perfusion pressure or to decrease in blood volume, is supported by the present observations.

Except for patients 2, 3, 5 and 6, all others were normotensive. The explanation for the apparent dissociation between pressor activity and amounts of angiotensin found in the arterial blood of these patients is not clear. Although there is a reduced responsiveness to angiotensin in cirrhosis of the liver(15) and in experimental edematous conditions in animals(24), this explanation is not entirely satisfactory because of the high levels found in some patients. Another hypothesis is that of the possible increase in vasodepressor substances, such as bradykinin, in conditions with edema. Such possible evidence is suggested by the work of Diniz and Carvalho in patients with nephrotic syndrome and with liver cirrhosis(25). This hypothesis appears attractive, because both angiotensinogen and bradykininogen come from the same $\alpha 2$-globulin fraction of plasma and are activated by proteolytic enzymes. Another possibility would be a change in cationic balance in the intracellular arteriolar compartment, depressing vascular reactivity in edematous condition and preventing the pressor activity of angiotensin.

It is of interest that in our previous report concerning arterial angiotensin blood levels in hypertensive patients(18), the highest level (820 nanogram percent) which was completely out of line with the other results obtained in such patients with essential hypertension, was obtained in a patient with a 2+ edema due to congestive heart failure secondary to hypertensive cardiovascular disease.

Summary and conclusion. Fifteen patients with generalized edema were studied for circulating angiotensin levels in arterial blood. Out of 10 patients with congestive heart failure, 9 had very high levels and 7 of the latter presented, after total or partial relief of edema, a very marked decrease in their angiotensin levels. One presented a rise and one showed no significant change. One of 2 patients with the nephrotic syndrome and one of 3 with cirrhosis of the liver had high arterial angiotensin levels.

We wish to express our deep gratitude to Dr. Walter Murphy and Dr. Robert Schwyzer, Ciba Co., Montreal and Basle, for generous gifts of valine-5 angiotensin II, aspartic β-amide; to Mr. Claude Grisé, Misses Alice Laflamme, Lucille Tremblay, Marjolaine Comeau, for technical help, to Miss Isabelle Morin for illustrations.

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Received May 6, 1963. P.S.E.B.M., 1963, v113.

Chemical Protection Against Early Radiation Mortality of the Young Chicken.* (28536)

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The acute radiation syndrome that follows exposure to lethal amounts of X- or gamma-radiation has been studied extensively in mammals where death occurs 5 to 15 days post exposure largely from damage to the gastrointestinal tract and the bone marrow (1). Acutely irradiated birds die in a comparable period and, although the exact mechanisms involved are not clearly understood, fluid imbalance caused by gastrointestinal damage, and hematopoietic failure are likely involved(2). In the young chicken, however, additional lethal processes occur following acute irradiation. Jacquez and Karnofsky(3) showed that with exposure rates above 15 roentgens per minute the majority of the animals died within 48 hours of exposure to 1000 r. At very large radiation doses mammals also die within 48 hours of exposure due to interference with nervous system function. Stearner *et al.*(4), however, have excluded central nervous system damage as the cause of death in chickens at radiation doses below 1000 r. Renal failure, hypotension and circulatory failure have been the major characteristics associated with the early death in the chicken(5).

Since 2-aminoethylisothiouronium bromide (AET) and similar compounds have been shown to protect mammals against gastrointestinal and bone marrow mortality(6,7), it was decided to investigate the protective capacity of AET against the early mortality of the young chicken. During the course of these studies it was noted that the early (0-48 hr) deaths fell into 2 separate periods, each with a different time interval between radiation exposure and death.

Materials and methods. Three-day old, White Leghorn cockerels were exposed to 0 r, 750 r, 850 r, or 950 r of X-rays, with or without prior AET treatment. Fifteen minutes before exposure half of the animals were injected subcutaneously with 10.5 mg (approximately 300 mg/kg of body weight) of AET in 0.1 cc of 0.1 *N* NaOH. These animals were then combined for exposure with a similar number injected with saline so that in all cases the AET-treated chicks and their controls were irradiated under identical conditions. The animals were exposed in groups of 20 in a cylindrical polyethylene chamber 9¾″ in diameter and 1¾″ in height which was rotated in the X-ray field at approximately 2/3 rpm.

The conditions of irradiation were as follows. X-rays were obtained from a conventional therapy X-ray machine operated at 250 kv and 15 ma with 0.5 mm Cu and 1.0 mm Al filters. The dose rate of 103 r per minute at a target distance of 55 cm was held constant throughout the exposure periods, the various doses being obtained by changing the total exposure time. The X-ray dose was measured in air with a commercially-calibrated Victoreen condenser r-meter placed at the midpoint of the rotating exposure chamber. A decrease in dose of less than 10% was found at the perimeter of the exposure field.

Throughout the experiment, the chicks

* Supported, in part, by USPHS Grant.