DEVELOPMENT OF ULTRAVIOLET BLOOD IRRADIATION

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THE development of ultraviolet blood irradiation therapy was an outgrowth of an attempt to utilize the bactericidal properties of ultraviolet rays in the treatment of blood stream infections. If the greatest advantage was to be derived from the bactericidal properties of the rays, a method of applying them directly to the blood stream of the patient had to be developed. The problem faced was twofold in nature: (1) to develop a method of application and (2) to determine the necessary dosage.

The first step taken was to review the literature on ultraviolet irradiation in general to determine what, if anything, had been accomplished along this line and the extent of success or failure. The literature, mostly from European sources, was voluminous and seemed to establish the fact that some researchers in the field believed that most of the systemic reactions observed following exposure of the skin to ultraviolet rays were due to the influence of the rays upon the blood.

It was noted in the literature that the source of the ultraviolet energy was inconstant and varied widely. This fact alone would produce variable results and often a failure to obtain any measurable results. A source of ultraviolet of known intensity was sought that could be easily controlled so that a uniform dosage could be achieved and duplicated at will. The Burdick water-cooled ultraviolet generator was selected as having the desired characteristics.

It was believed that a method of exposing the blood directly was feasible. An irradiation chamber was developed by Knott and Edblom to allow direct exposure of the blood. The irradiation chamber was circular and approximately 2 inches in diameter and about 1 inch thick. The inside of the chamber had a labyrinthian passage connecting the inlet and outlet formed by baffle plates that were ground to fit flush against the quartz window that formed the top of the chamber. Thus the blood must flow through the labyrinth by passing around one end of each baffle plate instead of across them. The labyrinth was approximately 1 cm. deep.

The irradiation chamber was so designed as to provide maximum turbulence of the blood to accomplish two desired effects: (1) to prevent the formation of a film of blood forming on the chamber window that would absorb and filter out much of the desired wave lengths of ultraviolet. In an opaque substance, such as blood, it is necessary to turbulate the substance to prevent the formation of a film of blood that absorbs the ultraviolet and prevents it from reaching the flowing substance. (2) To insure that all parts of the blood be equally exposed to prevent overexposure of some parts and underexposure of others. If the blood flowing through the chamber is not turbulated, a portion of it remains next to the window and absorbs the ultraviolet thus preventing uniform exposure of the total volume and resulting in the overexposure of one portion and underexposure of others. The development of the irradiation chamber provided a method of exposing blood uniformly so that all parts were equally exposed and that a uniform and repeatable dosage could be administered.

The first step taken in the original work by Knott and Edblom was to determine roughly the tolerance of the red blood cells to ultraviolet rays when directly exposed in whole blood. Small quantities of whole blood were placed in a quartz test tube and citrated 1 to 5 with a 2½ per cent solution of sodium citrate. With

the ultraviolet generator operating at 60 volts and 4+ amperes supplying wave lengths 2399 to 3650–54 Angstrom units, the blood samples were exposed at contact with the source of ultraviolet from 0 to 280 seconds in five-second and ten-second graduations of exposure. After each interval the specimens were microscopically examined to note any change in the form of the red blood cells. No change was noted up to seventy seconds and then a slight poikilocytosis occurred. This condition disappeared after eighty seconds and no further change was noted up to 280 seconds when disintegration took place.

This same procedure was followed with whole citrated blood inoculated with cultures of Staphlyococcus aureus. Cultures were taken after each interval. Growth of the organisms occurred only in the first three samples with no growth showing in any sample exposed more than ten seconds. These experiments were repeated until it was demonstrated that the bactericidal properties of the rays were effective well within the tolerance range of the red cells.

The next step was to undertake animal experiments. Strains of Staphlyococcus aureus and hemolytic streptococcus of known virulence to dogs were used. These organisms were injected in gross amounts intravenously into dogs and cultures taken periodically to insure that acute septicemia developed. The animals were then irradiated by tapping two veins and pumping the blood from one to the other through the irradiation chamber. The pumping was accomplished with a Luer syringe and a three-way valve. The process was continued until the estimated total volume of the animal's blood had been irradiated. As the blood passed through the irradiation chamber, it was subjected to ultraviolet irradiation from a Burdick water-cooled ultraviolet generator held in contact with the chamber, the actual source of the ultraviolet being approximately 3 cm. from the chamber window. The test animals all died on the fifth to seventh day from what appeared to be a combination of profound depression, a progressive respiratory slow-up and failure. All the animals at the time of death had negative blood cultures, thus indicating that the organisms had been destroyed, a marked contrast to the control animals in whom death was preceded by an overwhelming septicemia. The literature suggested that overexposure to ultraviolet rays could conceivably produce a profound depressive effect.

