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CURRENT PROBLEMS IN RESEARCH

Antimetabolites

They help in discovery of metabolic pathways and in the understanding and treatment of some diseases.

D. W. Woolley

In recent years much study has been directed at the antimetabolites. These compounds have two distinguishing features: (i) they resemble in chemical structure some naturally occurring compound which is essential in living processes, and (ii) they specifically antagonize the biological action of such an essential compound. The vitally essential compounds have been called "essential metabolites" and are exemplified by the vitamins, the hormones, and certain other substances. The net result of the interference of the antimetabolite with the essential metabolite is to bring about a deficiency of the essential metabolite. The consequences of such a deficiency may be far-reaching for the organism and may bring about its death. These effects can, however, be beneficial, and it is this fact which has led to the use of the antimetabolites in attempts to treat disease.

The purpose of this article is to give some indication of what the antimetabolites are, and of the sort of thing that is being done with them, both in the elucidation of the mechanisms by means of which living things carry out their physiological reactions, and in the practical applications to the treatment of disease. This article is not intended to be a critical review of the field or an adequate summary of it. Several monographs are available, such as that of Woolley (*1*) or of Work and Work (*2*) if a more comprehensive discussion is desired. Only the bare elements can be mentioned here.

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Enzyme Function

To understand what an antimetabolite is, we must recall how an enzyme functions. An enzyme is believed to bring about the specific chemical reaction which it catalyzes by combining reversibly with its particular substrate. For many of the enzymes this specific substrate is one of the essential metabolites such as a vitamin, a purine, or an amino acid. The unstable enzyme-substrate complex which is thus formed undergoes some sort of molecular rearrangement or fission which yields the products derived from the substrate plus the enzyme. The cycle is then repeated because the enzyme has not been consumed in the process. The enzyme usually has two substrates instead of one, but this does not alter the mechanism now under discussion, since for the second substrate one conceives of the same basic process, but of a different combining site in the protein.

The specificity of the enzyme depends on its ability to combine with a given substrate, and not to combine with unrelated substances. The nature of the combining groups of the enzymes is one of the most fascinating puzzles of biochemistry. Some beginnings have been made in understanding the chemical structures of such combining groups of a few enzymes, but for none is it yet possible to write an adequate structure. It must be for each enzyme a configuration such as to form a reversible, dissociable union with a specific compound (the substrate) and not with many other substances.

In addition to its substrate, an enzyme usually will combine reversibly with a few structural relatives of the substrate. If the relative is of the same general structure (shape) and has some of the functional groups which are also present in the substrate, the fit is frequently good enough so that the analog will combine with the specific site in the enzyme. This is the first requisite of an antimetabolite. It must "look like" the substrate to the enzyme; in other words, the enzyme will combine with it in the same fashion as it does with the substrate. The structural analogy with the substrate is the important concern.

When the analog (the antimetabolite) has combined with the active site of the enzyme, this site is occupied so that the normal substrate cannot combine. The result is the exclusion of the substrate from its normal role and the creation of a deficiency of it. If the substrate is a vitamin or a hormone, a characteristic deficiency disease may thus be produced by the antimetabolite.

If the union between analog and enzyme is reversible, then an increase in the concentration of the substrate will allow the analog to be displaced. A deficiency disease induced by an antivitamin can thus be prevented or cured merely by an increase in the amount of vitamin in the food. The ratio between analog and essential metabolite which just allows the metabolite to displace the analog is different for each pair of compounds and each enzyme. What determines the ratio required is the relative combining affinities of substrate and analog for the enzyme. Almost always the enzyme prefers the substrate to the analog, so that much more antimetabolite than essential metabolite is required in order to produce a biological effect of the analog. However, it has been possible

to construct antimetabolites which the enzyme prefers to its normal substrate, and these are very potent compounds in biological test systems.

The second essential point about a compound which makes it an antimetabolite, then, is the ability to antagonize some of the biological effects of an essential metabolite. To call forth the characteristic signs of a deficiency disease is thus an important property of a compound if it is to be considered an antimetabolite. If, in addition, the biological effects can be reversed by the essential metabolite, the evidence is considerably strengthened. However, it is not necessary that a demonstration be made of the ability of a metabolite to reverse the effects of an antimetabolite, despite the fact that this is a point about which much argument has raged. Some have maintained that without the demonstration of reversibility a compound cannot be considered to be an antimetabolite. The plain fact is that one can construct an analog of some essential metabolite in such a way that it will be attracted specifically to the combining site of the enzyme and will react with this site irreversibly rather than reversibly. Once this has happened, no amount of extra essential metabolite will dislodge it. As might be expected, such irreversible analogs have frequently proved to be of high potency, since they have such an avidity for the enzyme. Some of the antimetabolites now used in the treatment of certain diseases are such irreversibly acting compounds. Aminopterin (Fig. 1), which is used with more or less success in the treatment of childhood leukemia, is such an example.

