Appendix 2: Dr. F. W. Heyl. Brief Review of His Publications

Dr. Heyl published, under the supervision of Professor T. B. Johnson, his first scientific paper entitled "On 5-Nitrocytosine and Its Reduction to 2-Oxy-5, 6-Diaminopyrimidine" in 1906. He wrote, with Milton Herr, his last on "Progesterone from 3-Keto-bisnor-4 Cholenaldehyde" in 1949. During the forty-three years between these publications he contributed some eighty articles to various American scientific journals.

His zeal for the chemical investigation of naturally occurring substances was stimulated during 1907-8 by his close association with Dr. Thomas B. Osborne at the Connecticut Agricultural Experiment Station where he held an assistantship supported by the Carnegie Institution. With Dr. Osborne he published seven articles which described the amino acid content of seven purified proteins. They also wrote on nucleic acid composition.

Upon graduation he worked as an assistant chemist under Dr. A. L. Winton At the Chicago analytical laboratory of the U.S. Department of Agriculture am he became familiar with the methods of control work in foods and drugs. The following year he went to the University of Wyoming.

Here he returned to private laboratory work with the pyrimidines but nothing came of it and this remained an unsatisfactory experience which he never remembered with pleasure, particularly when he saw Luminal first introduced in 1912, to he followed in the 20's by Amyta1, Nembutal, Delvinal, Dial, Ipral, Neonal, Seconal and others. It would appear in retrospect that nothing should have been more obvious or easier to a student who had the post-graduate experience which Heyl had then to enter the field of the barbiturates.

At the University of Wyoming a life long friendship with Dr. L. Charles Raiford, for many years Professor of Organic Chemistry et the University of Iowa, developed and they wrote two papers which

dealt with the replacement of halogen by the nitro group in such substances as triiodo, tribromo, and trichlorophenol. Independently he was also engaged in the investigation of the alkaloid bearing plants of the Rocky Mountain States. For his project the University of Wyoming Experiment Station received federal support from the Adams fund. His chief publication described a new alkaloid from Death Camas leaves which he obtained in crystalline form and was named Zygadenine. The first formula assigned in 1912 we $C_{39}H_{63}NO_{10}$ but in 1948 he prepared a number of salts of the alkaloid and showed that it belongs among the alkamines of the veratrine series which are steroidal and always contain C_{27}. The corrected formula is $C_{27}H_{43}O_7N$.

It was at this time that the chemical work of Dr. Frederick Belding Power became the model which Dr. Heyl sought to emulate. This author, et the head of the Wellcome Research Laboratory in London, had exhaustively examined many well known drugs such as chaulmoogra oil, colocynth, jalap, scammony, pumpkin seed, watermelon seed, caulophyllum, sarsaparilla root, hops, jambul, as well as exotic plants shipped from South Africa, India, Malaya, the Dutch Indies and also from different parts of the British Empire. Heyl first employed the methods of Dr. Power on Death Camas leaves and on Wyoming larkspur.

In 1913, upon the recommendation of Dr. Winton, Heyl came to The Upjohn Company where he was first busied with the establishment of an analytical control laboratory. It was at this time that the bureau of Chemistry investigated the pharmaceutical market and found, among other things, the lack of accuracy in nitroglycerine preparations. Heyl and Staley published the first paper from the Upjohn Research Laboratory in the American Journal of Pharmacy (May, 1914). It was entitled "Notes on the Estimation of Nitroglycerine." There followed several other papers in analytical chemistry including "Standardization of Papain" (with C. R. Caryl and J. J. Stanley); "Laboratory Notes on the Standardization of the Mercurials" (with D. K. Strickland). During this period Heyl actively

cooperated with the Bureau of Chemistry in the establishment of uniform methods of chemical control and also in the establishment of reasonably close limits of permissible error in pharmaceutical products. He was chairman of the Scientific Section of the American Drug Manufacturers' Association during 1924-1925 when this important cooperative work was carried through.

