William Shockley, Bell Telephone Laboratories
Hertha Sponer, Duke University
Julius Stratton, Mass. Institute of Technology
John D. Strong, California Institute of Technology
George E. Uhlenbeck, University of Michigan
John A. Wheeler, Princeton University
William H. Zachariasen, University of Chicago

Physiologists

David B. Dill, Harvard University
Carl A. Dragstedt, Northwestern University
Conrad Elvehjem, University of Wisconsin
William F. Hamilton, University of Georgia
Paul J. Hanzlik, Stanford University
Rafael Lorente de Nó, Rockefeller Inst., New York
Franklin C. McLean, University of Chicago
Henry A. Mattill, Iowa State University
Carl F. Schmidt, University of Pennsylvania
Arthur L. Tatum, University of Wisconsin
Maurice B. Visscher, University of Minnesota

Psychologists

Charles W. Bray, Princeton University
Elmer Culler, University of Rochester
Clarence H. Graham, Brown University
Joy P. Guilford, University of Southern California
Edwin R. Guthrie, University of Washington
Ernest R. Hilgard, Stanford University
Carlyle F. Jacobsen, Washington University
Donald G. Marquis, Yale University
Gardner Murphy, College of the City of New York
Burrhus F. Skinner, University of Minnesota
Stanley S. Stevens, Harvard University
Robert C. Tryon, University of California, Berkeley
Morris S. Viteles, University of Pennsylvania

Zoologists

James E. Ackert, Kansas State College
Howard B. Adelmann, Cornell University
Lester G. Barth, Columbia University
George W. Beadle, Stanford University
H. W. Beams, State University of Iowa
Alan A. Boyden, Rutgers University
Charles M. Breder, Jr., Am. Museum of Natural History
S. C. Brooks, University of California, Berkeley
J. William Buchanan, Northwestern University
Elmer G. Butler, Princeton University
Lee R. Dice, University of Michigan
Emmett R. Dunn, Haverford College
Boris Ephrussi, Johns Hopkins University
G. F. Ferris, Stanford University
Herbert Friedmann, U. S. National Museum
Myron Gordon, New York Aquarium
Viktor Hamburger, Washington University
Hope Hibbard, Oberlin College
Laurence Irving, Swarthmore College
M. R. Irwin, University of Wisconsin
Clarence H. Kennedy, Ohio State University
Harold Kirby, Jr., Univ. of California, Berkeley
R. R. Kudo, University of Illinois
S. F. Light, Univ. of California, Berkeley
Norman E. McIndoo, U. S. Department of Agriculture
Ernst Mayr, American Museum of Natural History
Peter Okkelberg, University of Michigan
Thomas Park, University of Chicago
Arthur W. Pollister, Columbia University
James A. G. Rehn, Acad. of Natural Sciences, Philadelphia
Karl P. Schmidt, Chicago Museum of Natural History
Francis O. Schmitt, Mass. Institute of Technology
Oscar E. Schotté, Amherst College
Tracy M. Sonneborn, Indiana University
C. L. Turner, Northwestern University
Albert Tyler, California Institute of Technology
William C. Young, Yale University

Much discussion has appeared in the columns of SCIENCE in regard to the desirability of the starring system and in regard to possible changes from the present method of selection.

It was planned to revise the system of starring for the seventh edition. A distinguished committee was appointed by the American Association for the Advancement of Science to study and to look into methods that might be used in order that a fair distribution of stars among the different sciences be made. Special attention should be given to those working in related and cross-over sciences, which under the present system do not necessarily have full consideration. Owing to the war, however, the committee of the Association was not able to function in time for the publication of the seventh edition, but it is hoped that a completely revised plan beginning with the eighth edition will be evolved.

JAQUES CATTELL,
Editor

SPECIAL ARTICLES

ANTIBIOTINS[1]

IN accordance with our interest in antibiotin compounds we have explored further the antibiotin activity of certain derivatives of biotin and other compounds which are structurally related to biotin. The antibiotin activity of desthiobiotin for some microorganisms has already been reported.[2,3]

We thought it also might be timely to record the microbiological activity of compounds which did not possess antibiotin activity but which stimulated the

[1] The authors wish to express their appreciation to Mrs. Glenn Ellis, Miss Carol Tompkins and Miss Kate Redmond for technical assistance in the bioassays.

[2] K. Dittmer, D. B. Melville and V. du Vigneaud, SCIENCE, 99: 203, 1944.

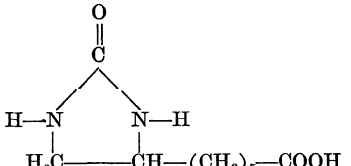
[3] V. G. Lilly and L. H. Leonian, SCIENCE, 99: 205, 1944.

growth of either or both *S. cerevisiae* and *L. casei* and to record the ability of these compounds to combine with avidin.