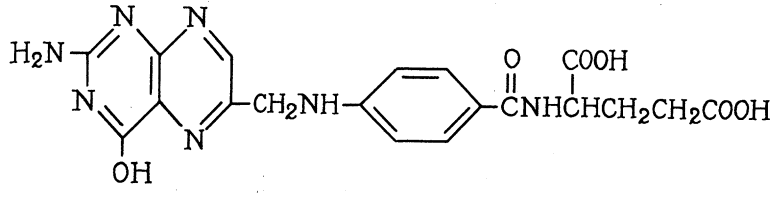
Conversion of Analogs

Sometimes the analog combines with the enzyme but, instead of stopping things at this stage, is actually converted into products analogous to those formed from the normal substrate. In other words, the enzyme uses the analog much as it does the natural substrate. The unnatural products formed may now act in the usual way to inhibit the next biological reaction in the physiological pathway. This has been shown to happen with certain analogs of purines and pyrimidines which go into the formation of nucleic acids.

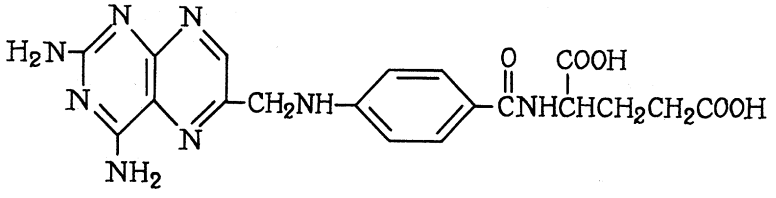
Thus, 8-azaguanine (Fig. 2), an analog of guanine, is incorporated into the nucleic acids of bacteria, viruses, and certain other forms of life. The nucleic acids of tobacco mosaic virus can thus be made to contain this unnatural substance. Some evidence suggests that this unnatural virus fails to function normally in the infection of the host plant, although this point is not entirely clear. Similarly, the pyrimidine thymine of the deoxynucleic acid of certain bacteria (*Escherichia coli*) can be partially replaced by the analogous 5-bromouracil (Fig. 3). The unnatural nucleic acid is then passed on for generations with each cell division, but the organisms so produced tend to form abnormal (pleomorphic) cell bodies, and to be at other disadvantages.

In like fashion, antimetabolites of some of the amino acids may be incorporated into proteins, as has been demonstrated with analogs of methionine and of phenylalanine. The analog *p*-fluorophenylalanine is thus incorporated into proteins of rabbits or microorganisms. One of these unnatural proteins has recently been isolated in crystalline form and shown to possess normal enzymatic activity (aldolase). In this case, therefore, the unnatural product formed from the analog functions in some respects as well as the natural one. It must be that some of the other unnatural products also formed do not function so well.

We must not think that these findings of incorporation of analogs mean that all antimetabolites function by being passed through the metabolic chain of reactions usually followed by the substrate. In many instances, no evidence for such incorporation has been found, despite concerted search. In other instances, such incorporation reactions are impossible because of the chemical structures of the analogs. Such, for example, is the case with malonate acting as an antimetabolite of succinate. The incorporation reactions are variations of the major theme of antimetabolite action. However, it is important to remember that they do occur, because it shows that an analog can often function in place of the real substrate. The specificity of enzymes is not as exquisite as is sometimes thought.



Folic acid



Aminopterin

Fig. 1. Structures of folic acid and aminopterin.

Sulfanilamide and Pyrithiamine as Antimetabolites

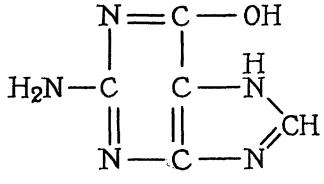
Two classical examples of antimetabolites can be used to illustrate the basic phenomenon. One of these is sulfanilamide as an antimetabolite of *p*-aminobenzoic acid, and the other is pyrithiamine as an antimetabolite of thiamine. Sulfanilamide, the structure of which is shown in Fig. 4, was developed rather empirically as a drug able to control some bacterial infections in man and other animals. Several years after its usefulness had been established, D. D. Woods in 1940 was studying why it inhibited bacterial growth and observed that its harmful effects on microorganisms could be overcome with small amounts of *p*-aminobenzoic acid. Woods was fully aware of the structural resemblance of sulfanilamide to *p*-aminobenzoic acid, and, in fact, had been led to test *p*-aminobenzoic acid because of the structural resemblance. He predicted that *p*-aminobenzoic acid would be found to be an important compound in the metabolism of bacteria, and this prediction was soon amply substantiated.

