for a world at peace, and "Fundamental Physics," its sequel stripped for wartime action. Both books are dedicated to the principle that physics is of its very nature and background a liberal and a cultural subject. And if physicists will teach their science in this spirit then it has a contribution to make to education that as yet is only partly realized. Physics is the foundation of much of technology. And the stories of its coming into being and its present-day content are the stories and the creations of men who strove during recent generations, and who strive to-day, to make the scientific method and the scientific outlook a vital part of human thinking and action.

Teachers of physics have not failed to heed the work of the author of these books. They have called him to positions of leadership and have invited him to expound his philosophy before gatherings that have considered major problems of policy.

Even if the teacher does not select "Fundamental Physics" for his classes, he should read and read again the preface and the epilogue and should absorb much of the spirit that quickens the book.

Hausmann and Slack's "Physics" was first published in 1935. It reached a second edition in 1939. Two years later a special edition for use at the U. S. Naval Academy was brought out by E. W. Thomson. And now the staff in physics at the Naval Academy has revised the special edition.

The members of the staff have aimed to adapt the book still better to the education of a midshipman. They have reconsidered the topics to be treated, the order of their presentation and their adaptation to the more advanced courses in mathematics, engineering, ordnance and navigation that the midshipman will pursue.

And the staff has aimed to introduce "desirable corrections." Their efforts in this direction will appeal to all who, like the reviewer, have taught from the regular edition of the text. One of its arresting characteristics is the large number of "corrections" that need to be made.

As instances (all taken from the second edition, twelfth printing):

(*a*) The physical pendulum oscillates, its center of mass *accelerates*, under equal and opposite forces, that is, under *no force!* (p. 158).

(*b*) The center of oscillation of a physical pendulum is that point at which the concentration of the whole mass of the pendulum would cause no change in its moment of inertia! (p. 159).

(*c*) The pressure arising from weight at a depth $h$ in a liquid of uniform density $d$, in a uniform field $g$, is (1) $hdg$ if metric absolute units are used, (2) but $hd$ if British gravitational units be employed! (pp. 183–184).

Have the British at last found a screen against gravitation?!

(*d*) And so on! and on! and ON!

Since "the crimes of Clapham are chaste in Martaban" it may be that such statements are accepted as sound science on the east bank of East River. On other shores, however, these are plain blunders and who uses the book is honor bound to warn his pupils to "weigh and consider" all that they see in print.

The men of the Navy have led the way, let the civilians follow it. Let the cargo of the good ship Hausmann and Slack (of the civilian fleet) be thoroughly inspected. Let all errors, blunders and other questionable goods found on board be jettisoned. And let the space thus cleared be stocked with sterling physics.

And may the men of the Navy continue their conquests, both of islands infested with Japs and of textbooks infested with errors!

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# SPECIAL ARTICLES

## FURTHER STUDIES ON THE RELATIONSHIP BETWEEN XANTHOPTERIN, FOLIC ACID AND VITAMIN M *

A NUMBER of more or less contradictory reports concerning the hemopoietic activity of xanthopterin (uropterin) have appeared in the literature in recent years. Tschesche and Wolf[1] found a reticulocyte and red blood cell increase following administration of a very small dose of uropterin to milk-anemic rats. Koschara and Hrubesch[2] stated that uropterin from the sample used by Tschesche and Wolf was assayed by Rominger and found to be entirely inactive. The effects of synthetic xanthopterin[3] and xanthopterin isolated from liver were tested in anemic salmon by Simmons and Norris.[4] Both preparations were highly active. Totter and Day[5] reported that xanthopterin

* Research paper No. 543, Journal Series, University of Arkansas. The expenses of this work were defrayed in part by a grant-in-aid from the Nutrition Foundation. Accepted for publication December 5, 1943.

[1] R. Tschesche and H. J. Wolf, *Zeit. f. physiol. Chem.*, 248: 34, 1937.

[2] W. Koschara and A. Hrubesch, *Zeit. f. physiol. Chem.*, 258: 39, 1939.

[3] R. Purrmann, *Ann. Chem.*, 546: 98, 1940.

[4] R. W. Simmons and E. R. Norris, *Jour. Biol. Chem.*, 140: 679, 1941.

[5] J. R. Totter and Paul L. Day, *Jour. Biol. Chem.*, 147: 257, 1943.

exerted a curative effect on the growth inhibition and leucopenia in succinylsulfathiazole-treated rats. We have had difficulty repeating those results, as have other workers.[6, 7, 8] O'Dell and Hogan[9] have recently stated that xanthopterin is inactive when fed to nutritionally anemic chicks (vitamin $B_c$ deficiency).

In contrast to the irregular effects with rats, xanthopterin in our hands has invariably shown beneficial effects on nutritionally cytopenic monkeys.[10, 11] Incomplete experiments[11] indicate that it not only has a curative action, but also a definite preventive effect on the cytopenia resulting from vitamin M deficiency in the macaque. The preventive effect is not permanent, however, at least in a dosage of 1 mg per day.

