FARMER VICTORIOUS

MONEY, MART, AND MOTHER EARTH

BY WILLIAM J. HALE

CHEMOTHERAPHY

The use of specific chemical compounds to combat specific human ailments has long been the goal of the biochemist. The Incas of Peru had early hit upon cinchona bark extract for relief against malaria, and by 1639, this "quinine" was introduced into Europe. Though only partially effective it gave abundant indication of the manner in which certain chemicals may serve as specifics. Somewhat later this dreaded malaria, resulting from infection with the protozoan Plasmodia as transmitted by the female of the Anopheles mosquito, was brought up against two synthetic antimalarials—Schulemann's "Plasmochin" of quinoline base in 1926, and "Atebrin" of acridine base in 1930 by Mauss and Mietzsch, all from the I. G. Farbenindustrie laboratories.

But practically speaking, chemotherapy had its inception in the work of Ehrlich. In the application of various dyes for staining tissues Ehrlich, in 1907, modified benzopurpurin into an azo dye, Trypan Red, and found it effective in mice against trypanosome parasites—thereby constituting the first synthetic chemotherapeutic agent. Thus Ehrlich came to describe chemotherapeutic agents as possessing various degrees of specificity against protozoal and bacterial invaders in animals without injury to the host.

The appearance of Ehrlich's "arsphenamine" (Salvarsan) in 1910 marks the beginning of a new day in Medicine.

In 1913 Eisenberg discovered that the azo dye Chrysoidine (2,4-diamino azobenzene) was bactericidal in vitro; on December 25, 1932, Mietzsch and Klarer of I. G.

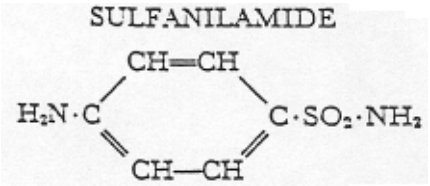
Farbenindustrie were granted a German Patent on Sulfonamido-chrysoidine or Prontosil. In 1932 Gerhard Domagk of the Institute of Experimental Pathology of I. G. Farbenindustrie at Elberfeld, Germany, proved that Prontosil was relatively nontoxic yet protected mice against hemolytic streptococcal infections—in fact his experiments were perfect: 100 percent of the mice infected came through alive. Strangely enough, Domagk showed that Prontosil displayed no bactericidal action in vitro to quote him: "It acts as a true chemotherapeutic agent only in the living animal." The announcement of these discoveries was not made until February 15, 1935.

Next in turn, the French took up the problem of ascertaining what part of Prontosil carried the effective group. Mr. and Mme. Trefouël, Nitto, and Bovet at the Pasteur Institute in Paris soon reported that Prontosil underwent a dissociation in animal tissues to yield para-aminobenzene sulfonamide. Whereupon Professor Fournenu of the same Institute prepared pure p-amino benzene sulfonamide (sulfanilamide) and tested it against streptococcal infections in mice and rabbits and found it just as effective as Prontosil, thus proving that the double-nitrogen or azo linkage (the dye-forming linkage) possessed no therapeutical value.

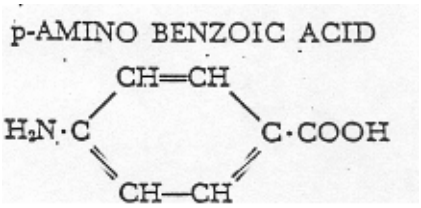
In England, Buttle, Gray, and Stephenson, in *Lancet* for June 6, 1936, confirmed the results of the French Scientists and undertook the synthesis of a large number of derivatives of the active p-amino benzene sulfonamide.

Eventually American biochemists awoke to the significance of this new synthetic. Drs. Perrin H. Long and Eleanor A. Bliss of Johns Hopkins Medical School led the way to far-reaching researches in this field. The first publication in this country was of January 2, 1937, in the *Journal of the American Medical Association.*

From the Lederle Laboratories came the announcement last year of a new sulfa drug called Phenosulfazole. This new drug, known also as Darvisul, has proved to be effective against poliomyelitis in mice and is now under test on humans at Columbia University.



The remarkable results securable by sulfanilamide against modern scourges may be measured by the reduction of pneumonia fatalities from 30 percent a decade ago to less than 10 percent today. The entire gamut of sulfanilamides is now known to interfere with the nutrition of bacteria setting up a virtual bacteriostasis. As bacteria require p-amino benzoic acid, a factor in the vitamin-B complex, they are confronted here with a closely analogous structure, and when once fixed by sulfanilamides, have no other recourse than starvation.