Not only did *p*-aminobenzoic acid

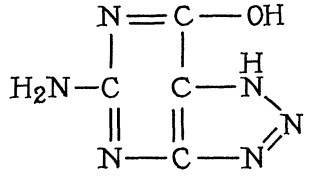
prove to be present in many living things in a combined form, but for some it was a dietary essential—that is, it was a vitamin. One of the combined forms into which it was built in living things also proved to be an important substance, namely, the vitamin known as folic acid (folacin or pteroylglutamic acid. See Fig. 1.) It has been demonstrated that in bacteria which are inhibited by sulfanilamide, the formation of folic acid and its derivatives is prevented. The enzyme system which makes this essential metabolite (folic acid) from *p*-aminobenzoic acid seems to be inhibited by sulfanilamide. For this enzyme system, *p*-aminobenzoic acid is the specific substrate, and this competes with the sulfanilamide for the enzyme system.

Sulfanilamide does not induce a deficiency of *p*-aminobenzoic acid in higher animals, in contrast to its action on some bacteria. The reason for this is not entirely understood, but seems to be related to the fact that the animals cannot synthesize folic acid, whereas the bacteria can. For the animals, then, folic acid is a vitamin which they must get from their food, but not for the bacteria which can make their own. It is the stoppage of this manufacturing of folic acid which is part of the mechanism of action of this drug. It is also intimately associated with the reason why the drug is selectively toxic and harms the bacteria without poisoning the host animal.

The original observation of Woods of the antagonism between sulfanilamide and *p*-aminobenzoic acid in bacterial

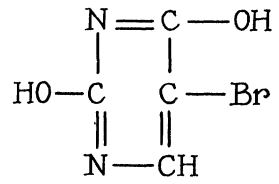


Guanine

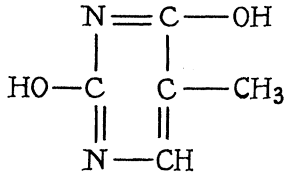


8-Azaguanine

Fig. 2. Structures of guanine and 8-azaguanine.



5-Bromouracil



Thymine

Fig. 3. Structures of 5-bromouracil and thymine.

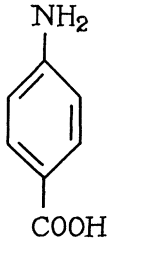
growth was a landmark in the study of antimetabolites. There had been other prior observations of antagonisms between structurally related compounds, but they had not been widely heeded or understood. Because sulfanilamide was a popular, and, at that time, the best therapeutic agent for the control of several infectious diseases of man, the full impact of Woods' demonstration was heeded.

The second example, that of pyrithiamine as an antimetabolite of thiamine (vitamin B_1), is of interest because it was discovered through the use of higher animals. The characteristic signs of dietary lack of thiamine were well known in laboratory animals such as mice, chickens and pigeons, and were thus readily recognizable. This was different from the signs of a deficiency in bacterial cultures, because with the microorganisms one has principally the failure of growth to indicate disease, and failure of growth may be caused by many things. The induction of characteristic signs of a vitamin deficiency disease in animals thus indicates more clearly what one is dealing with.

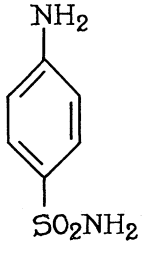
In 1943 pyrithiamine was shown to induce the characteristic signs of thiamine deficiency in mice. The structures of antimetabolite and vitamin are shown in Fig. 5, where it can be seen that the relationship is close indeed. The deficiency disease caused by the eating of pyrithiamine could be cured or prevented by increasing the thiamine content of the food, so that the antagonism proved to be of the competitive kind. These same kinds of demonstrations were made with many kinds of microorganisms, as well as with higher animals. Thus, the addition of pyrithiamine to the culture media for several species of bacteria and fungi caused inhibition of growth, and this could be overcome merely by increased thiamine in the solutions.