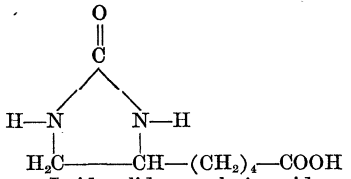
One of the most potent antibiotin compounds we have encountered in our experiments is the sulfone of biotin.[4] Biotin sulfone inhibited the growth of *L. casei, L. arabinosus* and *Staph. aureus.* For *S. cerevisiae,* however, biotin sulfone was found to act as a growth stimulant in place of biotin in the medium, although its activity was considerably less than that of biotin.[5]

The antibiotin action of biotin sulfone was thoroughly investigated with *L. casei.* For this organism when incubated for 66 hours, the molar inhibition ratio[6] was calculated to be 280, *i.e.,* 280 molecules of sulfone inhibited the effect of one molecule of biotin. The inhibition of growth exerted by biotin sulfone was completely reversed by the addition of more biotin. It has been observed that if the incubation time in the growth test is increased the inhibition ratio also increases.

Two analogues of desthiobiotin have been synthesized, namely, 4-(imidazolidone-2)-caproic acid and 4-(imidazolidone-2)-valeric acid.[7] The structures of these compounds are as follows:



Imidazolidone caproic acid



Imidazolidone valeric acid

Imidazolidone caproic acid differs from desthiobiotin only by lacking the methyl group attached to the imidazolidone ring, whereas the imidazolidone valeric acid, in addition to the lack of the ring methyl, has one less methylene group in the side chain.

Imidazolidone caproic acid was found to be an antibiotin for both *L. casei* and *S. cerevisiae.* This inhibitory effect on both of these organisms was reversed by the addition of more biotin. The molar inhibition ratio of imidazolidone caproic acid for *L. casei* was 126,000, and for yeast 760,000.

In contrast to the antibiotin activity of imidazolidone caproic acid, imidazolidone valeric acid stimulated the growth of yeast. Imidazolidone valeric acid in amounts sufficient to produce maximum yeast growth (equivalent to 0.005 microgram biotin) did not stimulate the growth of *L. casei* in a biotin-free medium. Furthermore, large amounts of imidazolidone valeric acid did not inhibit the growth of *L. casei* produced by small amounts of biotin. These tests would indicate that even though the yeast-growth-promoting activity of imidazolidone valeric acid is of a very low order, it is not due to contamination with biotin.

All the compounds tested which have a urea ring and a carboxylic acid side chain of 5 or 6 carbon atoms are able to combine with avidin, whereas all compounds which lack the cyclic urea structure are unable to do so. This is further evidence of the importance of the urea structure for the interaction of biotin with avidin.[8] The side chain also seems essential, for it was found that ethylene urea and 4-(imidazolidone-2)-carboxylic acid did not interact with avidin. Just how much the carboxylic acid side chain can be shortened without the loss of the ability to combine with avidin remains to be determined.

It has been possible to demonstrate that biotin sulfone, imidazolidone caproic acid and imidazolidone valeric acid can displace biotin from the avidin-biotin complex. Any one of these compounds when added to yeast or *L. casei* cultures in the presence of avidin-bound biotin is capable of displacing some of the biotin which then becomes available for the growth of the organisms.

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[4] K. Hofmann, D. B. Melville and V. du Vigneaud, *Jour. Biol. Chem.,* 141: 207, 1941.

[5] K. Dittmer, V. du Vigneaud, P. György and C. S. Rose, *Arch. Biochem.,* 4: 229, 1944.

[6] The molar inhibition ratio is a figure representing the antibiotin activity of the compound. It is expressed as the number of molecules of an antibiotin required to inhibit one molecule of biotin, and is determined experimentally as the amount of an antibiotin which is able to reduce the growth obtained with 0.0002 microgram biotin to a level equivalent to that obtained with 0.0001 microgram biotin. Thus the smaller the molar inhibition figure, the greater the antibiotin activity of a given compound.

[7] The imidazolidone caproic acid was synthesized from pimelic acid. Pimelic acid was converted to the half ester acid chloride. The latter was treated with diazomethane and subsequently with HCl to obtain ethyl-(8-chloro-7-keto)-octanoate. The 8-amino-7-keto-octanoic acid was obtained from the latter with potassium phthalimide followed by hydrolysis. With KCNO, the amino ketone was then converted to the imidazolone which upon reduction yielded the desired compound. Imidazolidone caproic acid melted at 145° and gave the following analysis:

$C_9H_{16}O_3N_2$	Calculated	C	53.98	H	8.06	N 14.00
200.2	Found	"	53.80	"	8.06	" 14.06

The imidazolidone valeric acid was prepared in a similar manner from adipic acid. This compound melted at 170° and gave the following analysis:

$C_8H_{14}O_3N_2$	Calculated	C	51.60	H	7.58	N 15.05
186.2	Found	"	51.66	"	7.61	" 15.10

The details of the syntheses will be reported elsewhere.

