Monthly in the name of the association and to accept the detailed unit cost estimate of the Science Press Printing Company for printing and mailing *The Scientific Monthly* for the calendar year 1943.

13. The following committees on resolutions were appointed:

(a) Resolution on interrelations of scientists of the Western Hemisphere. Dr. Walter B. Cannon was appointed chairman and Dr. E. C. Stakman was appointed a member of the committee. The chairman was authorized to appoint other members to the committee.

(b) Resolution in support of the war efforts of the Government. Dr. James B. Conant was appointed chairman, with authority to appoint other members to the committee.

(c) Resolution on freedom. Dr. Harlow Shapley was appointed chairman and Dr. Isaiah Bowman was appointed a member of the committee. The chairman was authorized to appoint other members to the committee.

(d) Resolution on declaration of scientific objectives. Dr. F. R. Moulton was appointed chairman with authority to appoint other members to the committee.

14. The following resolution in commemoration of the hundredth anniversary of the National University of Chile was adopted:

WHEREAS, the National University of Chile has recently celebrated its centennial, and,

WHEREAS, among its faculties are included many of the outstanding scientists of the Western Hemisphere, and,

WHEREAS, since science transcends national boundaries and forms part of a worldwide culture,

Therefore, be it resolved, in recognition of the identity of its interests with those of the distinguished scientists of the National University of Chile, and the strong cultural bonds that link the scientific workers of the hemisphere, that the American Association for the Advancement of Science send its felicitations to the National University of Chile and its rector, on the part of the scientists of the United States of North America, and,

Be it further resolved, That the American Association for the Advancement of Science, in anticipation of closer cooperation of the scientists of the hemisphere, cordially invite the university to take steps leading to such cooperation.

15. It was voted to cancel the New York meeting, previously postponed on request of the Office of Defense Transportation.

SPECIAL ARTICLES

ON ESTERS OF PENICILLIN[1,2]

THE chemotherapeutic effect of penicillin against the Gram-positive cocci in experimental animals and in man has been unequaled by any other agent so far tried. The practical use of penicillin, however, is still attended with some difficulties because of the instability and rapid excretion of the material. In a previous publication[3] we have described attempts to stabilize penicillin by selective acetylation and benzoylation of the hydroxyl groups. Though the stability of such derivatives, especially of the benzoyl compound, was greater than that of the original penicillin, the products held no great promise.

Since the instability of penicillin, especially in acid solution, is partly due to the lability of a carboxyl group,[4,5] experiments on esterification have been carried out by us during the past year and a half. The Oxford workers recently reported[4] unsuccessful attempts to esterify the silver salt of penicillin with alkyl iodides. We have prepared the methyl, ethyl, n-butyl and benzohydryl esters by reacting the free acid of penicillin with the corresponding diazo compound. In contrast to the starting material, the esters are insoluble in neutral or slightly alkaline buffers, they are very soluble in benzene and are not precipitated from chloroform-benzene solutions by dry ammonia. On analysis, the methyl and ethyl esters were found to contain around 10 per cent. of alkoxyl. Chromatographically the esters prepared from unfractionated penicillin showed three components.

In vitro the aliphatic esters have an activity of about 25 micrograms per cc in contrast to 0.08 to 0.3 micrograms per cc for the original penicillin fractions against hemolytic streptococci. The dilution method was used for these titrations.[6] The constant and low activity of the esters is probably due to a partial hydrolysis of the esters by the hemolytic streptococci.

The aliphatic esters show, in contrast to their relative inactivity *in vitro*, a marked activity in mice. Mice were infected by the intraperitoneal injection of 1 cc of 10^{-3}, 10^{-4} and 10^{-5} dilutions of a highly virulent strain of hemolytic streptococcus (C_{203}Mv). Treatment by the subcutaneous route was begun

[1] From the Departments of Ophthalmology and Medicine, College of Physicians and Surgeons, Columbia University, and the Edward Daniels Faulkner Arthritis Clinic, Presbyterian Hospital, New York.

[2] This work has been supported in part by a grant from the John and Mary R. Markle Foundation.

[3] K. Meyer *et al.*, SCIENCE, 96: 20, 1942.

[4] E. P. Abraham and E. Chain, *Brit. Jour. Exp. Path.*, 23: 103, 1942.

[5] Unpublished experiments.

[6] G. L. Hobby, K. Meyer and E. Chaffee, *Proc. Soc. Exp. Biol. and Med.*, 50: 277, 1942.

within two hours after infection and was carried out for a period of two to three days only. Table I shows the high degree of protection obtained with relatively small amounts of the ethyl ester.