It was then attempted to determine the susceptibility or tolerance of the host to ultraviolet rays impinged directly upon the blood stream. This was approached by two methods: (1) To irradiate the entire blood stream, but with reduced dosages to determine the maximum the animal could stand, and (2) to maintain the dosage of the earlier experiment and to reduce the total volume irradiated.

The latter method had been suggested by an incident in which the apparatus had failed and only partial irradiation had been accomplished; the test animal in this instance survived and negative blood cultures were achieved. Both methods were pursued until it was established that the second method was subject to less mechanical difficulty and productive of more uniform results.

From these experiments it was found that it was unnecessary to expose the blood sufficiently to kill the bacteria directly. It was also noted that it evidently was unnecessary to expose all of the blood to achieve a desired effect upon the entire blood stream. The total amount of blood to be irradiated was determined to be $\frac{1}{16}$ to $\frac{1}{20}$ of the estimated blood volume or approximately 1½ cc. per pound of body weight. Continued work, using the same virulent bacteria, established the fact that ten test animals treated by the newer system, all recovered from an overwhelming infection and that none showed any ill effects. All dogs were carefully checked with blood counts and continued observation; no untoward results were noted after four months in most of the animals, and

after four years in the case of one to which we became attached sentimentally. Four untreated dogs died of septicemia.

From observations made on the work done on animals a corrected or extended hypothesis was established. The evidence accumulated so far seemed to indicate that the impingement of small, carefully regulated doses of selected ultraviolet rays directly upon the blood stream of test animals in some way increased the bactericidal properties of the blood stream; that by this method of treatment some influence was exerted upon the vital resistance factors of the host, enabling it to overcome the infection and to progress to complete recovery; that some influence was exerted upon the toxic conditions produced by the disease, either by direct action upon the toxins themselves or by indirect action on the toxins through the host's rallied defense mechanisms. To what extent any of the above is true or false was not determined from the data available from the work done to this point. The literature searched earlier indicated that certain known toxins had been inactivated directly by ultraviolet rays under given conditions, but whether and to what extent it was possible to vary the conditions and still produce the result was not known, nor was it known whether such a detoxification effect could be produced *in vivo* as well as *in vitro*. The work on animals was carried on until it was definitely determined that the animals suffered no ill effects from the treatment and yet showed a clinical detoxification *in vivo*.

The first treatment on a human took place in 1928. Consultation held the patient to be in a moribund state from septic abortion complicated by hemolytic streptococcus septicemia. Ultraviolet blood irradiation therapy was instituted as a last resort to see if the septicemia in a human could be affected. The patient responded to treatment and proceeded to an uneventful recovery. She has since borne two children, and when last checked in 1940 was found to be in good health with a normal urinalysis and blood count. Nothing further was done in the treatment of human patients until 1933.

In the meanwhile some work was done in Chicago at a private research foundation where experiments were conducted to try to determine what particular component of the blood was most profoundly affected by ultraviolet irradiation and in what manner. This work had to be curtailed without definite results being obtained because of the difficulty of following the chain chemical reactions set up and the lack of equipment and money to pursue them to conclusion. To the author's knowledge, technics have not as yet been devised to determine the end result or the modus operandi of chain chemical reactions set up by the stimuli of ultraviolet rays to such a complex compound as human blood. No conclusions were drawn as to the results obtained in Chicago. Clinical observations seemed to us to be the most important procedure to follow next until sufficient knowledge could be accumulated from the use of the procedure upon which to base problems of basic research.

This first became possible in 1933. Virgil K. Hancock, M.D., of Seattle, Washington, with James Tate Mason, M.D., a consultant, felt justified in using the procedure as a last resort on a patient, apparently moribund, with advanced hemolytic streptococcus septicemia. This case was described in detail by Hancock and Knott[1] in the first published article reporting this technic. Successful conclusion of the case led to further use in similar cases of serious nature in which it was believed the patient was in a moribund state.