[8] V. du Vigneaud, K. Dittmer, K. Hofmann and D. B. Melville, *Proc. Soc. Exp. Biol. and Med.,* 50: 374, 1942.

The biological activities of the various derivatives of biotin and the simpler analogues are tabulated in Table 1. The growth-promoting activities are expressed as per cent. activity of biotin. If the compound has antibiotin activity its molar inhibition ratio is given.

TABLE 1

THE GROWTH-PROMOTING AND ANTIBIOTIN ACTIVITIES OF COMPOUNDS STRUCTURALLY RELATED TO BIOTIN AND THEIR INTERACTION WITH AVIDIN

Compound	*Growth-promoting activity*		*Antibiotin activity**		Combination with avidin
	Yeast	*L. casei*	Yeast	*L. casei*	
	per cent.	*per cent.*			
Biotin	100	100	none	none	Yes
Biotin sulfone	0.1	0	none	280	Yes
Desthiobiotin	100	0	none	9,100	Yes
Biotin diaminocarboxylic acid	10	< 0.01	none	none	No
Desthiobiotin diaminocarboxylic acid	10	0	none	none	No
Imidazolidone valeric acid	0.0017	0	none	none	Yes
Imidazolidone caproic acid	0	0	760,000	126,000	Yes

* Antibiotin activity is expressed as the molar inhibition ratio.[6]

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GERMINATION OF LETTUCE SEED AT HIGH TEMPERATURE STIMULATED BY THIOUREA

THOMPSON and Kosar[1] have shown that the germination of dormant lettuce seed can be stimulated by treating the seed with a dilute solution of thiourea. Investigations by the senior author demonstrate further that thiourea-treated lettuce seed can be germinated at a much higher temperature than untreated seed.

Ten different strains of lettuce seed were selected for these studies. A portion of each of the 10 lots of seed was soaked in a 0.5 per cent. solution of thiourea in Petri dishes in darkness in a constant temperature chamber at 18° C. for 7 hours. After soaking, the seed was washed in tap water to remove the thiourea solution from the surface of the seed. The treated seed was then spread out thinly on absorbent paper in diffused light and thoroughly dried. After drying the seed was placed in brown paper envelopes and stored at room temperature for 10 days when each lot was tested for germination on wet filter paper in Petri dishes in a germinator at 33°–35° C. Treated and untreated samples of each of the 10 strains were tested for germination in quintuplicate lots of 25 seed each with the results presented in Table 1.

TABLE 1

SUMMARY OF DATA ON THE INFLUENCE OF THIOUREA ON THE GERMINATION OF 10 STRAINS OF LETTUCE SEED AT HIGH TEMPERATURE, 33°–35° C. FOR 5 DAYS

Strain numbers	Thiourea-treated seed						Untreated seed					
	replications						replications					
	1	2	3	4	5	Total	1	2	3	4	5	Total
1541–1	22	21	19	24	21	107	0	0	0	0	0	0
1562–4	23	23	23	22	24	115	0	0	0	0	0	0
1562–8	23	22	25	24	24	118	0	0	0	0	0	0
1568–2	25	25	25	24	25	124	0	0	0	0	0	0
1592–12	24	24	25	25	24	122	0	0	0	0	0	0
1620–7	15	20	18	18	20	91	0	0	0	0	1	1
1624–4	25	25	25	25	25	125	0	6	0	1	1	8
1624–9	25	25	25	24	24	123	0	0	0	1	0	1
1640–4	16	23	17	21	20	97	0	0	1	0	0	1
1664–1	15	11	16	16	10	68	0	0	0	0	0	0
Total						1090						11
Per cent. germinated						87.2						0.88

The germination temperature used (33°–35° C.) is much too high for the ordinary germination of lettuce seed as is shown by the 0.88 per cent. average for all 50 lots of untreated seed. However, the 50 lots of thiourea treated seed gave an average germination of 87.2 per cent. The strains of seed responded differently to the treatment. Four of the 10 lots, numbered 1568–2, 1592–12, 1624–4 and 1624–9, gave almost 100 per cent. germination when treated as described.

Three strains, numbers 1620–7, 1640–4 and 1664–1, gave the poorest response to the treatment with 72.8, 77.6 and 54.4 per cent. germination, respectively. All but a few weak embryos appeared to be normal.

Numerous other variations of the treatment, including temperature, length of time of treatment and exposure to light while soaking, have been studied. The procedure outlined above has been found to be near the optimum for the strains so far tested.

Many lots of lettuce seed treated as described have been planted in soil; germination was rapid and normal plants resulted. Although none of the tests in soil have been carried out at the extremely high temperature of 33°–35° C., the maximum temperature frequently reached 30° during the warmest part of the day.

There is reason to believe that the thiourea treatment may have a practical application for assuring satisfactory germination where it is necessary to plant when the soil temperature is too high for germination of most commercial lettuce seed.

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[1] Ross C. Thompson and Wm. F. Kosar, *Plant Physiol.*, 14: 567–573, 1939.