benefits from it to be not restricted to any locality or any country, but to be available to all mankind. Moreover, in Smithson's will, there was no restriction in favor of any particular branch of knowledge, and Henry insisted that all researches which had for their purpose the increase of existing knowledge should receive due consideration. This broad-minded policy resulted in keeping the activities of the institution well diversified, practically all the branches of science sharing in its attention, and this ideal has been followed to the present time.

Henry served without compensation as chairman of the Lighthouse Board of the United States from 1871 until the time of his death and in addition to administering the work of this important body in improving our national lighthouse system, he personally made a number of valuable researches in the field of fog-signalling and on the illuminants for use by lighthouses, with the result that great advances were made in methods of the protection of shipping. During the trying days of the Civil War, when every available agency was called into service for the preservation of the Union, Henry was one of a commission appointed by President Lincoln to examine and report upon various investigations and experiments intended to facilitate the operations of war and to improve the art of navigation. From the valuable results of this commission arose the National Academy of Sciences with its national charter, with Henry as one of the prime movers. He was its second president, and held that office until his death. He directed the mobilization of scientific effort during the Civil War and a half century later the National Academicians organized, under its charter, the National Research Council for the purpose of mobilizing the scientific and technical men for service to the government in its time of need. He also took a leading part in the organization of the American Association for the Advancement of Science and the Philosophical Society of Washington.

Who can estimate the influence of such a career upon the progress of science in America? Entering upon the field just as this country was beginning to take a serious part in the world's scientific advance, Henry did more than any other one man to shape the progress of this initial effort and direct it into channels which have resulted in placing America among the forefront of the nations in the march of science.

I have often thought, when in the rooms in the Smithsonian Institution where Henry lived and worked, of the wonderful progress of his beloved science since he passed on, fifty years ago. He made his first contributions to fundamental research in electro-magnetics, and then for the cause of the advancement of science undertook the organization and development of a scientific institution in accordance with a plan that was very largely if not wholly his own creation. With great singleness of purpose and a superb devotion to duty he gave all that was in him to the interests of science in America. A man of vision, initiative and power, modest, thorough and sincere, he won the respect not only of the scientific men of his time but also of the great leaders of political, social and educational thought. The founder of many of the present great governmental scientific agencies, adviser and counsellor in the formation of others and the leading spirit in the organization of many of the scientific societies of to-day, Henry may well be called the organizer of American science. This work alone entitled him to a place among America's immortals: add to it his brilliant researches and fundamental discoveries in the field of electricity, and we are led to say of Joseph Henry, with one of his biographers, "there is no greater name in American science."

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THE SIGNIFICANCE OF HEXYLRESORCINOL AND ITS HOMOLOGUES IN RELATION TO THE PROBLEM OF INTERNAL ANTISEPSIS[1]

BIOLOGICAL ASPECTS OF INTERNAL ANTISEPSIS

"CHEMOTHERAPY," in the sense of complete disinfection of the blood stream and tissues by means of some substance more toxic to any invading microorganism than to the host, is a conception which may be traced directly to Ehrlich's first efforts to divert the trend of medical thought from a more or less intelligent empiricism to the interpretation of biological processes and pharmacodynamic effects in terms of chemical reactivity.

It is unfortunate that a term so broad as this should have come to be generally employed in the very restricted sense of the treatment of specific general infections by chemical means. The administration of iron in anemia, or morphia to relieve pain, or even of sodium bicarbonate to relieve gastric hyperacidity are all examples of "chemotherapy" in the real meaning of the word, although in the latter in-

[1] From the Department of Bacteriology, School of Hygiene and Public Health, The Johns Hopkins University. Read before the symposium on "Chemistry in the field of micro-biology," at the annual meeting of the American Chemical Society, Baltimore, Maryland, April, 1925.

stance we do not require a working hypothesis to explain the results.

