Summary. 1) Some patients with aplastic anemia had exceptionally high levels of erythropoietic activity in plasma. The urine of these patients was assayed, and in some it was equally as potent as the plasma. As little as 1 ml daily for 14 days of untreated urine from such a patient produced a significant polycythemia in normal adult rats. When a concentrate of such urine, prepared by ultrafiltration, was injected at a dose equivalent to 30 ml daily for 14 days into normal adult rats, a polycythemia was produced which exceeded that resulting from exposure to a simulated altitude of 15,000 feet for the same period of time. 2) The high potency of such urine has allowed its assay in normal rats. This finding, together with the easy availability of urine and the efficiency of ultrafiltration as a method for preparing concentrates of urinary erythropoietic activity, should allow for a more rapid investigation of the chemistry and biology of this factor.

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Received September 10, 1957. P.S.E.B.M., 1957, v96.

Effect of Corticoids upon Skeletal and Renal Changes Produced by Stylomycin Aminonucleoside.* (23534)

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The literature on stylomycin aminonucleoside (SAN) is somewhat confusing, owing to the fact that the antibiotic now known as "stylomycin" was first called "achromycin"—a name which was subsequently transferred to another antibiotic(1)—and then "puromycin"(2,3,4). Little is known as yet about the pharmacology of this antibiotic, apart from its efficacy in the treatment of infections, particularly those caused by certain trypanosomes. It has been noted, however, that stylomycin and its aminonucleoside can produce a nephrosis-like syndrome with renal lesions, subcutaneous edema, pleural fluid, ascites, hyperproteinemia, hyperlipemia and azotemia in laboratory animals(1,3). This condition is accompanied by an increased aldosterone secretion(4), osteitis-fibrosa-like changes in the bones(5) and, in advanced intoxication, by an interstitial pancreatitis(6).

The object of the present communication is to report upon experiments which show that both the renal and the skeletal changes elicited by SAN overdosage depend largely upon the balance between pro- and anti-inflammatory corticoids.

* Supported by National Research Council of Canada and by Lederle Laboratories Division of Amer. Cyanamid Co., the latter having also supplied the stylomycin aminonucleoside used.

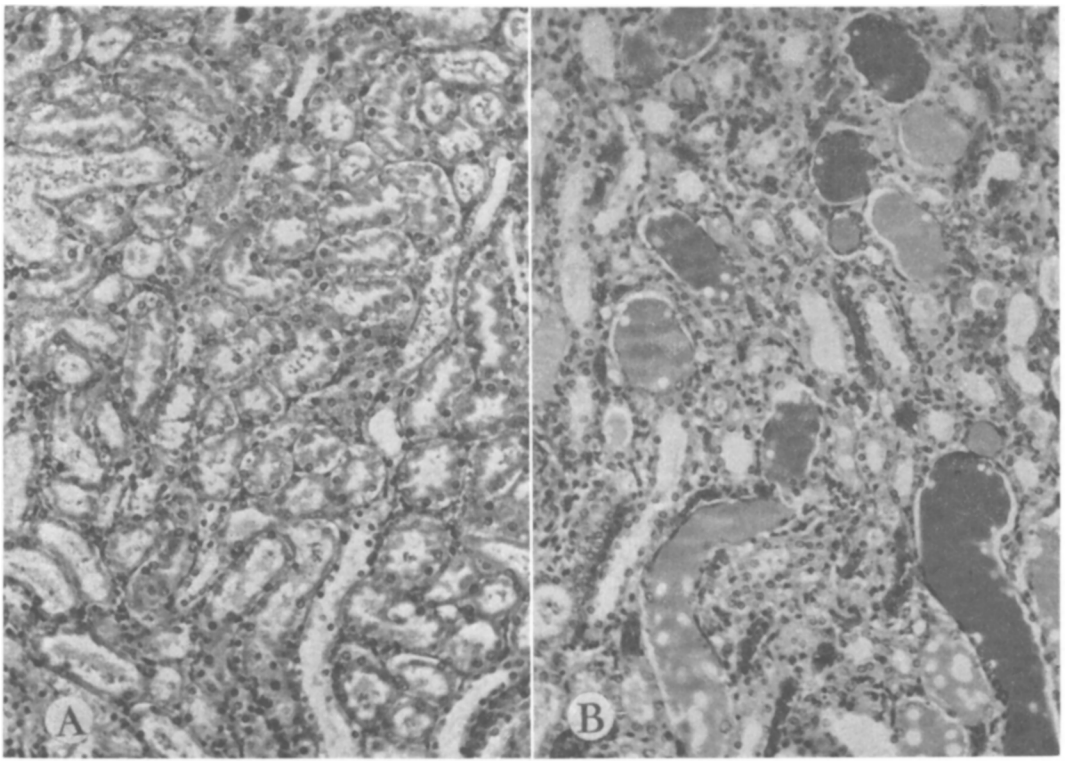

FIG. 1. Renal changes following combined treatment with SAN and corticoids. A. Virtually normal renal cortex following treatment with SAN + COL-Ac in a rat of Group II (X 150). B. Numerous hyalin casts and more or less granular protein precipitates in renal cortex of a rat of Group IV, treated with SAN + DOC-Ac (× 150).