Koschara and Haug[12] have determined uropterin photofluorometrically in a number of organs and tissues. The amount contained in liver as reported by these authors is probably too small to account for all of the vitamin M activity exerted by fresh liver. If their method is reliable and if they examined enough representative samples there must be other vitamin M active substances besides this one. From our own observations and those of Wilson *et al.*[13] it appeared possible that folic acid[14] (vitamin $B_c$[15]) might be such a compound.

We have recently compared the folic acid content of several substances with their vitamin M activity in monkeys. The data obtained[11] show that the folic acid present (as measured by *S. lactis R* growth stimulation) can account for only a small proportion of the vitamin M activity of some of these supplements, particularly dried pasteurized brewers' yeast.

Wright and Welch[7] have obtained evidence that fresh rat liver is capable of synthesizing extra folic acid from xanthopterin. They suggest that hemopoietically active substances may be produced in the liver from xanthopterin and perhaps other compounds and they imply that these hemopoietic substances may be measured by their effect on the growth of *L. casei* ε and *S. lactis R*.

A comparison of the distribution of vitamin M with that of these potential "precursors" of folic acid should give valuable evidence concerning the validity of this hypothesis. Accordingly, samples of a brewers' yeast preparation which previously had been tested for activity in the intact monkey were incubated with fresh rat liver, fresh chicken liver and monkey

TABLE I

Folic Acid Produced by Incubating 1 Gram Samples of Liver with Yeast* and with Xanthopterin

| Series and expt. No. | Kind of liver used with folic acid content† | Substrate tested | Initial folic acid† content of substrate | Folic acid† content after incubation | Extra folic acid† produced per gram of substrate |
|---|---|---|---|---|---|
| | | | μgm | μgm | μgm |
| R1 (2) | Rat (4.2) | 500 mg yeast | 2.1 | 51.0 | 89.4 |
| (3) | Rat (4.2) | 125 μgm xanthopterin | 0 | 13.4 | 73,600 |
| R2 (23) | Rat (5.0) | 250 mg yeast | 1.05 | 25.2 | 76.6 |
| R3 (32) | Rat (1.7) | 125 μgm xanthopterin | 0 | 5.9 | 33,600 |
| R4 (44) | Rat (5.2) | 50 μgm xanthopterin | 0 | 19.0 | 276,000 |
| (50) | Rat (5.2) | 250 mgm yeast | 1.05 | 21.0 | 59.0 |
| C1 (2) | Chicken (17.0) | 100 μgm xanthopterin | 0 | 17.0 | 0 |
| (5) | Chicken (17.0) | 500 mgm yeast | 2.1 | 27.5 | 16.8 |
| (7) | Chicken (17.0) | 500 mgm yeast + 100 μgm xanthopterin | 2.1 | 33.6 | 61,000‡ |
| M1 (2) | Monkey (0.76) | 100 μgm xanthopterin | 0 | 0.92 | 1,600 |
| M2 (6) | Monkey (0.36) | 100 μgm xanthopterin | 0 | 0.36 | 0 |
| (8) | Monkey (0.36) | 250 mgm yeast | 1.05 | 3.5 | 8.3 |
| (12) | Monkey (0.36) | 250 mgm yeast + 100 μgm xanthopterin | 1.05 | 4.5 | 10,000‡ |

* "Red Label" dried brewers' yeast, Vitamin Food Company, New York.
† μgm of material of potency 40,000.
‡ Values computed in terms of xanthopterin as the substrate.

6 A. E. Axelrod, P. Gross, M. D. Bosse and K. F. Swingle, *Jour. Biol. Chem.*, 148: 721, 1943.

7 L. D. Wright and A. D. Welch, Science, 98: 179, 1943.

8 F. S. Daft and W. H. Sebrell, *Pub. Health Rep.*, 58: 1542, 1943.

9 B. L. O'Dell and A. G. Hogan, *Jour. Biol. Chem.*, 149: 323, 1943.

10 J. R. Totter, C. F. Shukers, J. Kolson, V. Mims and Paul L. Day, *Fed. Proc.*, 2: 72, 1943.

11 J. R. Totter, C. F. Shukers, J. Kolson, V. Mims and Paul L. Day, *Jour. Biol. Chem.*, in press.

12 W. Koschara and H. Haug, *Zeit. f. physiol. Chem.*, 259: 97, 1939.

13 H. E. Wilson, C. A. Doan, S. Saslaw and J. L. Schwab, *Proc. Soc. Exp. Biol. and Med.*, 50: 341, 1942.

14 H. K. Mitchell, E. E. Snell and R. J. Williams, *Jour. Am. Chem. Soc.*, 63: 2284, 1941.

15 J. J. Pfiffner, S. B. Binkley, E. S. Bloom, R. A. Brown, O. D. Bird, A. D. Emmett, A. G. Hogan and B. L. O'Dell, Science, 97: 404, 1943.