The term *systemic disinfection* can mean but one thing—the complete elimination of an infecting organism from the blood stream and tissues. But this designation is by no means broad enough to include all the various types of researches now grouped under the inclusive term "chemotherapy" and especially those relative to the treatment of bacterial infections. The writer has therefore employed the term *internal antisepsis* in this paper as designating the treatment of infections, either general or local, by means of the internal administration of chemical substances, whether parenterally or by mouth, and has substituted the term *systemic disinfection* as a more exact designation of the generally accepted meaning of the word "chemotherapy."

Ehrlich's conception that the pharmacodynamic activity of a given substance is due to fixation by or chemical reaction with the cell protoplasm led him to distinguish two varieties of biochemical affinity. To the property of ready fixation by the protoplasm of tissue cells he gave the term *organotropism* and designated by the term *parasitotropism* the property of fixation by the cell protoplasm of microorganisms. The question at once presents itself: Might it not be possible by a study of these properties, as exhibited by various substances of known chemical constitution, to evolve some stable complex so highly parasitotropic and at the same time so slightly organotropic as to accomplish complete disinfection of the blood stream and tissues at one stroke (*Therapia sterilians magna*) or, failing this, a substance showing at least a large ratio between the smallest curative dose and the largest non-toxic dose (Therapeutic index)?

Unfortunately, efforts to discover such a substance have been so uniformly disappointing as to discourage the hope of developing any drug (whose parasitotropic action *in vivo* is not highly specific) which could, in the strict sense of the term, be considered a systemic disinfectant. Although Ehrlich and Bechhold were able to increase very greatly the bactericidal power (parasitotropism) of various phenolic substances, this was usually accompanied by an equivalent increase in toxicity (organotropism). In no instance, either in Ehrlich's work or in the many researches which have followed it, has it been found possible to introduce into any substance a non-specific *parasitotropic surplus* definitely attributable to chemical constitution and sufficiently pronounced to offer real encouragement.

Were we dealing with but two types of protoplasm, that of the parasite and that of the host, the problem of systemic disinfection might be a simple one, for we know that very slight differences in chemical constitution may result in profoundly dissimilar biochemical reactions. It becomes very complicated, not so much because of the fact that bacterial species may differ rather widely among themselves, but more especially because in the higher animal we are confronted not only with a large number of highly differentiated types of protoplasm which react differently to the same drug or chemical, but also with the probability that a substance introduced into the body will itself undergo a number of chemical changes. To this latter fact, indeed, we may attribute every important experimental and therapeutic advance which has been made in this field. The specific parasitotropic action of substances such as salvarsan, tryparsamide, atoxyl, Bayer 205, trypan red, the compounds of bismuth and antimony and even of quinine and emetine, can not be explained on the basis of any direct toxic action on the parasite which we can demonstrate, for none of them will injure it in the test tube in dilutions even remotely approaching those which are attainable in the blood stream and tissues. Whatever the mechanism by which the intense parasitotropic action of these drugs is produced in the body, it is necessary, on the basis of our present knowledge, to assume that they possess tissue affinities which are indispensable to their therapeutic action.

Comparing the complex biochemistry of the higher animal as a unit with the relatively simple metabolic processes of a unicellular organism, it seems quite reasonable that we should know of a great many violently toxic substances which possess no bactericidal properties, but, as yet of not a single non-specific bactericidal substance which can be said to be devoid of toxicity even in the clinical rather than in the strict physiological interpretation of the term. It is quite possible that, inherent in the fundamental chemical characteristics of protoplasm in general, there may be some definite and essential structural complex which precludes the possibility of a toxic action by any substance on bacteria and not on other types of protoplasm. We know that a great many species of microorganisms are extremely vulnerable to highly specific substances such as the various immune substances which are formed in the body. Furthermore, we know through the work of Churchman with gentian violet that a toxic action, specific not to individual species but to very large groups of microorganisms, readily distinguishable by microchemical means (the Gram stain), is possible. The Gram stain itself is sufficient proof of the existence of a particular chemical characteristic common to large groups of widely different unicellular forms. In their comparative simplicity lies the suggestion that unicellular organisms, as a whole, or at least certain groups of

them, may share some common characteristic essential to the chemistry of their life processes, which might be dissimilar to anything occurring in any of the tissues to the higher animals. The idea of systemic disinfection by chemical means is necessarily based upon the hope that some such difference exists, whether it be common to all bacteria, to large or small groups, or merely to definite species, and is supported by the possibility that such a difference might be utilized to our advantage without any accurate knowledge of its chemical nature.