Likewise, these sulfa compounds, as well as thiourea and thiobarbituric acid, serve as antihormone drugs inhibiting production of thyroxine because of their close structural relationship to the amino acid tyrosine, the precursor of thyroxine, thereby interfering with the enzyme system called upon for production of this thyroxine. Furthermore, this close analogy between sulfa antivitamin and antihormone compounds may indicate that hormone like carcinogens may, in their turn, actually interfere with normal metabolism under some particular cellular enzyme systems and thus make possible the metamorphosis of a normal cell into a cancer cell. Even vitamin D, which is a dehydrocholesterol closely similar to a sex hormone, can be pictured as one possible of such diversion.

As far back as 1877 Pasteur and. Joubert announced that certain airborne organisms were found to interfere with the growth of the anthrax bacillus; indeed they intimated that some day this phenomenon of antibiosis might be brought under such control as to be of value in treatment of infection. Today microorganisms are known to produce any number of chemical entities capable of combating the growth of other organisms. Hence the entree of antibiotics into the realm of chemotherapy.

To Alexander Fleming, of St. Mary's Hospital in London, goes the honor of being first to observe the destruction of bacteria by blood leucocytes concentrating in pus of wounds studied during World War I. His report in 1929 on the destruction of certain staphylococcal colonies on slides accidentally subjected to traces of mold growth prepared the way for extraction of this mold, Penicillium notatum Westling, to secure the active principle, penicillin; furthermore, Fleming was able to show that penicillin was nontoxic to animals and even to leucocytes.

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PENICILLIN
(thiazolidine-beta-lactam formula)
in Penicillin -X, R = para-hydroxybenzyl

Naturally the story of penicillin opened up the study of a vast array of microscopic forms of life, both pathogenic and saprophytic. From acid soils we had need to study fungi; from dry and alkaline soils we had need to study actinomycetes; from all soils the study of bacteria—aerobic bacteria of sandy, aerated soils and anaerobic bacteria of waterlogged and peaty soils; with a study of protozoal life everywhere. Generally speaking, an extensive root system of growing plants bespeaks highest aeration. In all of this, it must not be overlooked that the presence of trace elements and growth-promoting vitamins plays an all-important role in the nutrition of microorganisms. There is no doubt but that these antibiotic agents function as parts of enzyme systems, such systems being enabled to dissolve away or destroy the capsular material ordinarily protecting bacteria and thereby exposing the latter to the leukocytes of the bloodstream.

The resolution of Prontosil of dye-like structure into a far simpler type—para-aminobenzene sulfonamide, or sulfanilamide—is thoroughly elucidative of what may be expected in the entire realm of chemotherapeutic agents. The simpler structures not only carry the effective agency but are far less likely to undergo disintegration by body fluids. Penicillin will no doubt yield to centralization of its active residue. Already it is reported* that the effectiveness of penicillin against certain bacteria has been quadrupled by the addition of a mere trace of cobalt chloride. Among the other antibiotics from fungi, quite a few hark back in structure to just plain parabenzoquinone, than which few antibiotics are more active.

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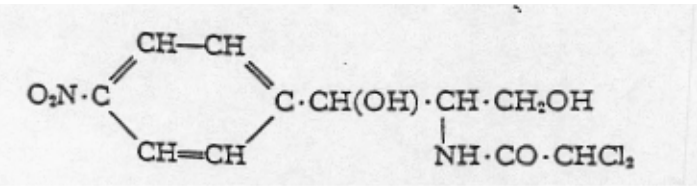

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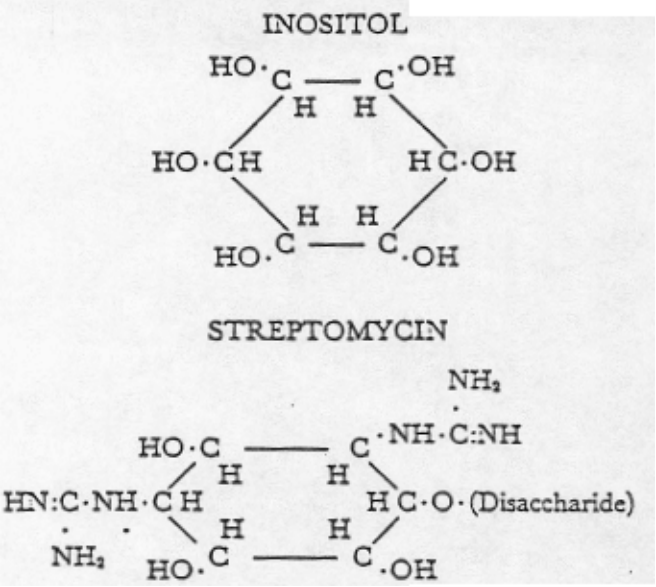