It is not necessary to use living organisms or even organized tissues to observe the antagonism between metabolite and antimetabolite. The phenomenon can be studied in isolated enzyme systems, provided that the enzyme concerned can be separated from living tissue. This separation is not always possible, but in several cases where it has been acomplished the antagonism of the structurally related compounds has been shown.

A large number of antimetabolites are now known. The two examples just mentioned were selected principally for their historical importance, but many others could have been used. In fact, there are antimetabolites for each of the vitamins (except A and D), for several hormones, for most of the amino acids, purines, and pyrimidines, and for some of the other essential metabolites of living things. The methods of testing for the antagonistic actions of these compounds are also varied. The variation is as great as is the divergence in methods of assay for biologically active constituents of



p-Aminobenzoic acid



Sulfanilamide

Fig. 4. Structure of *p*-aminobenzoic acid and sulfanilamide.

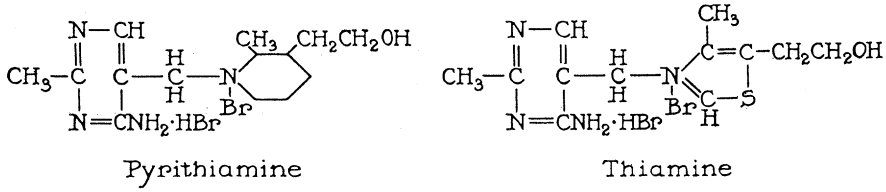


Fig. 5. Structures of pyrithiamine and thiamine.

living matter, because it is the interference in the assay procedure for a given metabolite which is usually used to demonstrate the activity of the antimetabolite.

Importance of Antimetabolites for Theory

The antimetabolites are of importance from a theoretical standpoint for several reasons. Through the use of a suitable antimetabolite, a specific deficiency can be created in a living organism. From the biochemical, anatomical, and functional changes which then arise, much information has been gained about the function of a given essential compound. Furthermore, when the changes induced in an animal in this fashion are seen to resemble the signs of a well-recognized but etiologically poorly understood disease, the cause of the disease may be suggested. This is a use of antimetabolites which is being much studied at the present time in the unraveling of the causation of certain mental diseases.

In addition, the demonstrations that some antimetabolites occur naturally, frequently in the same individual in which the metabolite also occurs and functions, has given considerable insight into the regulatory mechanisms at work in a living organism. Some of the "feedback mechanisms" by means of which cells check certain processes of synthesis, and thus prevent the useless accumulation of excessive amounts of their constituents, have been shown quite recently to be of this general kind. The finished molecule from a series of biochemical reactions frequently, because of its structural resemblance to one of the starting materials, is able to inhibit the enzyme which first directs this starting material through the metabolic pathway. These control mechanisms seem to offer a fertile field for future investigation along these lines.

The natural ocurrence of certain antimetabolites also has indicated the nature of some diseases. Thus, for example, a disease of tobacco plants, the so-called wildfire disease, which is the result of infection of the plant by a pathogenic bacterium (*Pseudomonas tabaci*), is caused by a toxin which this invader liberates. The toxin has been isolated in pure condition and shown to be an antimetabolite of methionine. The disease thus seems to be the expression of a methionine deficiency produced in the host by the invading pathogen.

Finally, the existence of antagonism between structurally related compounds is having a considerable influence on the course of thinking about the active sites of enzymes and hormonal receptors. People are beginning to explore the idea that these may have a structural resemblance to the specific essential metabolites with which they combine. This idea is motivating much of the research in this important and fascinating subject at the present time. The attraction (perhaps due to Van der Waal's forces) which exists between like groups of atoms may be the binding force which confers the specificity and provides the force of union in these cases. Let us then discuss briefly a few examples (in addition to those just indicated) of these uses of antimetabolites in theoretical science.

The original clues about the reactions by means of which purines are synthesized by living organisms came from the use of antimetabolites. When bacteria such as *Escherichia coli* are grown in an amount of sulfanilamide just sufficient to cause slight inhibition of growth, they form a new compound, which was isolated and characterized as 4-amino-5-carboxamidoimidazole. (See Fig. 6). Sulfanilamide inhibits the synthesis of folic acid from *p*-aminobenzoic acid, and there was evidence to suggest that folic acid participated in the biosynthesis of the purines. It was therefore not surprising to find that an antimetabolite of folic acid also caused accumulation of this imidazole. All that is required to convert the imidazole to the purine hypoxanthine is the insertion of a carbon atom by means of a reaction with formic acid. It thus became plain that the pathway