liver following the technique of Wright and Welch.[7] The monkey livers were obtained from two vitamin M-deficient animals (*Macaca mulatta*) with leucopenia and anemia. One of these (M1) had died some hours previously from intestinal obstruction, while the other (M2) died after having been given 40 mg of xanthopterin in four days in a belated attempt to prevent its death. Control experiments with liver alone and with xanthopterin added to liver were made. The xanthopterin was synthesized by the method of Purrmann.[3] Folic acid was assayed by the method of Mitchell and Snell,[16] using *S. lactis R* as the test organism. Values obtained in representative experiments are given in the table. Each series of experiments was made on one uniform batch of dispersed liver.

It can be seen from the table that yeast, which has a relatively low preformed folic acid content, is rich in the substances which give rise to folic acid when incubated with fresh liver; 15-fold or greater increases over the preformed folic acid were obtained. The high value of 89 μgm of extra folic acid produced per gram of yeast may be lower than the total amount of precursors present since it could hardly be expected that the synthesis would go to completion under the conditions of the experiment. Such a value for the precursors of folic acid is in much better agreement with the known high vitamin M content of this yeast than is the value for preformed folic acid (4.2 μgm per gram of yeast[11]).

Also supporting the belief that there is a relationship between vitamin M and the precursors of folic acid was the finding that livers from the two vitamin M-deficient monkeys were strikingly low in preformed folic acid. As predicted from our feeding experiments,[11] extra folic acid was produced from xanthopterin by the liver of the animal not receiving the pterin (M1). The small total increase may have been due to the fact that the liver was not fresh. Liver from the other animal (M2) produced extra folic acid from yeast and from xanthopterin when yeast was also added.

As expected from the finding of O'Dell and Hogan,[9] chicken liver failed to produce any extra folic acid (as measured by *S. lactis R* stimulation) from xanthopterin alone. Surprisingly, however, it produced folic acid from xanthopterin in the presence of yeast, and also from yeast alone. If folic acid is identical or isotelic[17] with vitamin $B_c$ this would seem to indicate that the *S. lactis R* method of assay is not suitable for measuring vitamin $B_c$ activity in some crude materials. The difference in behavior of livers from chickens and rats toward xanthopterin may be due to the absence of a required substance from chicken liver which is contained in variable amounts in rat livers. Such a substance is evidently present in yeast.

It would appear from our findings and those of Wright and Welch[7] that from a nutritional standpoint the determination of "potential" (preformed plus extra) folic acid may be of much greater significance than the determination of preformed folic acid.

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[16] H. K. Mitchell and E. E. Snell, University of Texas Publication, 4137: 36, 1941.

[17] For an explanation of the term "isotelic" see R. J. Williams, Science, 98: 386, 1943.

## VITAMIN A TOXICITY AND HYPOPROTHROMBINEMIA

Rodahl and Moore[1] have recently shown that the toxicity of bear and seal liver to humans may be due to a hypervitaminosis A. The effects of an overdosage of vitamin A have been studied by a number of investigators[2,3,4,5] and they are in general agreement on certain of the symptoms, which are roughening of the skin, rarefaction of bones, alopecia and profuse internal hemorrhage, often subcutaneous.

In an investigation of the mechanism responsible for the spontaneous hemorrhage caused by hypervitaminosis A, it was found that overdosage of vitamin A causes a pronounced hypoprothrombinemia. Doses of approximately 15,000 units of vitamin A per day produced a demonstrable hypoprothrombinemia in white rats within a period of ten days. Both the alcohol and the ester forms of vitamin A were fed in doses of 35,000 to 40,000 units per day, and appear to have had equal effect on the prothrombin level. Carotene in doses of 40,000 units per day was without effect on the prothrombin level in the blood.

This effect of vitamin A overdosage can be controlled by a simultaneous daily administration of vitamin K. A daily dose of 25 micrograms of vitamin K will maintain the normal prothrombin level in the blood of animals fed overdosages of vitamin A. Levels of 10 micrograms or less did not give complete protection.

One experiment will serve to illustrate the results obtained. Sixty-four white rats, having an average body weight of 135.3 grams, were divided into eight groups. Seven groups were fed a synthetic diet con-

[1] K. Rodahl and T. Moore, *Biochem. Jour.*, 37: 166–168, 1943.

[2] L. J. Harris and T. Moore, *Biochem. Jour.*, 22: 1461, 1928.

[3] K. Schuebd, *Med. Welt*, 11: 705, 1937.

[4] E. B. Vedder and C. Rosenberg, *Jour. Nutrition*, 16: 57–68, 1938.

[5] J. A. Collazo and J. S. Rodriguez, *Klinische Woch.*, 12: 1732, 1768, 1933.