At least one chemist has had the imagination and courage to strike at the very roots of this whole problem. I refer to the recent work of Treat B. Johnson, of Yale University, on the chemical composition of the bacterial cell. While at first glimpse the very boldness of this attack might seem to invite defeat, it must be remembered that we already have an excellent general knowledge of the decomposition products of various types of protoplasm and that work of this nature may well result in the identification of some relatively simple structural characteristic common to the protoplasm of certain types of pathogenic microorganisms and essential to their life processes. It might become possible, with this knowledge, not only to interpret such biochemical phenomena as disinfection, bacteriostasis, vital staining, etc., in terms of more or less definite chemical reactions, but might also point the way to the synthesis of new substances possessing a selective toxic action on the parasite.

Owing to the enormous complexity of the problem as a whole, the search for an internal antiseptic has followed two subsidiary methods of attack, both of which have sprung from Ehrlich's original conception of the ideal, and must be regarded as compromises with that ideal made necessary by the exigencies of the problem. These have been characterized respectively by

(1) Attempts to reduce the unfavorable effect on the tissues of the host of substances which, administered internally, are known to exhibit a high degree of specific toxic action towards the particular organism responsible for certain diseases.

(2) Attempts to impart active and non-specific bactericidal or bacteriostatic action to relatively non-toxic substances known to possess the property of rapid concentration in certain tissues or rapid elimination into certain body fluids.

The arsphenamines remain our best example of researches of the first type, the starting point being the powerful but highly specific parasitotropic action displayed *in vivo* by a substance of known chemical constitution (atoxyl); the goal being the reduction or elimination of its toxic action on the host in its derivatives or compounds without interference with its parasitotropic properties.

The work of Paul Lewis with the trypan dyes, some of which possess the remarkable property of penetrating the tubercle and staining its caseous contents when injected into the circulation of tuberculous animals, and that of Davis, White and their coworkers, with a large number of dyes of the xanthone and sulphonephthalein types which are eliminated in the urine with astonishing rapidity and completeness, are both characteristic of researches of the second type. The starting point is a relatively non-toxic substance of known chemical constitution which is possessed of the property of rapid concentration in certain issues or body fluids; the goal is the development or enhancement of bacteriostatic or bactericidal action in its derivatives or compounds without destroying its tissue or secretory affinities. Researches of this type have been concerned almost exclusively with dyes for the reason that their physiological affinities may be readily observed.

Neither of these methods aim at the ideal, but taken together they may be expected to narrow down the general problem appreciably and with the possibility always at hand that some chance observation may point the way to a more general solution.

Both are beset with difficulties.

Chief among these is the fact that test tube experiments offer little if any indication of the possible therapeutic usefulness of a given substance as a systemic disinfectant. Thus, Ehrlich abandoned atoxyl in 1903 because it would not kill the trypanosome in the test tube. It was only after Thomas and Breinl (1905) proved its effectiveness in experimental trypanosomiasis that Ehrlich returned to it as the starting point of the researches which led to the production of arsphenamine. In the present state of our knowledge we are not only forced to adopt the wasteful method of trial and discard, but even in this must employ the actual therapeutic experiment as the only trustworthy source of information.

The second method of attack is necessarily limited in its scope by the very specific physiological properties which form the basis of each starting point. Although it offers a wider opportunity for ruling out large numbers of compounds by simple physiological and bacteriological experiments rather than by actual therapeutic trial, there are a number of drawbacks which greatly increase the difficulties.