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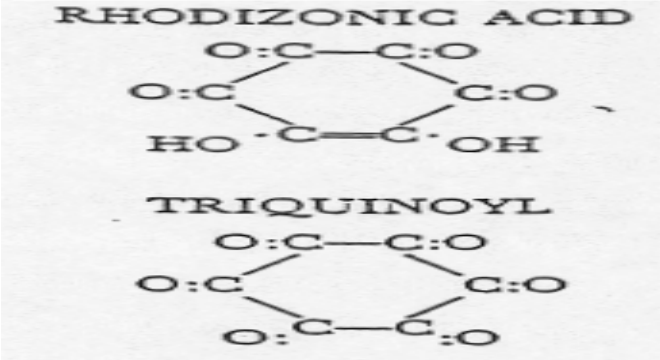

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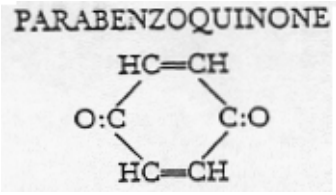

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Of outstanding effect here is the extreme dilution at which these antibiotic agents appear to function best. No one ever dreamed of such dilutions until penicillin made its entrance upon the stage of medicine, and here 1 part to 32,000,000 is nothing out of the ordinary. Dr. Koch merely stepped up this dilution some thousandfold when ideal results were found to arise. Of course, criticism emanating from unschooled biochemists scoffed at such dilutions: Ultimate analyses proved totally incapable of revealing the presence of the compounds used; and so they should. Only by application of radioactive techniques can the presence of such compounds in such high dilutions be detected. Yet in a dose of triquinoyl of 2 cc's in the dilution of 1:1,000,000,000, these 2 cc's introduce into the system the amazing number of more than 5,000,000,000,000 molecules of the active agent! Only so recently as in *Science Illustrated* for February 1947 is it reported that Professor Gilbert M. Smith, at Stanford University, was able to affect a metamorphosis of the cells of a microscopic plant from the sessile, or asexual phase, to the actively motile, mate-seeking sexual cells, by the application of one part of crocetin ($C_{13}H_{22}$ (COOH) 2) in 250 trillion parts of water!

Now the role of these polyketocompounds is definitely oxidative. By their presence a higher level of metabolism is made possible in the system, and, like a passing wave over a golden wheat field, this wave of oxidative influence continues unabated for months upon months— sufficient, indeed, to heal improperly nourished organs and slough off decadent tissues. All of this is in accordance with findings of H. Wieland proving first the hydration of an active Carbonyl group in body fluids into $=C=(OH)_2$ and its subsequent dehydrogenation by enzymes into a peroxide type, =C=O=O, whereupon nascent oxygen is liberated and the carbonyl group (=C=O) regenerated to repeat the process. Just as Pasteur identified the microscopic organisms that led to plant disease, so Koch identified the chemical agents that are capable of combating

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In Brazil, this new interpretation of immunity is meeting with wholehearted co-operation on the part of the government. Happily, the Brazilian authorities are sufficiently open-minded to recognize that the cure for many diseases, when once established, will prove to be an oxidant capable of restoring normal functions in cell growth. In this country many able physicians are applying the Carbonyl therapy, notably Dr. Edwin D. MacKinnon of Saginaw, Michigan, and Dr. George W. Palm of Prudenville and Detroit, Michigan. There is no more interesting presentation on this subject by a physician than that published by the late Dr. Albert L. Wahl of Mount Vision, New York. This brochure is entitled *A Least Common Denominator in Antibiotics.*

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Highly germane to the program of stepped-up oxidative processes within the human system is the absolute necessity for careful selection of proper foods to accompany these treatments. In fact, it is generally stated that half of the treatment lies in the diet. Thus highly reductive agents contained in foods and medicines must be shunned.

For perfect health there is only one correct course to follow: the selection of those foods that carry the whole gamut of vitamins and amino acids and. trace elements. It thus becomes necessary to learn something of the agricultural areas on which our fruits, grains, and vegetables are grown if we are to be assured of the proper nutrient. Meats, of course, will now and then need to be selected; but as time passes, the requirements for meat will fade away in the light of synthetic supply of the required amino acids and proteins. Above all, our foods must carry a sufficient supply of oxidants to maintain metabolism at its highest level. These oxidants are ever present in the coverings of seeds and tubers; they are not present in highly refined foods. Old age comes upon us primarily by reason of the absence of these oxidants. With oxidants in full supply, the digestion of foods proceeds normally and the wear and tear on our blood vessels is reduced to a minimum.

