Is the action of the thiols on ketonic antibiotics a simple *in vitro* reduction of the active keto- and lactone groups, thus inactivating the antibiotic? *In vivo* thiols of the host do not appear to inactivate penicillin. Does this necessarily mean that the attack upon the microorganisms is an attack upon specific sulfhydryl enzymes of the parasite affected, while there is little or no attack by some of the antibiotics, such as penicillin, on the essential SH enzymes of the mammalian host or of trypanosomes? Low concentrations of sodium thioglycollate accelerate the action of penicillinase to inhibit penicillin action (*12*). The rapid urinary and biliary excretion of unaltered penicillin would indicate little or no cumulative binding of it by host cells (*8*), such as occurs with arsenicals. The inactivation of penicillin by cysteine has been shown by Hirsh and O'Neil (*6*) to take place only in saline or on agar and not in the presence of broth or serum.

The writer suggests that until it can be proven that penicillin binds to the SH groups of reduced bacterial protein, in proportion to the number of SH groups in such protein, after the manner in which Peters' colleagues showed that As does so bind to kerateine (the reduction product of keratin), the actual point of attack of penicillin on microorganisms cannot definitely be concluded to be upon the thiols of the organism. The inactivating, reducing agents may be simply reducing the antibiotics to inactive substances *in vitro* rather than removing them from combination with thiols of the microorganisms. The lack of host toxicity of penicillin (except at high concentration on brain cells) leads one to consider it possible that its attack may be upon an essential enzymatic process of bacteria and spirochetes, which is not essential to the mammal or the trypanosome. Is this necessarily an "SH" enzyme?

It would be interesting to know the oxidation-reduction potentials of penicillin and clavacin and their position with respect to the oxidation-reduction potentials of the cystine-cysteine system and other oxidative enzyme systems of the organism. Perhaps some of the ketonic antibiotics are at an E_h level such that they can be reduced by both thiosulfate and thiols, while others are at a level requiring the reduction potentials of certain thiols to cause their reduction.

Apparently the ketonic antibiotics can be classified in two groups: (1) those which are inactivated by thiosulfate as well as by thiols, as are clavacin and p-benzoquinone, and (2) those unaffected by thiosulfate but inactivated by certain thiols, as are penicillin and penicillic acid.

References

1. CAVALLITO, C. J., and BAILEY, J. H. *Science,* 1944, **100,** 390.
2. CAVALLITO, C. J., BAILEY, J. H., HASKELL, T. H., MCCORMICK, J. R., and WARNER, W. F. *J. Bact.,* 1945, **50,** 61–69.
3. CHOW, B. F., and MCKEE, C. M. *Proc. Soc. exp. Biol. Med.,* 1945, **58,** 175–177.
4. COMMITTEE ON MEDICAL RESEARCH, OSRD, and MEDICAL RESEARCH COUNCIL (London). *Science,* 1945, **102,** 627–629.
5. GEIGER, W. B., and CONN, J. E. *J. Amer. chem. Soc.,* 1945, **67,** 112–116.
6. HIRSH, H. L., and O'NEIL, C. B. *J. lab. clin. Med.,* 1946, **31,** 90–94.
7. PETERS, R. A., STOCKEN, L. A., and THOMPSON, R. H. S. *Nature, Lond.,* 1945, **156,** 616–619.
8. RAMMELKAMP, C. H., and KEEFER, C. S. *J. clin. Invest.,* 1943, **22,** 425–437.
9. REINER, L., and LEONARD, C. S. *Proc. Soc. exp. Biol. Med.,* 1932, **29,** 946–950.
10. VOEGTLIN, C., DYER, H. A., and LEONARD, C. S. *U. S. Publ. Hlth Rep.,* 1923, **38,** 1882–1912; *J. Pharmacol.,* 1925, **25,** 297–307.
11. WALKER, A. E., JOHNSON, H. C., CASE, T. J., and KOLLROS, J. J. *Science,* 1946, **103,** 116.
12. WOODRUFF, H. B., and FOSTER, J. W. *J. Bact.,* 1945, **49,** 7.

Protective Action of Desoxycorticosterone Acetate Against X-Ray-induced Liver Changes[1]

FRIEDRICH ELLINGER

Laboratory for Experimental Radiation Therapy
Long Island College of Medicine
Brooklyn, New York

X-ray and radium radiations, besides producing local effects, cause a general intoxication clinically known as "radiation sickness." This intoxication is one of the limiting factors in the successful radiological treatment of cancers, especially if the irradiation of larger volumina of the body is required. Many efforts have been made to control this condition, but "the list of remedies recommended for X-ray sickness is noteworthy more for its length than for any benefit that it has provided for sufferers from this distressing complaint" (*7*). This is largely due to the fact that no objective method for the evaluation of these therapeuticals has so far been available.

Data obtained during our previous "lethal dose studies with X-rays" (*2*) and especially some observations concerning fatty changes in the livers made during these investigations (*3*) seem to offer possibilities of a more objective approach to this problem.

Furthermore, the accumulated evidence indicates that histamine-like substances, if not histamine itself, cause the symptoms of radiation sickness (*1*) and also the above-mentioned liver changes (*3*).

On the basis of the histamine theory of radiation effects (*1*), desoxycorticosterone acetate has been chosen in the present study for the evaluation of its usefulness as a remedy for radiation sickness. This sterone is known to counteract histamine effects (*4–6*) and has also been recommended for the treatment of radiation sickness (*8*).