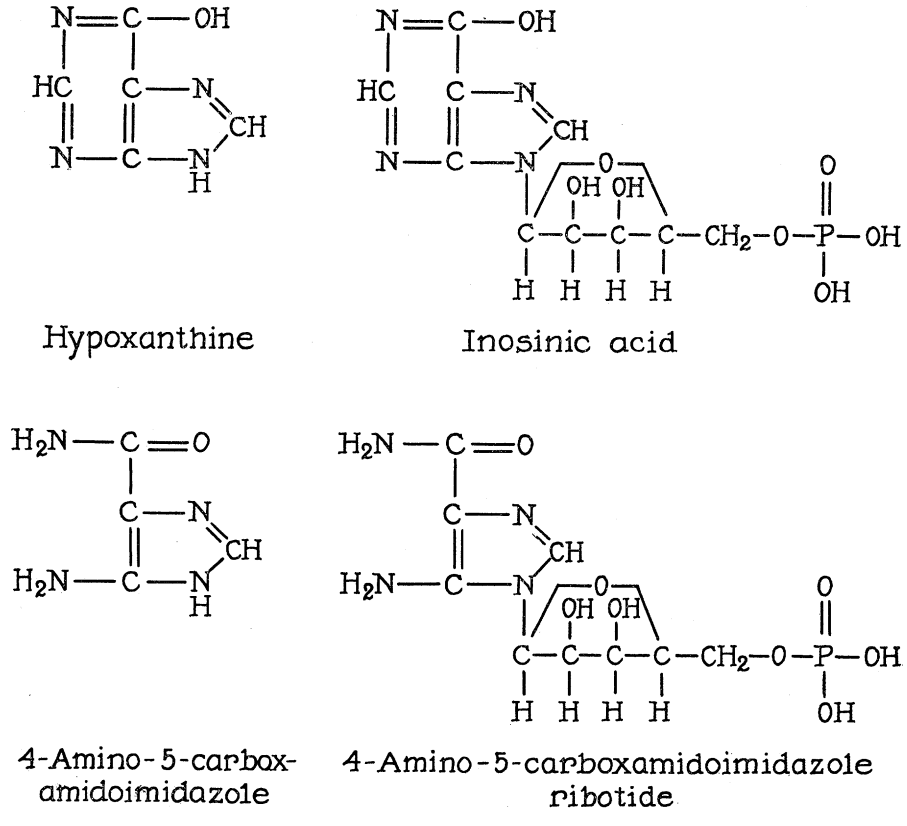


Fig. 6. Structures of hypoxanthine, inosinic acid, and the imidazole precursors.

of purine biosynthesis was to the formation of the imidazole derivative followed by insertion of a formyl group to yield the purine ring.

Prior to this work with sulfanilamide, the existence of such a pathway, or even of the imidazole derivative, in living things had not been indicated. More detailed investigation of these reactions with radioisotopes and by classical enzymology has shown that the ribotide of the imidazole is the real precursor, and that inosinic acid (hypoxanthine ribotide), rather than hypoxanthine itself, is the product. Other purines can be derived from inosinic acid by suitable enzymic steps. It is not without interest that the participants in some of these additional steps were also detected partly through the use of antimetabolites of them. The understanding of the biosynthesis of this group of biologically very important compounds was thus discovered to a considerable degree by the use of suitable antimetabolites.

Serotonin

The use of antimetabolites to elucidate the cause of noninfectious diseases could be illustrated by any one of several examples, but the one having to do with schizophrenia will serve to show the way it is done. Serotonin is a recently discovered hormone which causes smooth muscles to contract. Its chemical structure is shown in Fig. 7. It is an essential metabolite which is found in certain tissues such as the argentaffin cells of the stomach and intestines, in the platelets of the blood, in certain portions of the brain, and in some ganglia of the peripheral nervous system.

Antimetabolites of serotonin were synthesized recently with the idea in mind that these, when given to animals, would induce specifically a deficiency of serotonin, and that the changes thus incited might reveal some of the purposes for which an animal has this hormone.

There was also a practical reason for making these antimetabolites, which will be discussed presently. Some of these antiserotonins were found to call forth in animals and in men a kind of behavior similar to that seen in mentally deranged individuals. Certain other neurological disturbances were also called forth by some of these compounds. Thus, the nitroindole analog shown in Fig. 7 brought about a change in character of mice and induced deep mental depression in human beings. The analog medmain shown in Fig. 7 incited convulsions in mice which were reminiscent of the seizures of *grand mal* epilepsy in man. Such findings suggested strongly that serotonin had a role to play in the central nervous system which was associated with the maintenance of normal mental equilibrium and normal behavior.

