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THE SCIENTIFIC CONTRIBUTIONS OF JONATHAN L. HARTWELL, PH.D.

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On Friday morning, March 22, 1991, in Bethesda, Maryland, our profession and public service lost an outstanding pioneer of natural products chemistry, cancer chemotherapy, and cancer research in general. Dr. Hartwell began life on February 21, 1906, in Boston, Massachusetts, the son of John F. and Mary Eliza (Lutton) Hartwell. He proceeded to Harvard University and in 1928 and 1929 received, respectively, the B.A. and M.A. degrees in Chemistry. He then joined E.I. duPont de Nemours and Company as a research chemist until returning to graduate school with Professor Louis Fieser. Indeed, he was Professor Fieser's first doctoral candidate and completed the Ph.D. in organic chemistry in 1935 (private communication from Dr. Hartwell's close friend, Dr. Harry B. Wood, Jr.). He shared Dr. Fieser's strong interest in naturally occurring quinones and by 1933 was already investigating the chemistry of lapachol and mechanistic aspects of the Hooker oxidation (1). His graduate career was very productive and led to seven publications in the *Journal of the American Chemical Society* and in *Organic Syntheses* (1–7).

From 1935 to 1937, he was employed as a research chemist with Interchemical Corp. in New York and continued his earlier interest at duPont in the chemistry of dyes, especially phthalocyanine pigments (8). In this early part of his career, he synthesized the dye that became commonly used in leaded gasoline (private communication from H.B. Wood, Jr.). Jonathan Hartwell returned to Harvard in 1938, and joined the United States Public Health Service, Cancer Investigations, Walcott Gibbs Memorial Laboratory, a forerunner of the U.S. National Cancer Institute (NCI), which was being implemented in 1937–1938.

In 1938, Dr. Hartwell joined the NCI as its first research chemist and initiated a pioneering series of chemical and biological investigations aimed at the discovery of new anticancer drugs and furthering knowledge of carcinogenesis. Some of these early studies included investigations (with the NCI biochemist, Dr. M.J. Shear) of polysaccharide fractions from *Bacillus prodigiosus* that were highly potent hemorrhage producers in mouse sarcomas (9) and the effects of 5,9,10-trimethyl-1,2-benzanthracene on mouse skin (10). At the same time, he was pursuing the chemistry of 2,2′-dichloroethyl sulfide (sulfur mustard) (11,12) that preceded the extensive research and clinical applications of nitrogen mustard and various synthetic heterocyclic compounds (13). Most important was his pursuit of a 1942 report that local application of Podophyllin Resin N.F. (an alcohol extract of the dried rhizomes and roots of *Podophyllum peltatum* L., Berberidaceae), locally known in Maine, for example, as the May apple or mandrake (14), caused complete regression of *Condylomata acuminata* (venereal warts). Medicinal preparations from this plant have a long history in folk medical treatments and the substance now known as podophyllotoxin had already been isolated in 1881 (14). Hartwell and Shear (15) found that podophyllin caused a strong destructive action on sarcoma 37 in mice. Analogous results were obtained with sarcoma 180 and a transplanted mouse mammary carcinoma. That was the first demonstration of antineoplastic effects with podophyllin and, in turn, with its principal component podophyllotoxin. Those observations led Hartwell to what is most probably the first isolation of a naturally occurring anticancer

drug based on bioassay-directed fractionation using column chromatography (activated alumina) (16). The result was isolation of podophyllotoxin and the then new substance α-peltatin as active constituents (16), followed by the discovery of β-peltatin (17,18). To follow was a very important series of 20 research papers on the components of podophyllin (19), directed at structural elucidation and antineoplastic evaluations. The sixth paper of this series reported the discovery of 1-*O*-(β-D-glucopyranosyl)-picropodophyllin (20). That compound served as the structural model for one of the most important contemporary anticancer drugs, namely etoposide, the acetal derivative of the corresponding podophyllotoxin stereoisomer. In this period, Dr. Hartwell was able to discover other sources of podophyllotoxin, such as those found among the conifers, and in the process he discovered the potentially important deoxypodophyllotoxin (20). The overall study was essentially concluded in 1957 with a paper on the absolute configuration of these lignans and a review in 1958 (21). By this time the preclinical and early clinical investigations of podophyllotoxin were well under way and provided the chemical and biological foundation for the very simple structural modification of podophyllotoxin that gave rise to etoposide in the Swiss laboratories of Sandoz.