Materials and methods. Fifty female Sprague-Dawley rats, with an average initial body-weight of 106 g (range: 98-112 g), were subdivided into five equal groups, all of which received 1 mg of SAN* in 0.2 ml of water subcutaneously, daily. *Group I* was not otherwise treated. The other animals received, in addition to the SAN, injections of corticoids as follows: *Group II*: cortisol acetate (COL-Ac)† 1 mg of microcrystals in 0.2 ml of water subcutaneously, once daily; *Group III* was adrenalectomized and treated with COL-Ac, as Group II; *Group IV*: desoxycorticosterone acetate (DOC-Ac)† 3 mg of microcrystals in 0.2 ml of water subcutaneously, once daily; *Group V* was adrenalectomized and treated with DOC-Ac, as Group IV. After 17 days the animals were killed with chloroform. The femurs, ribs and kidneys were fixed in Susa, embedded in paraffin and stained with hematoxylin-eosin, for subsequent histologic study. The acidity of the Susa solution sufficed to decalcify the skeletal structures within two or three days.

Results. It was evident at autopsy that the ascites and pleural fluid accumulations characteristic of SAN overdosage were most pronounced in the rats which received DOC-Ac (Groups IV and V), but there was no significant difference in this respect between the rats treated with SAN alone (Group I) and those which, in addition, were also given COL-Ac (Groups II and III).

On the other hand, histologic examination revealed that the renal changes, which were of moderate intensity in the controls, were diminished by COL-Ac (Groups II and III), and greatly aggravated by DOC-Ac (Groups IV and V). In Groups IV and V, the convoluted tubules were replete with hyalin casts and, occasionally, fibrinoid material appeared in the parietal laminae of Bowman's capsules

* Generously supplied by Schering Corp.