While this work on the synthetic analogs of serotonin was in progress, it was shown that several classes of drugs which had been long known and traditionally obtained from plants were in fact structural analogs of serotonin and were capable of antagonizing the actions of this hormone in a reversible fashion on smooth muscles. It was thus clear that these drugs were naturally occurring antimetabolites of serotonin. Harmine and its relatives, yohimbine and its relatives, and the ergot alkaloids were the drugs so studied (Fig. 7). It was further noted that at least one member of each of these series of drugs was well known to induce in normal men a temporary condition resembling schizophrenia, with its visual hallucinations and changes in personality.

This ability of naturally occurring as well as of synthetic antimetabolites of serotonin to induce some of the signs of the mental diseases led Woolley and Shaw in 1954 to suggest that the natural disease commonly called schizophrenia was the reflection of a disturbance in the functioning of serotonin in the brain. This suggestion has been much debated recently, but it can be said that a considerable body of supporting evidence has been produced. One such piece of evidence which has received much attention is the finding that a drug which clearly affects the mind, namely, the tranquilizer known as reserpine, is a structural analog of serotonin, being a derivative of yohimbine. It behaves in some respects as an antimetabolite of this hormone.

Just as with the early finding of the antagonism between sulfanilamide and *p*-aminobenzoic acid, the fact that reserpine (like sulfanilamide) was a drug being widely used in the clinical treatment of a disease counted for more in men's minds than did prior demonstrations of the same fact with chemical compounds which were not being used as fashionable drugs. In the serotonin case, in contrast to the situation with sulfanilamide, the ideas and evidence had been clearly enunciated before the demonstrations with the practical drug. And yet the findings with the practical drug were the ones which seemed to carry more weight in most minds.

The evidence for the participation of serotonin in mental disorders is not yet complete. Work in this direction is going on actively at the present time. If it should prove possible to control adequately the disease as a result of the suggestion that serotonin plays a role in it, then we must say that the causation of this disease, or at least an etiological agent in it, was discovered through the use of antimetabolites.

The work which showed that several kinds of well-known drugs of plant origin were acting on animals as antimetabolites of serotonin, as outlined above,

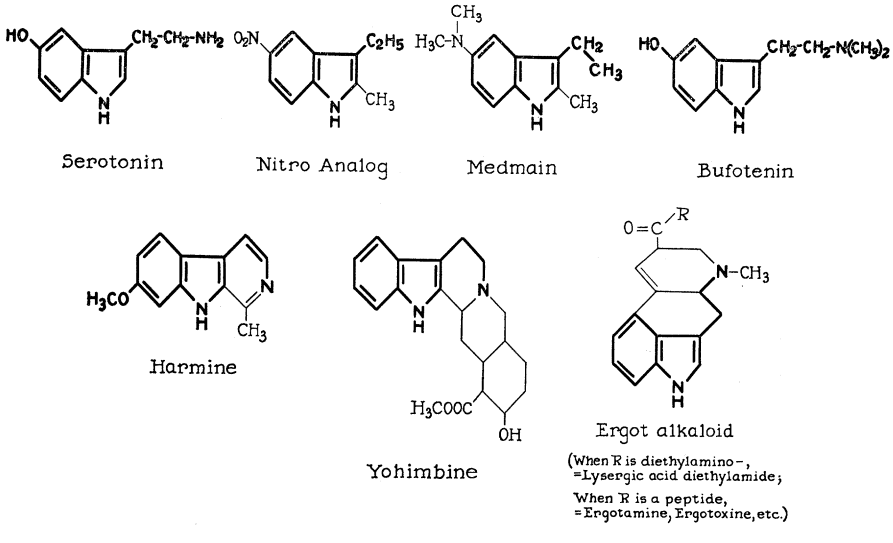


Fig. 7. Structures of serotonin and some psychosis-inducing antimetabolites of it.

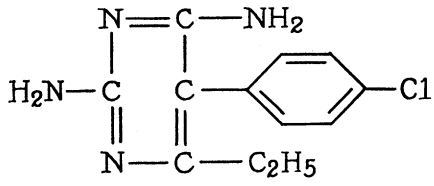
points to another use of the antimetabolite concept. The mechanism of action of these plant alkaloids, or at least a part of that mechanism, was made clear by these studies. These alkaloids act by creating a deficiency of the hormone serotonin in certain tissues. It must also be added that on some tissues some of these compounds act like serotonin, instead of being antagonistic to it. In these tissues the analog seems to fit the serotonin receptors well enough to function in its stead. I have shown earlier in this article how an analog may be near enough in structure to the essential metabolite to act as a substitute for that metabolite in some reactions.