Also, in the 1940s he was deeply involved in an investigation aimed at improving, by structural modification, the first known naturally occurring antineoplastic substance, namely, colchicine (22–25). His contributions to organic chemistry, not only directed at anticancer drug discovery, even included an investigation of more than 60 substances as substitutes for sulfuric acid in melting point baths. By this means he introduced silicone oil as a substitute for sulfuric acid in 1948 (26).

Reports from as early as 1806 that certain arsenic compounds might be useful in the treatment of cancer led Hartwell to synthesize or otherwise obtain nearly 100 organoarsenic compounds for antineoplastic evaluation. That study most probably constituted the first systematic investigation of organometallics for anticancer activity (27). His virtuosity in organic chemistry directed at the cancer problem led him to a variety of different areas including syntheses of phenazines (28,29) and other substances based on their ability to induce damage in sarcoma 37 (30).

In August 1945, he played a key part in organizing the first of what are now known as National Cooperative Drug Discovery Group (NCDDG) programs by implementing a "Joint Institutional Research Program on Chemotherapy of Cancer," which facilitated the procedure from the laboratory to the clinic with synthetic organic compounds and bacterial polysaccharides (31). This first national cooperative drug discovery group was composed of the National Cancer Institute, the Lankenau Hospital and Research Institute in Philadelphia, the National Institutes of Health Zoology Laboratory, Hahnemann Medical College in Philadelphia, and the Hospital Division of the Public Health Service in Bethesda.

Meanwhile, Hartwell was avidly evaluating large numbers of plants from various families for potential anticancer constituents. One of these important evaluations involved the Amaryllidaceae and provided the first scientific evidence of potential antineoplastic constituents in that family (32). Those observations became important later in the National Cancer Institute's research programs and provided clues that led to the discovery of pancratistatin (33).

The U.S. Public Health Service Office of Cancer Investigation at Harvard University (see above) had, by the time this program was terminated in 1953, screened more than 3,000 compounds and several hundred plant extracts (34). In the 1953–1955 period this anticancer drug evaluation program was restarted in earnest by the U.S. National Cancer Institute (35,36). Indeed, the NCI's anticancer drug discovery program formally began in July 1953. At that time, Congress directed the NCI to explore a broad program

focused on the chemotherapy of acute leukemia. That was followed in April 1955, by establishment of the NCI Cancer Chemotherapy National Service Center (CCNSC) to explore drug discovery and development for all areas of cancer. The first major chemical effort was begun in December 1955, and was initially focused on the steroid hormones. It then rapidly enlarged to encompass microorganism culture filtrates. By 1957, it was established that about one percent of microorganism broths contained substances with significant activity against experimental tumor systems in mice (37).

With the transfer of Hartwell to the CCNSC staff in the summer of 1957, to supervise the natural products programs, the search for plant antineoplastic constituents began in earnest. In a December 17, 1957, memorandum, Hartwell suggested beginning with the Compositae, Euphorbiaceae, Labiatae, Leguminosae, Liliaceae, and Umbelliferae families [J.L. Hartwell (CCNSC, National Cancer Institute), private communication]. In the fall of 1957, Hartwell and Dr. Burns Ross of the CCNSC encouraged Professor Werner Herz at Florida State University to continue his earlier studies of the Compositae on a collaborative basis with the NCI-CCNSC. At the same time, they encouraged Professor S. Morris Kupchan, then at the University of Wisconsin, and Professor Michael Cava, then at Ohio State University, to begin chemical studies of some of the other selected plant families. In September 1957, this author joined the University of Maine as Assistant Professor of Chemistry and was anxious to begin an investigation of plant anticancer constituents. As a result of negotiations [R.B. Ross (CCNSC, National Cancer Institute), private correspondence] with Ross of the CCNSC in October and November of that year (G.R. Pettit, private correspondence), we began in December 1957, a collaborative anticancer constituents survey of the Labiatae family (37). In 1958, Dr. Monroe Wall joined the CCNSC collaborative groups and the search for plant antineoplastic agents really began to accelerate. During the next few years, some 600 extracts from plants collected in the Western Hemisphere and Africa by the Eastern Utilization Research and Development Division of the USDA, in conjunction with their search for steroidal sapogenin sources, were evaluated along with several hundred more extracts contributed by Caldwell at the University of Arizona (38). Undoubtedly, the most significant contribution arising from these initial evaluation, isolation, and structural studies was the discovery of camptothecin by the Wall group (39).