[1] Aided by grants from the John and Mary R. Markle Foundation, New York, and the Schering Corporation, Bloomfield, New Jersey.

Methods: Total body irradiation with X-rays was given to white male mice. The doses were 500 and 1,000 r/air in one exposure or in fractions of 100 r daily. The radiation factors were: 200 kv., 10 Ma., 0.25 mm. Cu + 1.0 mm. Al filters, 50-cm. distance, 20 × 20 cm. field, 23.4 r/minute, HVL = 0.75 mm. Cu. The technic of exposure was the same as previously described (*2*).

Daily doses of 0.25 or 0.5 mg. desoxycorticosterone acetate[2] (in oil) were administered subcutaneously six times weekly. Total doses varying between 2.5 and 8.0 mg. were given within 10 to 18 days. The effects on mortality rate, fat content of the liver, and radiation changes in other organs were studied over a period of 40 days.

TABLE 1

Irradiated animals M = 1.43 σ = 1.42						
	Grading of fat					
X-ray dose	0	+	++	+++	++++	No. of animals
500 r	14	–	8	9	–	31
500 r frac.	8	1	2	5	3	19
1,000 r	11	1	3	3	1	19
1,000 r frac.	7	2	4	6	1	20
Total	40	4	17	23	5	89
Irradiated and desoxycorticosterone-treated animals M = 0.50 σ = 1.01						
	Grading of fat					
X-ray dose	0	+	++	+++	++++	No. of animals
500 r	21	1	3	3	–	28
500 r frac.	14	2	1	2	2	21
1,000 r	13	2	1	–	–	16
1,000 r frac.	13	–	1	–	–	14
Total	61	5	6	5	2	79

M = arithmetical mean = fat index; σ = standard deviation.

Microscopic sections of livers stained with Sudan III were used for the assay of fat, and the following grading was applied: 0 = no sudanophile fat; + = traces of sudanophile fat; ++ = increased amount of fat with definite arrangement around central vessels; +++ = considerable increase in fat; ++++ = fat making up an entire lobule. For the quantitative evaluation of these histological changes the "fat index," *i.e.* the arithmetical mean of the various grades of sudanophile fat, was used.

Results: The outstanding observation made in these studies was a striking reduction in the amount of sudanophile fat in the irradiated and desoxycorticosterone-treated group of animals as compared with those receiving irradiation only. The data are summarized in Table 1.

No striking difference in the radiation effects on bone marrow and spleen was noticed between the irradiated and desoxycorticosterone-treated group and the solely irradiated controls.

However, there was a slight decrease in the mortality rate produced by the various doses of X-rays in favor of the desoxycorticosterone-treated group.

Further details will be given in a later publication.

The protective action of desoxycorticosterone against X-ray-induced liver changes seems to be of interest from various points of view: (1) These results give experimental evaluation to, and support the clinical impression of, the value of desoxycorticosterone in the treatment of radiation illness. They also seem to support the histamine hypothesis of radiation effect. (2) The protective power of desoxycorticosterone against radiation effects in the liver appears of particular interest in the clinical application of radioactive substances known to be selectively deposited in the liver. In utilizing this effect the clinical efficiency of radioactive substances in the treatment of leukemias and cancers may be improved.

[2] We wish to express our gratitude to Dr. E. Henderson, of the Schering Corporation, for generously supplying us with desoxycorticosterone acetate.

References

1. Ellinger, F. *The biologic fundamentals of radiation therapy.* New York: Elsevier Publishing Co., 1941.
2. Ellinger, F. *Radiology,* 1945, **44,** 125.
3. Ellinger, F. *Radiology,* 1945, **44,** 241.
4. Graham, J. S. *Proc. Soc. exp. Biol. Med.,* 1943, **54,** 101.
5. Laurens, H., and Graham, J. S. *Med. Rec.,* 20, August 1941.
6. Perla, D., Freiman, D. G., Sandberg, M., and Greenberg, S. S. *Proc. Soc. exp. Biol. Med.,* 1940, **43,** 397.
7. Smithers, D. W. *Brit. J. Radiol.,* 1942, **15,** 233.
8. Weichert, U. *Strahlemtherapie,* 1942, **71,** 127.

Redox Potentials and Photoreduction by Chloroplast Granules

S. Aronoff[1]

Chemistry Department, Fels Fund, University of Chicago

The over-all reaction for photosynthesis,

$$CO_2 + HOH \xrightarrow[\text{pigment-system}]{\text{Light}} (CH_2O) + O_2, \qquad (1)$$

is remarkable not so much for the apparent decomposition of water but for the ability of the system to utilize efficiently as poor an oxidant as CO_2. Light may be used to effect the decomposition of water by inorganic sensitizers, e.g. Hg, if the wave length is sufficiently short. Redox couples (as $Co^{+3} \rightarrow {}^{+2}$, $Ce^{+4} \rightarrow {}^{+3}$) with a favorable potential (E° greater than −1.23 volt) are able to oxidize water in the dark. The potential of CO_2—HCHO (formaldehyde) is +0.08 (*8*) and probably any "first product" of photosynthesis is of the order of +0.1 volt; that of $Fe^{+3} \rightarrow {}^{+2}$ is −0.771.

[1] Present address: Radiation Laboratory, University of California, Berkeley.