In this work with Hancock, daily blood counts and cultures were taken on all patients treated. Careful study of these blood counts revealed that in cases of overwhelming infection, when leukopenia was present, there was following ultraviolet blood irradiation a rise in the white cell count to a degree consistent with the severity of the infection, the count then

diminishing with clinical improvement. An increase was also noted in the red cell count in patients suffering from hemolytic streptococcus septicemia. Consistent responses were achieved in the treatment of septicemia, but it was noted that streptococcus blood stream infections were more easily controlled than were staphylococcus, the latter requiring usually more than one treatment, while the former usually responded favorably to one. In a large majority of the cases, a marked cyanosis was present at the time of initiation of ultraviolet blood irradiation. It was noted that during the treatment or immediately following the treatment a very rapid relief of the cyanosis occurred with a corresponding easement of respiratory embarrassment. This response was consistent and was, in a majority of cases, accompanied by a noticeable flushing or reddening of the skin with a distinct loss of pallor. It was not determined at first whether this phenomenon was due to a greater assimilation of oxygen or a vasodilation effect, or both.

The easing of respiratory embarrassment that occurred consistently in septicemia led to the application of the procedure in cases of well defined and well diagnosed pneumonia. In a series of seventy-five cases in which the diagnoses were confirmed by x-rays, all patients were treated by this method and, according to Hancock, the method was found to be extremely valuable in combatting the pneumonia. The course of the disease following ultraviolet blood irradiation was marked by a rapid fall in temperature, disappearance of cyanosis, often within three to five minutes, cessation of delirium if present, a rapid subsidence of toxic symptoms generally, a marked reduction in pulse rate and a rapid resolution of consolidation. A shortening of hospitalization and convalescence occurred regularly. This procedure was later found by Miley to be especially valuable in the treatment of virus type pneumonia in which chemotherapy had proven of doubtful value.

The consistent results obtained in treatment of cases of septicemia gave rise to the question as to the modus operandi of irradiated blood. In an endeavor to find out the process of sterilization of the blood stream, opsonic index studies were made to see if the phagocytic power of the polymorphonuclears was influenced by ultraviolet blood irradiation. These studies were started in 1936. When proper exposure *in vitro* had been determined, it was noted that the average increase in the bacterial ingestion by polymorphonuclears was 50 per cent plus. This work was repeated in 1946 with improved technic and the ingestion of bacteria by polymorphonuclears was found to be increased up to 78 per cent. It was also determined that there was very little latitude between the proper exposure at which the polymorphonuclears were stimulated to a maximum degree of ingestion and the amount of exposure at which they were destroyed. Destruction of the polymorphonuclears was characterized by a blowing out of the surface of the cells. Although bacteria were present within the cell, the cell was destroyed on one surface. It was not determined just how this destruction took place but it is significant that when the proper exposure was exceeded by 25 to 40 per cent such destruction consistently took place. The general literature on the subject cites examples of this phenomenon on cells from overexposure.

From the information up to this point and considering the clinical experiments, personal experience and observation, the technic was improved, and this improved technic is known as the "Knott Technic of Ultraviolet Blood Irradiation." The irradiation chamber was also redesigned to give a more thoroughly uniform exposure to the blood and became the Knott Hemo-Irradiation Chamber now in use.

A number of irradiation units were made up and placed in the hands of physicians interested in the procedure so that wide clinical data could be accumulated. It is noteworthy that none of the physicians

using the procedure in different parts of the country found any cause from their observations to disagree with the early hypothesis that had been set up to govern its use. It is also significant that all the physicians using the procedure enjoyed parallel results in like conditions as long as the prescribed technic was strictly adhered to. It was determined from the work done that the established technic was not subject to variation. While the technic was simple, it had to be adhered to strictly. Any variation at all would produce variable results. Investigations that led to the development of the established technic revealed that exposure factors have to be varied as the media exposed are changed, i.e., whole blood requires different handling than does plasma. The depth of the channel in the exposure chamber is a critical factor. Exposures of culture media for the production of vaccines necessitates a different chamber construction and a corresponding change in the time factor to achieve the desired results. The established Knott technic of ultraviolet blood irradiation therapy was worked out for the exposure of whole blood and was arrived at by correlating all of the factors of energy, time cell tolerance and turbulation of the blood. In all media being irradiated it was noted, as set forth in the literature, that intermittent exposure required less total exposure time than a continuous exposure to produce the same end result. Intermittent exposure also facilitates a more uniform dosage being administered.

