Two isolated observations are in agreement with our point of view of a greater erythropoietic activity of anabolics as compared with testosterone. Gurney and Fried(8) observed a moderately greater Fe^{59} incorporation with nandrolone than with testosterone in mice, and Meineke and Crafts(9) reported that norethandrolone but not testosterone stimulates the Fe^{59} incorporation in hypophysectomized rats.

On the basis of these studies it is apparent that some androgenic steroids have more erythropoietic activity than testosterone. Our data also suggest that the erythropoietic effect of androgens may be a third type of activity of these steroids, independent of their virilizing and myotrophic activities. This possibility is suggested by the observation that compounds having less than one fourth of the virilizing effect of testosterone, like methenolone(10), are more active erythropoietically than testosterone. On the other hand, metholone which has lesser anabolic effect than testosterone, oxymetholone and methenolone (10,11) appears to be the more potent erythropoietic agent of all the 4 steroids tested.

Summary. The erythropoietic effects of testosterone, oxymetholone, methenolone and metholone were compared in normal and fasted rats as well as mice on a protein free diet. The results of these androgenic-anabolic steroid studies are as follows: 1) methenolone and metholone produced a more marked erythropoietic response than testosterone when tested in normal female rats; 2) Fe^{59} incorporation in RBC of male fasted rats was higher with oxymetholone than with testosterone; and 3) testosterone was markedly less effective than oxymetholone, methenolone and metholone in increasing Fe^{59} incorporation in RBC of mice on a protein free diet. These results suggest that the erythropoietic activities of the above steroids are independent of their virilizing and anabolic effects, since testosterone is the most virilizing of the four agents and metholone, which induced the greatest erythropoietic effects, has the least anabolic action.

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Juxtaglomerular Cells in CCl_4-Treated Experimental Hypertension.* (32269)

HUBERT F. LOYKE AND JOHN S. MACKRELL
(Introduced by Matthew N. Levy)
Department of Clinical Investigation, Research Division, St. Vincent Charity Hospital Cleveland, Ohio

Renal and endocrine (DCA) hypertensive rats have been rendered normotensive by CCl_4 injections(1,2). The possibility that alterations in renin secretion were taking

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TABLE I. Blood Pressure at 20 Weeks Refers to the Hypertensive Period and 28 Weeks at the End of the CCl_4 Period.

Group	No. animal	Blood pressure (mm Hg) 20 wk	28 wk	No. CCl_4 injections	Mean JG index	± S.D.
Normotensive untreated	15	139	138	0	29	14
" + CCl_4	8	134	136	15	35	14
Renal hypertensive	3	190	185	0	12	7
" " + CCl_4	8	196	127	15	8	6
DCA hypertensive	3	181	—	0	18	12
" " + CCl_4	9	178	137	15	45	20

place during CCl_4 induced normotension suggested examination of the juxtaglomerular (JG) apparatus. The Hartrofts(3) noted increased granulation following sodium restriction and degranulation following a high salt regimen and DCA administration. Tobian has noted alterations in granulation of the JG cells in Wistar strain rats during hypertension and has associated renin secretion with the granularity of the JG cell (4,5). Hartroft(6), using fluorescent antibodies, found antirenin antibodies bound to JG cells. Demopoulos *et al*(7) have shown a correlation between JG cell granularity and renin levels in the kidney. The purpose of this investigation was to study the granularity of the JG cells in experimental hypertensive animals, and during the normotensive phase induced by injections of CCl_4.