In the first place most antiseptics and germicides become inert or suffer marked deterioration of their active properties in solution in such fluids as blood serum, urine, etc., or even in the presence of rela-

tively small amounts of organic matter. The germicides of the chloramin type, of which so much was formerly expected, are excellent examples of this imperfectly understood interfering action. On the other hand, substances which retain at least a portion of their bacteriostatic or bactericidal properties in solution in biologic fluids are very likely to be destroyed in the body or rendered inert by conjugation.

Finally, antiseptics and germicides which retain their activity in biologic fluids seem to lose the special physiological affinities characteristic of similar substances which are either without any antibacterial action whatever or which lose it in solution in biologic fluids. As an example, Davis found in his elaborate search for an internal urinary antiseptic that among the hundreds of compounds he examined those which were rapidly excreted into the urine invariably lost their bactericidal action in solution in this fluid, while those substances which retained their bactericidal properties in urine were not excreted by the kidney, in spite of the fact that in many instances they were closely analogous compounds and might have been expected from their chemical constitution to possess a considerable degree of renal affinity.

ALKYL RESORCINOLS

The investigations which have led recently to the synthesis of hexylresorcinol and its application as an internal urinary antiseptic were begun some twelve years ago. At that time the lower homologues of this series of alkyl resorcinols, synthesized by Treat B. Johnson, of Yale University, and subjected to a biological examination by Leo F. Rettger and myself, were found to possess not only a very high degree of bactericidal power, but were found also to be relatively non-toxic substances. The examination of propyl resorcinol, which I found to be excreted in the urine quite promptly after oral administration to rabbits, and a comparison of its biologic properties with those of resorcinol and ethyl resorcinol, led to the hypothesis that alkylation of resorcinol increases its bactericidal power and decreases its toxicity in direct proportion to the sum of the atomic weights of the atoms in the alkyl chain. Application of this idea, however, to practically every available phenolic nucleus, other than resorcinol, with the object of developing a very powerful germicide of minimum toxicity, led to indifferent or negative results.

A study of the higher members of the resorcinol series which had never been made seemed to be desirable for the reason that they held some promise of usefulness in the field of urinary antisepsis, owing to the rapid elimination of the lower members of the urine. Through the cooperation of Dr. A. R. L. Dohme, who generously diverted the activities of his chemical research organization to a furtherance of this research, and through the splendid technical work of Dr. Edward H. Cox, Dr. Daniel Twiss and Dr. Ellis Miller rapid progress was made. The entire series was synthesized and each product, including the intermediate ketones, obtained in pure crystalline form—a chemical feat necessitating the solution of a great many serious difficulties.

A biological examination of these compounds led to astonishing results. Each increase in the weight of the alkyl chain resulted in a remarkable increase in bactericidal power and this with at least no apparent increase in toxicity when administered to rabbits by stomach tube. The peak of bactericidal power was reached in hexylresorcinol, which, with a phenol coefficient variously estimated at from 46 to 56.3 by the United States Hygienic Laboratory method now in use, is probably the most powerful phenolic germicide ever described. In spite of this, however, daily administration by mouth of doses of 0.5 gm to rabbits for twenty-one consecutive days, and single doses as large as 2.5 gm (1.0 per Kilo) resulted in no immediate or remote toxic effects which could be detected either by renal function tests, urine and blood examinations during the period of observation or later, by microscopic examination of stained sections of all the more important organs. In fact, most of the animals saved for late observation after prolonged courses of hexylresorcinol showed remarkable gains in weight.

The details of the experimental work with hexylresorcinol in the test tube, in rabbits and in normal men have been published elsewhere and will not be repeated at this time. Suffice it to say that by a technic closely similar to that employed by Davis the administration of hexylresorcinol to normal men in doses of from 0.3 to 0.6 gm three times a day was found to result in the secretion of a practically continuous flow of bactericidal urine which, in the test tube, was found to be capable of destroying strains of *B. coli* as well as *Staphylococcus albus* and *aureus* isolated from cases of active pyelitis. In both rabbits and normal men hexylresorcinol was found to answer Davis's qualifications for an ideal internal urinary antiseptic in the following manner:

Hexylresorcinol was found to be:

(1) Chemically stable.
(2) Non-toxic in highly effective doses.
(3) Non-irritating to the urinary tract.
(4) Bactericidal (not merely bacteriostatic) in high dilution in urine of any reaction.