Dr. George P. Miley, of New York, was one of the early workers with the procedure after Knott improved the chamber and released them to physicians for further accumulation of clinical data. Miley became interested in the oxygen exchange factor, suspected and commented upon by Knott. He was particularly impressed by the rapid disappearance of cyanosis following treatment. Miley made extensive studies on the combined oxygen values of venous blood before and after irradiation in pathologic states. This work[2] was published in June, 1939, and showed a general increase in the combined oxygen value of venous blood following irradiation.

Another early worker, Dr. E. W. Rebbeck, and his co-worker, Glassburn, of the Shadyside Hospital in Pittsburgh, became interested in the relief of toxic symptoms following treatment and surmised that if such was the case, it should be reflected in the lipoidal fraction of the blood and show a change in the chylomicron picture. They made interesting observations in the chylomicron study of about 100 patients. They observed that in advanced pathologic states the clumping of the blood fats was restored to a normal state, both *in vivo* and *in vitro* immediately following the exposure of the blood to the Knott technic, i.e., they noted the dispersal and breaking up of the blood fat clumps present in a toxic patients' blood, plus a return to normal of the lost Brownian movement of lipoid particles, the fats indicating a return to normal of the whole chylomicron picture. As the Brownian movement of the blood fats return, there is often but not always a return to normal of the blood sedimentation rate and a decrease of the toxic symptoms. This latter result is most consistent and is noticeable within twenty-four to forty-eight hours following treatment. Usually a marked drop of temperature to normal is evidenced concomitantly.

The procedure has been used clinically and reported upon by several workers following Hancock and Knott's[1] article on the treatment of infections with the method. Barrett[3,4] discusses five years' experience and reported on irradiation of blood with ultraviolet spectral energy in two articles. Miley[2,5-14] published articles on the use of the procedure in the treatment of thrombophlebitis,[5] staphylococcemias,[6,9] botulism,[7] poliomyelitis,[8] non-healing wound,[10] acute pyogenic infection,[11,14] and Miley and co-workers have reported its use in peritonitis,[15] acute infections[16] and asthma.[17,18]

In 1947 Miley reported the use of this method in seventy-nine consecutive cases of acute virus and virus-like infections, stating that he believed ultraviolet blood irradiation therapy could be relied upon consistently to control an infection of a virus or virus-like nature in a safe and efficient manner. In discussing this paper Barger gave a report of twenty-three cases of bulbar poliomyelitis and six cases of spinal poliomyelitis in which he definitely believed he could confirm Miley's observations. In addition Barger quoted in detail three cases of advanced encephalitis in which he had used ultraviolet blood irradiation, stating that in each case following this type of treatment a rapid disappearance of all signs and symptoms of encephalitis occurred, and that no residuals were apparent after from six months to three years.

Rebbeck has reported its use in Escherichia coli septicemia,[21] postabortional sepsis,[22] puerperal sepsis,[23] and its use preoperatively,[20] and Rebbeck and co-workers reported on peritonitis[15] and double septicemia.[19] Rebbeck and Lewis[30] have found in nine consecutive cases of typhoid fever that in six patients who received ultraviolet blood irradiation there was a remarkably rapid recovery as contrasted with three control cases in which one death occurred.

Olney has reported on the treatment of pelvic cellulitis[24] and biliary disease[25] with ultraviolet blood irradiation. Hancock[26] discusses its use in blood stream infections. Davidson[27] further discusses oxygen reaction in anoxia and bends. Sullivan and Beroza[28] discuss short time irradiation on biochemical compounds and the influence on phagocytosis.

From the published reports of the clinical use of the procedure evidence has been accumulated upon which to found further basic research and investigation.

Up to 1940 the administration of ultraviolet blood irradiation had been carried on by a gravity and manual method of flow and timing. Such a method of application, of course, left a margin for human error, as the operator had to observe the rate of flow and time exposure as well as other factors in the irradiation treatment. To eliminate this margin of error, an apparatus was designed to control mechanically all the factors of irradiation and insure dosage that could be repeated at will. This apparatus now known as the Knott Hemo-Irradiator was first displayed at the Scientific Exhibit Section of the American Medical Association's meeting in New York in 1940.

The apparatus consists of a self-contained, water-cooled, ultraviolet generator and an electrically driven transfusion pump and exposure device that mechanically controls the rate of flow and exposure of the blood to the rays. The apparatus can be accurately controlled as to the amount of ultraviolet generated as well as the time of exposure of the blood to the ultraviolet ray. Between the source of the ultraviolet rays and the blood irradiation chamber there is a revolving shutter that subjects the blood to intermittent exposure to the rays. The turbulence within the chamber augmented by the pump causes the blood to turbulate against the quartz window of the chamber so that a uniform exposure of all parts of the blood is insured.