Methods. Eleven male Sprague-Dawley rats were made hypertensive by figure-of-8 ligature of one kidney, followed in one week by contralateral nephrectomy. Endocrine hypertension was produced in 12 rats by subcutaneous insertion of one pellet containing 20 mg of DCA.† Twenty-one other rats served as pair-fed, normotensive controls, without surgical intervention. All groups were fed Purina chow, and given tap water *ad lib.* Animals were weighed and blood pressures recorded twice weekly by the Friedman microphonic method(8) in pre-heated, unanesthetized animals. On reaching and maintaining hypertensive systolic pressures (namely, greater than 160 mm Hg) for 3 months, 8 renal, 9 DCA and as a control, 8 normotensive animals were begun on biweekly subcutaneous injections of CCl_4 (0.15 ml per 100 g) for 15 doses. Three renal hypertensive rats and 3 DCA hypertensive rats did not receive CCl_4. All of the animals were sacrificed at the end of the experiment; their kidneys were removed and placed in fresh Zenker's-formol fixative to prepare for JG staining. The JG index was computed using the Hartrofts' method(3).

Results. Blood pressure. The blood pressure of animals in the renal hypertensive group rose from a control level of 135 to 196 mm Hg (± 8.84 S.E.) (Table I). Treatment with CCl_4 decreased the mean pressure to 127 (± 9.54 S.E.) which was significantly less than the pressure during the hypertensive period ($P<.01$). Three rats with untreated renal hypertension had a mean pressure of 190 mm Hg at 20 weeks; one was sacrificed at this time. The remaining two exhibited a mean blood pressure of 185 mm Hg when sacrificed with the others at 28 weeks.

The DCA-treated animals developed hypertension with mean pressures of 178 mm Hg (± 3.33 S.E.) which fell to 137 mm Hg (± 4.70 S.E.) following CCl_4 treatment ($P<.01$). The DCA hypertensive rats, not given CCl_4 had pressures averaging 181 mm Hg at 20 weeks.

There was no significant change in blood pressure in the normotensive untreated nor the CCl_4 groups throughout the entire experiment.

JG studies. Table I reveals that the JG index declined in the figure-of-8 ligated kidneys of the rats with renal hypertension (mean count = 12), as compared to the index of the normotensive, pair-fed controls (mean count = 29). After CCl_4, there was a slight further decline in the renal hypertensive group. DCA induced hypertension also reduced the granulation index, but it rose sig-

† DCA pellets supplied by Dr. S. W. Hoobler.

nificantly above the normotensive untreated control group ($P<.05$) during CCl_4 normotension (mean = 45). The normotensive group which received CCl_4 also showed an increase in the index (mean = 35).

Discussion. Blood pressure reduction was again observed following CCl_4 injections in DCA hypertension in the rat(2). The mean JG index for the Sprague-Dawley rat was found to be 29, as contrasted with 35 as reported(4) for the Wistar strain.

After renal hypertension was induced, the figure-of-8 kidney showed a JG index reduced to 12. CCl_4 injections in the renal animals produced an unimportant further decline in JG count in this form of hypertension. Attempts to produce renal hypertension in cirrhotic rats has been found to be relatively unsuccessful (23%) while 77% of their controls became hypertensive(9). The JG index of these rats with renal artery stenosis and cirrhosis were found to be elevated(9). Hence, it is assumed that the observed blood pressure reduction with CCl_4 in the present study is not the result of an inhibition of renin secretion by the sole remaining "ischemic" kidney.

DCA pellet implantation, associated with a high sodium diet, evokes hypertension and causes degranulation(9) of the JG cells. In our experiments, no sodium was added to the drinking water, nor to the food, which was Purina chow. This regimen produced a lesser decline (from 29 to 19) in JG count than reported by Tobian(10). After treatment of the hypertensive rats with CCl_4, the animals showed a rise in JG index to 45 at the same time that they were becoming normotensive. It is therefore evident that in this form of hypertension, CCl_4 does not reduce blood pressure by reducing renin secretion, if JG cell granulation is considered to reflect secretory activity of the kidney for renin. The paradoxical appearance of JG hypergranulation in the presence of a normal blood pressure might suggest an effort by the kidney JG cell to compensate for some deficiency in the renin-angiotensin system in this situation. The different responses of renal and DCA rats is not understood. We have demonstrated elsewhere that, after CCl_4 administration, predominantly angiotensin I is found in the animals' serum, and that incubation with normal serum shows a failure of angiotensin I to convert to angiotensin II, even in the presence of presumably normal amounts of converting enzyme(11,12). Thus, some substance appearing in serum after CCl_4 treatment inhibits the action of converting enzyme, so that inactive angiotensin I is not converted to the vasoactive angiotensin II. It is possible that this failure to generate sufficient angiotensin II is sensed by the JG apparatus which then undergoes hypergranulation. This hypergranulation then is associated with more renin production which is thwarted in its action on renin substrate to produce angiotensin II. Experimental support for angiotensin II, as a feed back control for renin secretion, has been presented by Vander(13).