TABLE I

Total amount of ester in mgs	Dilution of culture (strain $C_{203}Mv$)	Number of mice	Number died (< 48 hrs.)	Number survived (> 7 days)
2.5–4.5	10^{-3}	11		11
	10^{-4}	12		12
	10^{-5}	13	1	12
1.37	10^{-3}	3		3
	10^{-4}	3	1	2
	10^{-5}	3		3
0.6	10^{-3}	3	2	1
	10^{-4}	2	1	1
	10^{-5}	3	1	2
Controls	10^{-6}	12	12	
	10^{-7}	12	12	

A total dose of less than 1.5 mg of the ethyl ester gives complete protection against a 10^{-3} dilution (20,000 to 100,000 lethal doses) of hemolytic streptococci. With the methyl ester, essentially the same results have been obtained, except that a total of at least 2.5 mg was necessary. With penicillin preparations having an activity similar to that of the fractions from which these esters have been made, considerably larger amounts were necessary. The increased stability of the methyl and ethyl esters is illustrated by preliminary experiments indicating that partial protection is obtained by oral administration.

The benzohydryl ester mixture, in contrast to the aliphatic compounds, is hydrolyzed by the test organism. It has a constant *in vitro* activity of 0.3 to 0.6 micrograms per cc which is comparable to the activity of the starting material. The mouse seems to be unable to hydrolyze this compound, however, as no protection was obtained with the dosage employed. The compound is of interest, nevertheless, since it can be split by catalytic hydrogenation with colloidal palladium, giving a highly active acid fraction.

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THE INFLUENCE OF BIOTIN UPON SUSCEPTIBILITY TO MALARIA

IT has long been known that individuals differ in their degree of natural susceptibility to malaria. Almost nothing is known, however, concerning the factors responsible for these differences, nor has it been possible in the past to markedly affect the degree of natural susceptibility to experimental malaria, whether human, simian or avian. Experiments with avian malaria have now shown that the level in the host animal of biotin,[1] an important growth factor, greatly influences the severity of the infection. Also significant is the fact that the concentration of biotin in the blood reaches two or three times its normal value at the peak of an acute experimental malarial infection, and then returns to normal when the infection has subsided.

Most of the work has been done with *Plasmodium lophurae*[2] infections in young chickens and ducks. Chickens or ducks, rendered biotin-deficient by maintenance on an egg-white diet[3] for two or three weeks and subsequently inoculated with large doses of *P. lophurae,* showed peak parasite numbers 50 to 100 per cent. higher than those shown by control animals. Among the biotin-deficient animals, the parasite number persisted at a high level several days longer, and more animals died of the malarial infection than among the controls. The greater susceptibility of the biotin-deficient animals was not directly connected with any general weakness resulting from the biotin deficiency. Chickens or ducks made extremely weak on a pantothenic acid-deficient diet did not develop any heavier infections with *P. lophurae* than did the robust animals which received the same diet supplemented with calcium pantothenate. Moreover, chickens which were provided with just enough biotin so that they grew well and were quite normal, except for a mild scaly dermatitis of the feet, developed more severe infections than chickens provided with more nearly adequate amounts of biotin. Here, in the presence of a small degree of biotin deficiency, the administration of additional biotin acted as a specific therapeutic measure to lessen the severity of the infection. It is also pertinent that older chickens, which are more resistant to *P. lophurae* infection than young chickens,[2] showed a higher level of biotin in the blood.[4]

Chickens kept on egg white diet and infected with *Plasmodium gallinaceum,*[5] either by sporozoites or by blood inoculation, showed higher average peak parasite numbers in the blood than control animals on a similar diet with the egg white replaced by casein. Biotin-deficient ducks infected with *P. cathemerium*[6] did not show higher peak parasite numbers than the non-deficient animals, but their infections persisted at a high level for several days after the blood of the

[1] V. du Vigneaud, SCIENCE, 96: 455, 1942.
[2] L. T. Coggeshall, *Am. Jour. Hyg.,* 27: 615, 1938.
[3] R. E. Eakin, W. A. McKinley and R. J. Williams, SCIENCE, 92: 224, 1940.
[4] Total biotin (after acid hydrolysis by the method of J. A. Lampen, G. P. Bahler and W. H. Peterson, *Jour. Nutrition,* 23: 11, 1942) was determined by the microbiological assay method of G. M. Shull, B. L. Hutchings and W. H. Peterson, *Jour. Biol. Chem.,* 142: 913, 1942.
[5] The work with *P. gallinaceum* was done at the laboratories of the International Health Division of the Rockefeller Foundation with the generous cooperation of Dr. J. Maier.
[6] Duck strain 3 T kindly sent me by Dr. Fruma Wolfson.