Now he began a long series of investigations of plant drugs, most of which were carried out with Dr. M. C. Hart. These included Echinacea, Sumbul, Jambul, Ragweed pollen, Adonis Vernalis, Digitalis, Viburnum prunifolium and Viburnum opulus. Powers and Heyl unintentionally duplicated a study of jambul at about the same time and the published work of the latter compares favorably with the report of Power and Callan. The unfortunately negative spirit of moat plant investigations is illustrated by the case of Jambul. This is an imported drug from the East Indies and Malaya. It was official in the pharmacopeia of the Netherlands. A continental pharmaceutical chemist published his discovery of a new glucoside which had the suggestive name "antimellin." However, in neither laboratory could this glucoside be isolated. In the case of Echinacea, Heyl found the drug to have a wide use, but no active principle could be isolated. Since the Council of Pharmacy and Chemistry had made an issue of the therapeutic value of this plant, the chemical publication was cited editorially in the Journal of the American Medical Association. "No physiologically active substance was isolated and the results may, therefore, be considered as partially confirmatory of the report of the Council." In the case of the viburnum, drugs which intrigued Heyl because of his observations on the sale of Hayden's Viburnum Compound and Wine of Cardui and other preparations, the finding of considerable amounts of valerianic acid combined in several different forms raises more questions than the chemical investigation answers. It is interesting, in passing, to observe that Adonis vernalis is now an official drug in some of the Soviet States and that the glucoside which eluded Heyl in 1918 was finally described in recent years as a result of the cumulative work of some of our greatest chemists (and new methods) including Karrer, Reichstein, Stoll and others.

Heyl demonstrated the nature of the deterioration curve of digitalis and its preparations and studying also the distribution of cardiac activity between water and chloroform, when infusion of digitalis is exhausted with this immiscible solvent, he came to the conclusion that all patented aqueous solutions were artifacts and failed to represent the whole leaf as claimed.

In studying ragweed pollen, on which subject he wrote six papers, he gave the most complete demonstration of the application of systematic methods of plant investigation recorded in the chemical literature. Searching for the antigen, be isolated an albumin, a proteose and a glutelin. In the protein free water and saline extracts he isolated guanosine, guanine, adenine, histidine, lysine and agmantine. He showed that the yellow coloring substances were flavanols, which amounted to 0.6% of the pollen. He isolated quercitin glucoside as well as a glucoside of isorhamnetin.

Dr. Heyl visited a number of physicians in connection with the development of ragweed pollen therapy. He found that one expert preferred fresh pollen extracts, whereas another would use nothing other than an aged solution. When he looked into digitalis therapy he found a similar confusing state of practice. From this experience he derived a pharmaceutical approach which he often brought into practice whenever the product under consideration permitted dehydration. Thus, in a pollen extract, a digitalis leaf, or Solu B or Gonadogen, in all of which the problem of deterioration recurs, Heyl recommended a desiccated product.

The Germans had imported at New London a submarine cargo of neoarsphenamine which sold at $3.00 a tube. Ovarian products were more and more widely used and there were widely diverse opinions on the relative usefulness of whole ovary, corpus luteum, ovarian residue and various other tissue extracts. There now appeared six publications on the arsphenamines end sixteen more on the chemistry of corpus luteum, liquor folliculi, ovarian residue, and on the water soluble constituents of the whole ovary. The chemical studies were accompanied with a complete development of the

pharmacological work required for pharmaceutical studies. Mr. Payne studied the arsenica1 preparations for trypanocidal effectiveness and for toxicity. The ovarian studies led to the development of the methods for measuring estrus producing and estrus inhibiting hormones. The chemistry of corpus luteum lipoids stands today where these papers placed the subject, that is, the course of the fatty degeneration of the complex lipoids to neutral fat and fatty acids as pregnancy progresses has been described, any incidentally an entirely new fatty acid -- a hexa-unsaturated acid of the C_{20} series, having the formula $C_{20}H_{34}O_2$ and named ovarenic acid -- was discovered.

When Dr. Heyl was studying the subject of alkaline therapy he became for a time involved in nutrition studies. Sherman and others had studied a variety of calcium salts to find out which one might be most available to the growing animal. In feeding children, it was found that 2.5 times as much calcium as calcium lactate had to be fed to establish Calcium equilibrium while one part of calcium as calcium in milk sufficed. Balance experiments here also showed that calcium is somewhat better utilized by the simultaneous administration of an alkaline citrate, or stated another way a base forming or neutral diet is more favorable to calcium retention than an acidotic diet.

It so happened that at exactly this time the question of the effect of vitamin D on calcium retention in the human came up for investigation and in an interesting and oft quoted paper worked out in 1927 and entitled "The "Effect of Irradiation and Cod Liver Oil on the Calcium Balance in the Adult Human" (with Hart and Tourtelotte) it was proved that neither irradiation nor cod liver oil favorably increases calcium or phosphorus retention in adults. As far as cod liver oil was concerned, the vitamin D is important only in the immature.

This paper took Heyl directly into the sterol field. But first one more paper in nutrition about another plant drug may be mentioned. It was claimed at this time that Jerusalem artichoke might be safely utilized by diabetics. Inulin and similar products appeared on the pharmaceutical market. In a paper (with E. C. Wise) it was shown that

neither dried artichoke nor purified inulin prepared from artichoke was utilized in a carefully controlled diabetic patient.

