individual blindness for their shortsighted policy is surely an error.

No human institution is perfect, and our patent system is a human institution. Indeed the advisory committee appointed by President Roosevelt has recommended certain minor changes in it, which informed opinion quite generally believes might be adopted with advantage by Congress, but the basic principles of that system the committee found to be sound.

Their finding seems supported by the record. With that system in force, our Nation has achieved the greatest fertility in invention and the greatest industrial progress the world has yet seen. Many a small manufacturer, protected by his patent, has built up a highly prosperous business with some meritorious specialty. Manufacturers large and small, to the number of over 2,500, relying on the patent protection they could obtain for applications of research, have founded and are profitably operating research laboratories and thereby helping in the advancement of their industries, the national economy, and scientific knowledge. As for the scientist himself, if he wishes to take advantage of the facilities offered by an industrial laboratory for research in his special field of interest and if he finds that he may do so with no sacrifice of his precious privilege of free discussion with his fellow scientists, whatever their associations may be, he should give thanks where thanks are due—to our patent system.

Theory of Reactions of Cells to Goitrogenic Thiopyrimidines

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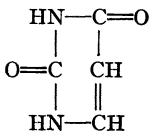
CERTAIN SULFANILAMIDES, as well as thiourea and its derivatives, have been found by Astwood (*1*) to be effective in the treatment of hyperthyroidism. One of the most potent of these derivatives is thiouracil (II). Clinical tests (*7*) on more than 1,000 patients have proved its curative value. In about 10 per cent of the patients, however, toxic reactions such as skin rashes, urticaria, fever, agranulocytosis, and leukopenia occur in the first five weeks of treatment and, as a result, a number of deaths due to the administration of thiouracil have been reported. Thiothymine (IV), or 5-methyl thiouracil, has also been tested (*10*) on rats and clinically, and found to be less effective than thiouracil in cases of thyrotoxicosis.

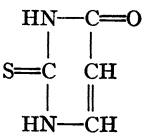
Reports by Astwood (*2*) and by Leys (*4*) have shown that alkyl substitution in the 6-position of the pyrimidine yields products which are as active, or more active, than thiouracil without any toxic reactions appearing in clinical tests. Thus, 6-normal propyl thiouracil (VI) (*2*) is about 11 times as active as thiouracil. Miller, *et al.* (*6*) showed that thiopyrimidines react with several equivalents of iodine, supporting the hypothesis that these compounds may prevent thyroid hormone synthesis in the gland by blocking the iodination of hormone precursors. They also state that these compounds may decrease iodine liberation by action on the appropriate oxidative enzymes and suggest this also as an explanation for the antithyroid action of the sulfa drugs.

We would like to go somewhat further in explaining the action of the mercaptopyrimidines, basing the explanation on the available evidence. We would postulate that thiouracil and thiothymine, in addition to reacting with iodine, act as antivitamins or antibiotics. The term "antibiotic" is used here somewhat more generally than may be customary, for lack of a better way of expressing the effect of any agent whose presence interferes with or prevents normal cell proliferation *in vivo*. The cells may be those of microorganisms foreign or injurious to the host, or cells of the body tissues or circulatory system of the host proper.

Snell and Mitchell (*8*) have proved uracil to be an essential metabolite for the growth of microorganisms, very strongly suggesting vitamin action. Similarly, thymine (*9*) can partially replace folic acid as an essential nutrilite for lactic acid bacteria. The structural similarities of uracil (I) and thiouracil (II) and of thymine (III) and thiothymine (IV) are shown below.



(I)



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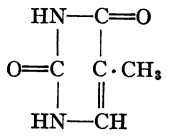

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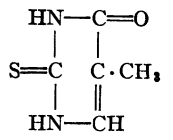


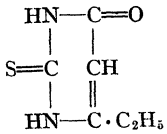
(IV)

The conversion of a vitamin or an essential nutrilite

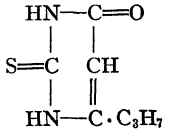
to an antivitamin or antibiotic by alteration of the chemical structure of the vitamins has been demonstrated by Woods (*11*) for para-aminobenzoic acid and sulfanilamide; by Woolley and White (*12*) for 2-methyl-4-amino-5-pyrimidylmethyl-(2-methyl-3-hydroxyethyl) pyridium bromide and vitamin B_1; and by McIlwain (*5*) for pyridine-3-sulfonic acid and nicotinic acid.

The toxic reactions of thiouracil and thiothymine *in vivo*, especially the incidence of agranulocytosis and leukopenia, bear a marked resemblance in this respect to the toxic action of sulfanilamide, another antivitamin (*11*). Apparently, with some individuals these drugs interfere with the normal metabolism of certain body cells such as leucocytes, and even those occurring in the thyroid gland (*6*).

It would seem as if a competition for thiouracil and thiothymine between iodine and other compounds which normally react with uracil and thymine occurs *in vivo*. This is borne out by the fact that 6-ethyl thiouracil (V) and 6-normal propyl thiouracil (VI) (*2*) are



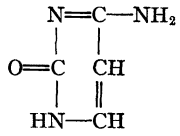
(V)



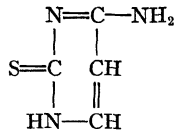
(VI)

8 and 11 times more effective, respectively, than equivalent amounts of thiouracil and exhibit no toxic reactions when tested clinically. Evidently these two mercaptopyrimidines have had their chemical structure sufficiently altered to react wholly with iodine, hence showing only a goitrogenic action and no antibiotic tendency.

It is of interest to note that uracil occurs only in ribonucleic acid and thymine only in thymus nucleic acid. Both nucleic acids occur in normal cells; thymus nucleic acid, only in cell nuclei; ribonucleic acid, in both nucleus and cytoplasm. A pyrimidine which occurs in both nucleic acids is cytosine. It might be predicted, therefore, that while thiocytosine (VIII), structurally analogous to cytosine (VII), would exhibit antithyroid



(VII)



(VIII)

action, it might also be more toxic or show greater antivitamin action than either thiouracil or thiothymine, because structurally it is analogous to cytosine, a building block in not only one but two fundamental cell components.

While these mercaptopyrimidines have been tested *in vivo*, no study has been made to assess their value as antivitamins with microorganisms. Hitchings, *et al.* (*3*) report one test at low concentration on the effect of thiothymine on *L. casei* with inconclusive results.

A thorough study of the action of thiouracil, thiothymine, and especially thiocytosine on a variety of microorganisms including pathogenic forms might be of interest not only to see if antivitamin or antibiotic activity is a characteristic of these sulfur-bearing pyrimidines, but also to obtain evidence of the importance of the normal oxycompounds to cell metabolism. Such a study might also reveal in mercaptopyrimidines and their homologues and derivatives a new class of compounds with antiseptic properties for external use.

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Section E (Geology and Geography) is planning to schedule sessions at the Chicago meeting of the AAAS, on Friday and Saturday, December 26 and 27. Several special sessions are now in the planning stage. Any suggestions concerning the section program should be sent to G. W. White, secretary, Section E, Orton Hall, Ohio State University, Columbus 10, Ohio. Titles of papers offered for presentation at the meeting should be sent to the secretary by May 1, except for papers now being arranged by the various symposium organizers.