By 1959, the plant anticancer constituents research looked very promising, and under Hartwell's guidance, by 1964, it was well under way (37). Some of Hartwell's achievements in this time frame included, in 1960, formal arrangements with Wall, then at the USDA, and Caldwell for providing plant extracts to the CCNSC. He was able to make similar arrangements with government laboratories in India (1962) and Australia (1963) and to initiate an extraction and screening contract with the Wisconsin Alumni Research Foundation. He also arranged more extensive plant collection activities under contract (beginning in 1960) between the NCI and the U.S. Department of Agriculture. The latter field botanical activities were directed first by Dr. Earlinson, followed by Drs. Jones and Perdue. Another very significant achievement by Hartwell in this period was the initiation of research contracts with Wall, Kupchan, (40,41) and Caldwell (later continued by Professor Jack Cole), followed later by the additions of Professor Norman Farnsworth at the University of Illinois and Professor John M. Cassady, then at Purdue University (37).

Advances in the CCNSC Natural Products Anticancer Drug Discovery Programs up to about 1968 were nicely reviewed by Hartwell and Abbott (42). By this date the total number of plant extracts screened for antineoplastic activity amounted to some 40,000. With duplication and/or multiple extracts of the same plant this represented a much smaller number of actual plant species. However, at this point it was clear that some 3.5

percent of plant species would give extracts with a confirmed level of antineoplastic or cytotoxic activity. In general, the NCI's evaluation of plant extracts from 1966 to 1971 averaged about 4,000 per year with a greater number being tested during the years 1972–1974. Also, in the 1960s, Wall and Wani discovered taxol (43) and Kupchan and colleagues (44) uncovered maytansine. Other well-known plant antineoplastic constituents discovered in this time frame include tripdiolide, bruceantin, steganacin, indicine *N*-oxide, harringtonine, homoharringtonine, ellipticine, fagaronine, thalicarpine, and tylocrebrine (37,45).

Unfortunately, due to the retirements of Dr. Z. Gordon Zubrod (Director, NCI, Division of Cancer Treatment) in 1974, and Hartwell in 1975, combined with NCI policy decisions, collection and evaluation of new plant specimens continued to decline until temporary termination (in spite of the courageous efforts of Drs. John D. Douros and Matthew Suffness) in 1981. Fortunately, by 1983–1984, the pioneering achievements of Hartwell were becoming better appreciated and, under the brilliant leadership of Dr. Michael R. Boyd, the NCI's natural products anticancer drug discovery research was revitalized and now represents a major component of the U.S. cancer conquest programs.

Because of Hartwell's scholarly approach, excellent intellect, imagination, and creativity as head of the natural products section of the CCNSC, and later of the same branch in the Division of Cancer Treatment of the NCI, he was able to achieve remarkable results in the 1957–1975 period for our government's cancer conquest program. During that historic interval he was responsible for guiding research that led to a number of important naturally occurring anticancer drugs that are now well known. Some of his other noteworthy contributions, as published first in this journal include the unique and important compilation of "Plants Used Against Cancer" (46–57).

Hartwell's enthusiastic support for the research program this author initiated in 1965–1966, to undertake the first systematic investigation of marine animals (58) and terrestrial arthropods (59,60) as new sources of anticancer drugs, was again far-sighted. At that time, this approach seemed a very far-fetched concept to many, and his capable assistance and that of Dr. Harry B. Wood (CCNSC) will always be warmly appreciated. Part of the very reassuring sequel includes our discoveries of the bryostatins (61,62) and dolastatins (63). Furthermore, while this chemist had developed an early interest in attempting to direct the powerful resources of organic chemistry to the discovery of potentially useful anticancer drugs, reading (as a graduate student) some of Dr. Hartwell's podophyllotoxin papers in the *Journal of the American Chemical Society* in 1954 stimulated me to begin the long-term research program beginning in 1957 (see above), aimed at discovery of plant antineoplastic constituents. More broadly, his beneficial impact on the chemistry of natural products, and the steady progress being witnessed in cancer treatment, will continue to be far-reaching.

In addition to his considerable talents as an organic and bioorganic chemist, he was also an expert botanist and intensely interested in nature. After retirement, he never lost interest in the National Cancer Institute's natural products research and continued to help whenever possible. In person, he was a most interesting, pleasant, and witty colleague and friend. His remarkable contributions to our government's cancer conquest program and to improving human cancer treatment will remain a lasting memorial to this splendid person and special friend who will be deeply missed by all of us who knew him (64).

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