(5) Eliminated in high percentage by the kidney, largely as an inert conjugate, but unchanged in sufficient amount to impart definite bactericidal properties to the urine.

These theoretical requirements were known and clearly stated years before any substance possessing them was known. Hexylresorcinol is the only substance ever described which has been proved to meet them.

To these qualifications must be added the advantage of the feasibility of prolonged administration of hexylresorcinol by mouth in repeated doses and the clinical possibility of a continuous rather than an intermittent action in the urinary tract.

During the past year the results of this work have been applied clinically by myself and by a number of physicians in the larger medical centers through the administration of hexylresorcinol in the treatment of infections of the urinary tract. The results have been extremely satisfactory. Many cases of pyelitis and cystitis which have resisted for years all known forms of treatment have yielded promptly and completely without any other treatment than hexylresorcinol by mouth. On the other hand, no untoward effects of the drug have been observed in an experience now exceeding five hundred cases.

In summary, hexylresorcinol is by far the most powerful germicide ever described as possessing anything like its degree of non-toxicity to animals and to man. It has been developed and applied as an internal urinary antiseptic by a logical and orderly application of the chemical and biological characteristics of its lower homologues and exemplifies a method by which specific problems in internal antisepsis may be gradually narrowed down through the enhancement of desirable biological properties definitely attributable to chemical constitution.

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SCIENTIFIC EVENTS

ENGLISH SUPPORT OF SCIENCE

THE report for 1924–25 of the British Committee of the Privy Council for Scientific and Industrial Research has just been published. It shows an active campaign in England, chiefly supported by the government, for the development of scientific research and the applications of science in English industrial work.

As is well known, the larger part of the funds provided the council by the government are used to assist industrial associations to develop useful scientific studies pertaining to their special interests. During the academic year 1924–25, however, 258 grants were made to research workers and students-in-training involving total expenditure estimated at £35,000, compared with £40,820 in 1923–24.

The expenditure on headquarters administration during the financial year 1924–25 was £35,920, and the total expenditure of the department was £539,-199. This sum was made up of £311,286 from the exchequer, £38,669 from the interest of the million fund, £100,118 from the capital of the fund, and £89,126 from fees for tests and special investigations for outside bodies, from contributions towards research funds for the Froude tank, alloys of iron and bridge stresses researches and from repayment by the service departments.

VERNON KELLOGG

NATIONAL RESEARCH COUNCIL

PROGRAM OF THE INTERNATIONAL CONGRESS OF PLANT SCIENCES

THE International Congress of Plant Sciences (Fourth International Botanical Congress) will be held in Ithaca, New York, from August 16 to 23, 1926. As has been announced[1] by the organizing committee (B. M. Duggar, *chairman;* H. C. Cowles, *secretary;* H. H. Whetzel, *local arrangements*) "the work of the congress shall be primarily with problems of fundamental research and teaching." Although the congress is not to provide an occasion for legislation on regulatory matters of international significance, the organizing committee has expressly provided that "adequate opportunity shall be accorded all sections for the discussion of regulatory recommendations of international significance."

Except for some sessions of the congress as a whole for addresses of general interest and for the transaction of certain business, the program of the congress will be conducted by sections, the organization of the programs for each section being in charge of a secretary, who will also be secretary of the section during the congress. The sections thus far authorized by the organizing committee, and the corresponding secretaries, are the following:

Agronomy—C. H. Myers, Cornell University, Ithaca, N. Y.

Bacteriology—J. M. Sherman, Cornell University, Ithaca, N. Y.

Cytology—L. W. Sharp, Cornell University, Ithaca, N. Y.

Morphology, Histology and Paleobotany—D. S. Johnson, Johns Hopkins University, Baltimore, Md.

Ecology—H. L. Shantz, Bureau of Plant Industry, Washington, D. C.

[1] SCIENCE, LXI: 58–59. 1925.