Antimetabolites and Chemotherapy

In addition to the uses of antimetabolites in solving questions of theory, uses of a practical kind have been envisioned, and some have been found. These are the uses in chemotherapy of infectious and noninfectious diseases. After the demonstration of the antagonism between sulfanilamide and *p*-aminobenzoic acid there was a wave of enthusiasm, because it was held that the control of infectious diseases by rational rather than chance means was just around the corner. All that would be required would be to make a suitable antimetabolite of some bacterial growth factor.

This proved to be an oversimplification. No attention was paid to the question of how to make drugs of this sort which would not poison the host animal as well as the parasite. No attention was paid to many other important considerations. This, and the fact that the empirical approach through the search for antibiotics paid off so well in the discovery of new drugs for the control of infections, made many turn away from the antimetabolites as a practical solution. This was especially so among those looking for drugs with which to control infections.

Despite this, however, some noteworthy results were achieved, principally in the suppression of malaria. Two kinds of antimetabolites were found effective, firstly, some of the antipantothenic acids, and secondly, certain antifolic acids. The antifolic acids are now being used on a rather considerable scale in some equatorial countries. For this purpose, daraprim, shown in Fig. 8, is the compound most used. It is not a close structural analog of folic acid but appears to be more closely related to thymine, a pyrimidine which is formed in living things through the participation of folic acid. Nevertheless, existing evidence seems to suggest that daraprim is more of an antifolic acid than an antithymine.



Daraprim

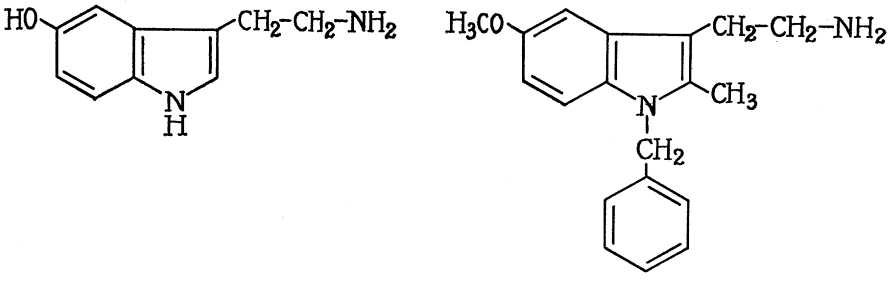
Fig. 8. Structure of daraprim.

Among investigators dealing with noninfectious diseases, the antimetabolite concept has been somewhat more popular as a means to the discovery of therapeutic agents. Among those attempting to control cancers, this has been particularly true, but among students of endocrine disorders there are also those who have had some success in its application.

A few of the concepts should concern us here. If a disease arises, as some do, from an excessive amount of a given hormone in the body, it should be possible to control this disorder by administration of a suitable antimetabolite of the hormone. For example, suppose that an excess of serotonin were to arise in the body, either as the result of too great a production or too slow destruction of it. One can measure some of the effects of such an excess merely by injection of some of the hormone. One does not thus see all of the possible effects, but does see some. One feature of injection of serotonin into man is an increase in blood pressure. This is probably the result of the contraction of the smooth muscle of the walls of the arteries and arterioles. Such increases in blood pressure can be prevented by administration of a suitable antimetabolite of serotonin. If, then, some of the cases of human hypertension are related to an excess of serotonin in the body, such an antimetabolite would be expected to bring about a reduction in blood pressure in the disease. It is by no means established that some cases of human hypertension do result from an excess of serotonin, but the reduction of pressure in such patients would be evidence to suggest it as an etiological agent. Especially would this be true if it were found that the antimetabolite did not reduce blood pressure in normal human beings.

The antimetabolite of serotonin shown in Fig. 9 was synthesized and tested in human hypertension with the idea in mind that the disease in some individuals might be the expression of an excess of serotonin. The compound was found not to reduce the blood pressures of normal animals and men, but did bring about such reduction, and other beneficial effects, in a considerable number of people suffering from high blood pressure.