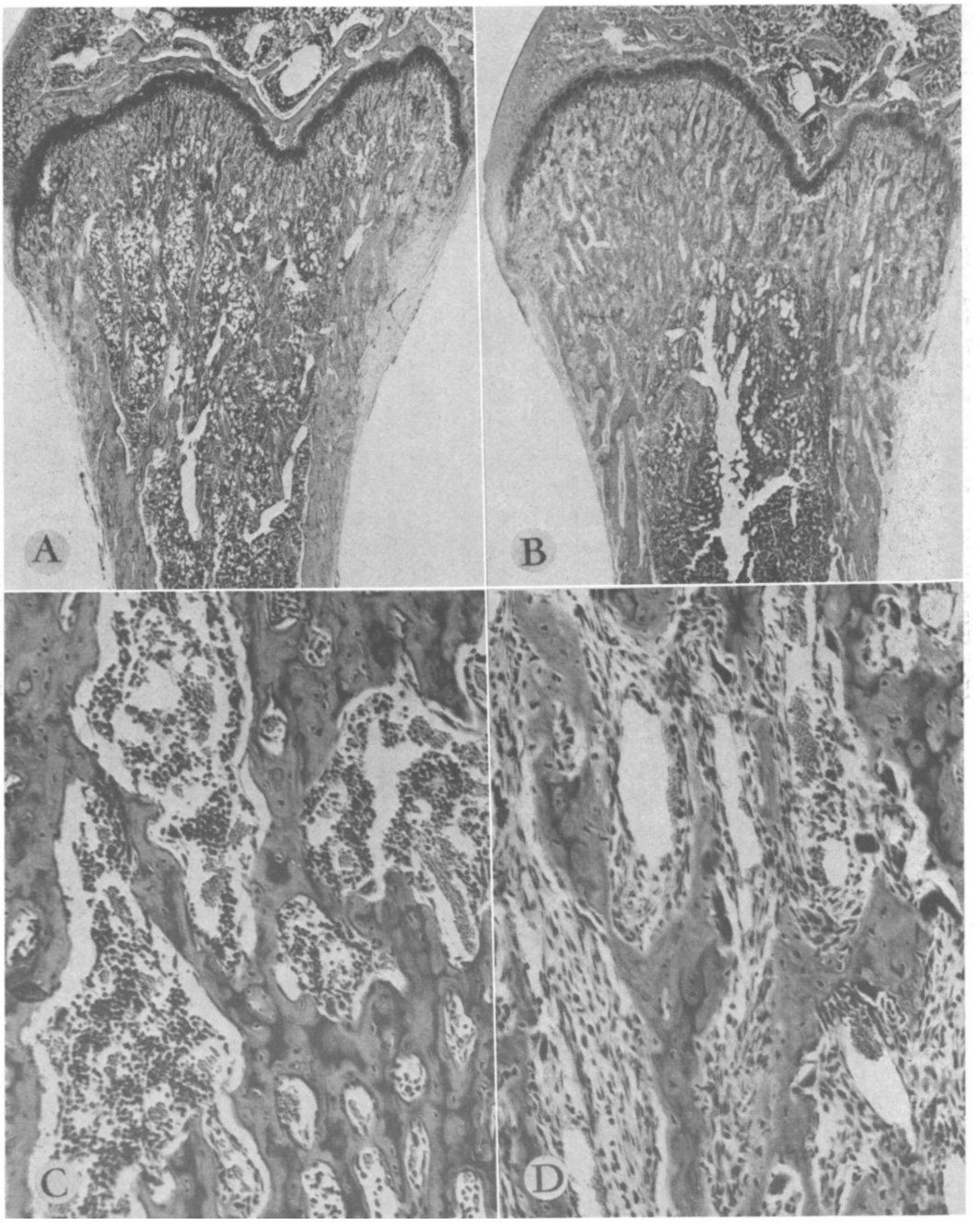

FIG. 2. Skeletal changes following combined treatment with SAN and corticoids. A. Cross-section through distal end of femur of a rat of Group II, which was treated with SAN + COL-Ac. Skeletal structure is essentially normal (X 15). B. Distal end of femur of a rat of Group IV, treated with SAN + DOC-Ac. Here the myeloid tissue has almost completely disappeared and is replaced by light, fibrous tissue between the trabeculae underneath the growth cartilage (X 15). C. Higher magnification of a region from Fig. A. Bone structure essentially normal (X 120). D. Higher magnification of a region from Fig. B. Here the myeloid elements are replaced by fibrous tissue with numerous, large (dark) osteoclasts (× 120).

or free in the glomerular spaces. It is known from previous work that, under similar conditions (that is, in short-term experiments and without "conditioning" by unilateral nephrectomy plus an excess NaCl), DOC-Ac produces no detectable signs of renal damage(7).

This has again been verified on 2 groups of 10 rats each, treated as the Groups IV and V of the previous experiment, but not given SAN.

On the other hand, chronic overdosage with DOC-Ac in suitably "conditioned" rats causes malignant nephrosclerosis with hyalinization of the afferent glomerular arterioles(7), that is, a change qualitatively different from that observed here (Fig. 1).

The femurs and ribs exhibited manifestations of mild osteitis fibrosa in Group I. The bone-marrow elements were partly replaced by a fibrous tissue that contained many osteoclasts. These changes were almost completely suppressed in the two groups that received COL-Ac (Groups II and III) and enormously aggravated in the animals treated with DOC-Ac (Groups IV and V). There was no significant difference, however, between the intact and the adrenalectomized animals, either as regards the suppression of renal and skeletal changes by COL-Ac, or their aggravation by DOC-Ac (Fig. 2).

Discussion. It is not known whether the osteitis fibrosa produced by SAN represents a form of "renal rickets." Parathyroidectomy, which prevents the development of osteitis fibrosa after nephrectomy(8), does not abolish the histologically similar lesions induced by SAN(5). This suggests that SAN can influence the bones through a mechanism other than an increased parathyroid hormone secretion. The experiments reported here furnish no information concerning the possible interrelations between the renal and skeletal manifestations of SAN intoxication, since COL-Ac inhibited, while DOC-Ac exacerbated both; hence it is impossible to say whether the action of the corticoids upon the bones was a consequence of their effects upon the kidney. It is also evident that SAN does not affect the renal or skeletal tissues merely by virtue of changes in corticoid secretion, since adrenalectomy does not prevent its toxic actions upon these structures. However, these observations furnish yet another instance of morbid changes, whose development is decisively influenced by the "conditioning" influence of the balance between pro- and antiphlogistic corticoids.

Summary. Experiments on albino rats indicate that stylomycin aminonucleoside (SAN) produces renal changes, accompanied by manifestations of osteitis fibrosa. Both renal and skeletal lesions elicited by SAN are inhibited by cortisol acetate (COL-Ac) and aggravated by desoxycorticosterone acetate (DOC-Ac).

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Received August 19, 1957. P.S.E.B.M., 1957, v96.