Kenneth de Courcy, Chap. 5, *Intelligence Digest,* Vol. XI (April 1. 1949).

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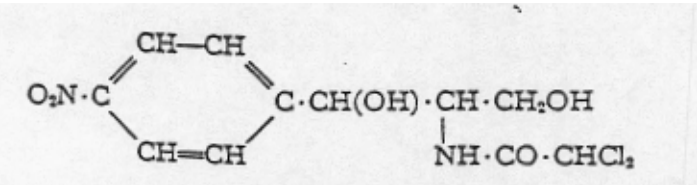

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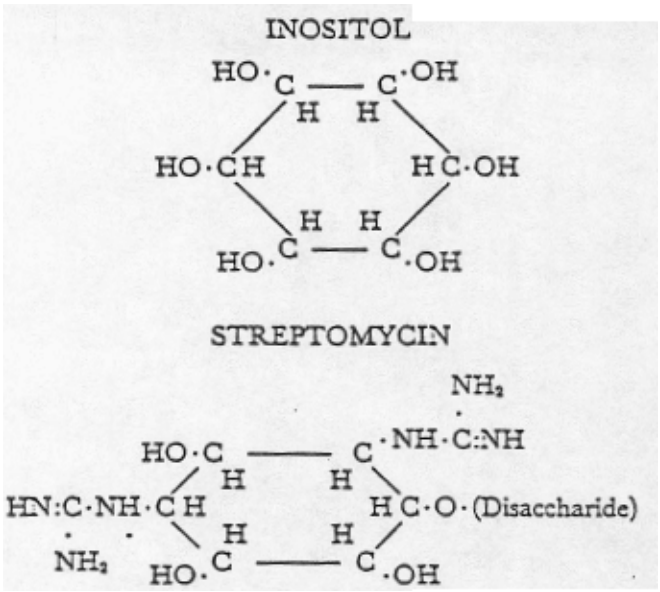

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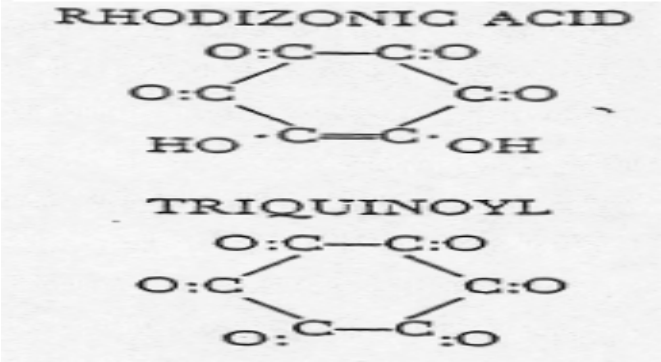

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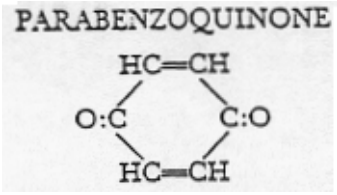

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*Intelligence Digest** has recently published a short account of the remarkable curative properties of H. 11 against cancer. This H.11 is prepared by the Hosa Research Laboratories Windmill Road, Sunbury-on-Thames) of London, England, and is an oxidant similar to the Koch compounds in structure.

Highly germane to the program of stepped-up oxidative processes within the human system is the absolute necessity for careful selection of proper foods to accompany these Treatments. In fact, it is generally stated that half of the Treatment lies in the diet. Thus highly reductive agents contained in foods and medicines must be shunned.

For perfect health there is only one correct course to follow: the selection of those foods that carry the whole gamut of vitamins and amino acids and. trace elements. It thus becomes necessary to learn something of the agricultural areas on which our fruits, grains, and vegetables are grown if we are to be assured of the proper nutrient. Meats, of course, will now and then need to be selected; but as time passes, the requirements for meat will fade away in the light of synthetic supply of the required amino acids and proteins. Above all, our foods must carry a sufficient supply of oxidants to maintain metabolism at its highest level. These oxidants are ever present in the coverings of seeds and tubers; they are not present in highly refined foods. Old age comes upon us primarily by reason of the absence of these oxidants. With oxidants in full supply, the digestion of foods proceeds normally and the wear and tear on our blood vessels is reduced to a minimum.

Kenneth de Courcy, Chap. 5, *Intelligence Digest,* Vol. XI (April 1. 1949).