A similar clinical situation has been postulated for the cases described by Bartter, which are characterized by normotension in the presence of hyperplasia of the JG apparatus, hyperaldosteronism, and presumably increased amounts of circulating angiotensin (14). This perplexing combination may be compared with our experimental findings in the DCA hypertensive rat after CCl_4 treatment, where converting enzyme is inhibited. The JG hypergranularity of our experiments, and in the clinical cases described by Bartter (14) are postulated to be associated with an increase in renin release(15) and no elevation of blood pressure presumably due to failure of feed back control of the JG cells. Bartter also reported an increased response to injected renin and a greater pressor response to norepinephrine than to angiotensin II in his cases(14) as we have also observed after CCl_4 administration to renal hypertensive rats(16). Our DCA animals after CCl_4 treatment have also been found to have hyperaldosteronism with high urinary excretion of aldosterone, high potassium and low urine sodium values (11). Thus, our experiment conforms to Bartter's syndrome in man. He has suggested (14) that a partial block in the renin angiotensin mechanism with a primary impairment of vascular response to angiotensin probably explains the clinical finding of

normotension. In the experimental situation described herewith (DCA hypertension rendered normotensive with CCl_4), we have evidence that the block is at the level of converting enzyme, with the resulting presence of vasoinactive angiotensin I, rather than vasoactive angiotensin II.

Summary. Renal and DCA hypertension was produced in rats, and blood pressure was then reduced to normal levels with CCl_4 injections. The juxtaglomerular (JG) index of these Sprague-Dawley rats was determined. After CCl_4 treatment of the renal hypertensive animals, no significant decline in JG granulation appeared as the blood pressure fell to normal. In the DCA hpertensive and the normotensive rats, CCl_4 induced normotension was accompanied by a large increase in granulation. It is thus apparent that the blood pressure decline induced by CCl_4 is not accompanied by any decrease in renal renin secretion. DCA hypertensive rats rendered normotensive by CCl_4 treatment exhibit a normal blood pressure in combination with a high JG index. This paradoxical situation may be the experimental analogue of the clinical syndrome described by Bartter, and attributed by him to an unknown defect in the renin-angiotensin-aldosterone secreting mechanism. Experiments published elsewhere, suggest that, in our experiments, the defect is caused by an inhibition of the enzyme converting angiotensin I to angiotensin II, so that the normal feed back to the JG cell is prevented.

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Inhibitory Effect of Carcinogenic Aromatic Hydrocarbons on the Splenomegaly of Friend and Rauscher Virus Leukemias.* (32270)

ALVIN G. FISCUS,† GERD T. SCHLOSS AND KENNETH F. WERTMAN‡
(Introduced by W. S. Jeter)
Department of Microbiology and Medical Technology, University of Arizona, and Virus Laboratory, Tucson Medical Center, Tucson, Ariz.

Inhibition of splenomegaly in Friend and Rauscher virus leukemias is currently being used as a convenient index for testing of antileukemic drugs. To examine the validity of this method, 7,12-Dimethylbenz[a]anthracene (DMBA) and 3-Methylcholanthrene (3-MC), two carcinogenic polycyclic aromatic hydrocarbons (PAH), were selected for use

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