Because of the ability of certain antimetabolites of serotonin to induce mental changes, one may wonder how it was possible to use this antimetabolite safely. The drug was found not to induce the mental changes which are called forth by many other antiserotonins. This resulted, not simply from a lucky chance, but because, in fact, the drug was designed with the intent of keeping it out of the central nervous system. In so far as has been determined, it passes into the brain only with great difficulty, and possibly for this reason it does not cause mental disturbances. We thus see that many factors related to distribution of a drug through the tissues may be of great importance in the designing of therapeutic agents. The antimetabolite concept tells something about the de-



Serotonin

1-Benzyl-2,5-dimethyl-serotonin
Benzyl analog of serotonin(BAS)

Fig. 9. Structure of serotonin and a benzyl analog of serotonin.

signing of drugs but it does not tell all.

There seem to be many disorders which arise from excesses of this or that hormone. The possibility of controling some of these in the manner indicated seems enticing. Especially is this so when it begins to become clear that several drugs which have been discovered and used empirically for the control of certain disorders are in fact antimetabolites of some hormone or other essential metabolite.

The practical applications of the antimetabolites to attempts at chemotherapy could have been illustrated equally well with a variety of other drugs which have been introduced recently. None of these is completely satisfactory from a practical standpoint, and there are still those who maintain that it is unlikely that this record can be improved. The examples chosen were selected because they are well known to me and because they indictate the status of the field as it exists today.

References

1. D. W. Woolley, *A Study of Antimetabolites* (Wiley, New York, 1952).
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CURRENT PROBLEMS IN RESEARCH

New Research on Old Gravitation

Are the observed physical constants independent of the position, epoch, and velocity of the laboratory?

R. H. Dicke

While fully aware of the hazards, both natural and occult, incident to the discussion of experiments not yet completed, I welcome the opportunity to say something about our research on gravitation, particularly about its motivation, for there appears to be considerable misunderstanding of the state of knowledge of this important force field.

With the exception of a few isolated experiments, there has been essentially no basic experimental research on gravitation in the past 30 years. There are several reasons for this. First, because of the weakness of the gravitational field, such experiments are invariably difficult, and many of the most important are impossible. Second, because of the successes as well as the basic simplicity and elegance of Einstein's relativistic theory of gravitation, the feeling has been widespread that this theory must be correct. Third, it has been generally believed by physicists that the gravitational interaction is too weak to be important for modern physics.

Needless to say, my coworkers and I do not agree with this diagnosis. First, new experimental techniques now make possible experiments formerly impossible. Second, while Einstein's theory is admittedly elegant, we are not sure that nature has quite the predilection for an elegant theory that man apparently possesses. Third, although gravitation is weak, it may play a crucial role in the structure of a particle. If, as is believed by many physicists, an elementary particle is a complex structure of very small size consisting of a core particle surrounded by a swarm of attendant virtual particles, the gravitational interaction may be one of the dominant forces acting on very-high-momentum particles found at the core. It has been suggested that it is the failure to take into account such interactions which is the root of the difficulty leading to divergences in quantum-field theories.

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Observational Evidence for Theory of General Relativity

The experimental and observational support for Einstein's theory of general relativity consists primarily of facts available before the construction of the theory. These consist of the large body of data on planetary motion, including the anomalous rotation of the perihelion of Mercury's orbit. There is also the accurate experiment of Eötvös (*1*) and others on the equivalence of inertial and gravitational mass. The only observational facts found subsequently are the gravitational deflection of light by the sun and the gravitational red shift. Because of the smallness of these effects, both of these checks of the theory of general relativity are inaccurate. The astronomical observations of planetary orbits are very accurate; however, a comparison between the observed orbits and calculated orbits always shows small systematic discrepancies (*2*). The discrepancies are believed to be due primarily to computational errors and systematic errors in observation. While this may be true, there is always the possibility that some of the systematic error may be of a more fundamental character. It should also be remembered that the velocities of the planets are so low that gravitational retardation effects are essentially unobservable.

Conceptual Difficulties

In addition to dissatisfaction with the scanty observational evidence supporting Einstein's theory of gravitation, there are certain conceptual difficulties which are a source of doubt concerning the complete correctness of the theory in its present form. These difficulties are associated with the problem of inertial coordinate systems and the existence of inertial forces.

In the mechanics formulated by Newton in the 17th century it was assumed that there existed an absolute physical space which could be characterized by a Euclidean geometry. An acceleration of a particle with respect to this space required a force. Equivalently, in the accelerated coordinate frame for which this particle was at rest, there appeared an inertial force acting upon the particle.

This situation long appeared enigmatic, and some of the difficulties were