It was at the time that Heyl was engaged in studies of calcium balance that the discovery of irradiated ergosterol by Windaus and also its influence on calcium metabolism was announced. Since the manufacture of fat-free Tincture of Ergot supplied the laboratory with an abundance of starting material, Heyl isolated ergosterol from this fat and wrote three papers on the sterols of ergot.

Heyl showed that these sterols include, besides ergosterol, dihydroergosterol (5 dihydroergosterol; m.p. 174, $[\alpha]_D$ -20°, i.e. the $\Delta^{7.22}$ compound) and in the filtrate he isolated a third sterol which was optically inactive. He denied the existence of Tanret's "fungisterol." He showed that the fat from Spanish ergot contains 30% of the dihydro-compound and somewhat less than 70% ergosterol, the difference being made up by his third sterol. More recently Professor Wieland claims to have isolated fungisterol. However he assigns to fungisterol $[\alpha]_D$ -0.2°, while Tanret gave $[\alpha]_D$ -15.9°,. The substance which Heyl isolated is not fungisterol of Wieland but a new sterol, closely related to ergosterol.

Heyl became interested in the isomerism shown by ergosterol and was the first to isolate ergosterol, i.e. Δ^{14} ergostenol, m.p. 141°, $[\alpha]_D$ +21°. When he esterified ergostenol he found that some acid chlorides isomerized the sterol while others gave the true ester. Thus benzoyl chloride forms benzoate which is a mixture of α and β ergostenol benzoates but m-nitrobenzoyl chloride or p-nitrobenzoyl chloride form true esters of β-ergostenol

At this time publications in the pediatric literature gave a good deal of attention to the properties of spinach end it was suggested that irradiation produced vitamin D. There now appeared four papers on the sterols of spinach as well as a complete examination of spinach fat. He discovered ν-spinasterol, m.p. 168°, $[\alpha]_D$ -2.7°; β-spinasterol, m.p. 148-150°, $[\alpha]_D$ +5.9°; γ-spinasterol, m.p. 159.5-160°, $[\alpha]_D$ -0°. The last was isolated from a new phytosterol-glucoside. The reduction

of α-spinasterol gave α-spinasterol, m.p. 110°, $[\alpha]_D$ -24.2°, which in turn could be isomerized similarly to the isomerization of α-ergostenol, whereupon it yielded β-spinastenol, m.p. 127° $[\alpha]_D$ +36.5°.

The hydrogenation of α-spinasterol saturated but one of two double bonds present, and the resulting α-spinastenol was isomerized with acid to β-spinastenol which could further be reduced then to a saturated sterol spinastanol. Larsen moved to the University of Rochester where he took this materiel and proved the identity of spinastanol and stigmastanol.

In 1933, Heyl directed the expansion of the research laboratories and left laboratory work. The interest in sterols and hormones was carried on by Cartland, Kuizenga and others. The vitamin expansion, which brought out Cod Liver Oil Concentrate, Super A Concentrate and Cerelexin, was carried on by Wise, Caldwell, Delor and others. The organic chemistry section was developed by Hart, Woodruff, Kolloff and others. The pharmacy section was developed further by Terpening, Wruble and others. Heyl engaged in the supervision of the transfer of laboratory work to the newly equipped pilot laboratory for fine chemicals. Among the subjects thus transferred were estrone, gonadogen, natural progesterone, adrenal cortical hormones, mercarbolide, pentacresol, bismuth-ethyl-camphorate, b-(o-methoxyphenyl) isopropyl methylamine hydrochloride, (orthoxine) diethylstilbestrol, a new enteric coating, while several other substances including nicotinamide and pantothenic acid were not transferred.

In 1942, Heyl returned to laboratory work and carried on some work which had begun as a cooperative research project with Professor Riegel at Northwestern University. The work was directed to the possibilities of using the sterols of soy-bean oil, especially stigmasterol, in hormone synthesis. There followed several papers which hinged on his discovery of a new sterol aldehyde, 3-acetoxy-bisnor-cholenaldehyde, which was ultimately utilized for an original

synthesis of progesterone in which the yield of the hormone was increased over that of earlier methods.

The scientific work which has been reviewed may be surveyed in tabulated form in the appended bibliography copied from the Index of the Abstract Journal of the American Chemical Society. This list gives the names of those who were at one time or another associated with Dr. Heyl in laboratory work and published with him.

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Editor's note: the Journal of the American Chemical Society Legacy Archives on-line search engine lists several publications after the last one listed here. The most recent was:
James L. Johnson, Milton E. Herr, John C. Babcock, Anne E. Fonken, James E. Stafford, Frederick W. Heyl, "Enamine" Derivatives of Steroidal Carbonyl Compounds. IV. Structural Considerations, *J. Am. Chem. Soc.*, 1956, *78* (2), pp 430–436