Since development of the Knott Hemo-Irradiator, clinical application of the procedure has greatly increased. Since 1923, when ultraviolet irradiation of the blood was first conceived, approximately 45,000 treatments have been administered in various pathologic conditions. The field of use has widened materially from the original application of the procedure in the treatment of blood stream infections, as experience and research indicated that it would be adaptable to pathologic conditions other than blood stream infections. As a result of extensive clinical experience and a certain amount of basic research, workers in this field are generally agreed that the favorable clinical results observed are due to many biochemical and physio-

logic effects: notably an increase in blood oxygen absorption, a rise in phagocytic action and general immunologic status, the setting up of an efficient detoxifying mechanism, and increased rate and volume of blood flow through the capillary circulation and beneficial alteration chemically of certain important constituents of the blood, e.g., adrenalin, dihydroxy-phenyl-alanine, cysteine hydrochloride, glutathione and ergosterol.

Thus ultraviolet blood irradiation therapy must be considered as a powerful therapeutic agent which the skilled physician and surgeon can use in a wide variety of disease processes, since in using this method one is applying certain fundamental biochemical and physiologic effects.

The favorable results experienced from the clinical use of the ultraviolet blood irradiation certainly warrants extensive investigation of the modus operandi of the procedure and detailed, intensive clinical studies to determine fully its potentialities.

REFERENCES

1. HANCOCK, V. K. and KNOTT, E. K. Irradiated blood transfusion in the treatment of infections. *Northwest Med.*, 33: 200, 1934.
2. MILEY, GEORGE. The ultraviolet irradiation of auto-transfused human blood; studies in oxygen absorption values. *Am. J. M. Sc.*, 197: 873, 1939.
3. BARRETT, HENRY A. The irradiation of auto-transfused blood by ultraviolet spectral energy: results of therapy in 110 cases. *M. Clin. North America*, 24: 723, 1940.
4. BARRETT, HENRY A. Five years' experience with hemo-irradiations. *Am. J. Surg.*, 61: 42–53, 1943.
5. MILEY, GEORGE. The control of acute thrombophlebitis with ultraviolet blood irradiation therapy. *Am. J. Surg.*, 60: 354–360, 1943.
6. MILEY, GEORGE. Efficacy of ultraviolet blood irradiation therapy in the control of staphylococcemias. *Am. J. Surg.*, 64: 313–322, 1944.
7. MILEY, GEORGE. Recovery from botulism coma following ultraviolet blood irradiation (Knott technic). *Rev. Gastroenterol.*, 13: 17, 1946.
8. MILEY, GEORGE. Ultraviolet blood irradiation therapy in acute poliomyelitis. *Arch. Phys. Therapy*, 25: 651–656, 1944.
9. MILEY, GEORGE. Disappearance of hemolytic staphylococcus aureus septicemia following ultraviolet blood irradiation therapy. *Am. J. Surg.*, 62: 241–245, 1943.
10. MILEY, GEORGE. Ultraviolet blood irradiation therapy (Knott technic) in non-healing wounds. *Am. J. Surg.*, 65: 368–372, 1944.
11. MILEY, GEORGE. The Knott technic of ultraviolet blood irradiation in acute pyogenic infections. *New York State Med.*, 42: 38–46, 1942.
12. MILEY, GEORGE. Present status of ultraviolet blood irradiation (Knott technic). *Arch. Phys. Therapy*, 25: 368–372, 1944.
13. MILEY, GEORGE. Ultraviolet blood irradiation. *Arch. Phys. Therapy*, 23: 536, 1942.
14. MILEY, GEORGE. Ultraviolet blood irradiation therapy (Knott technic) in acute pyogenic infections. *Am. J. Surg.*, 57: 493, 1942.
15. MILEY, GEORGE P. and REBBECK, E. W. The Knott technic of ultraviolet blood irradiation as a control of infection in peritonitis. *Rev. Gastroenterol.*, 10: 1, 1943.
16. MILEY, GEORGE and CHRISTENSEN, JENS A. Ultraviolet blood irradiation therapy: further studies in acute infections. *Am. J. Surg.*, 73: 486–493, 1947.
17. MILEY, G. P., SEIDEL, R. E. and CHRISTENSEN, J. A. Preliminary report of results observed in eighty cases of intractable bronchial asthma. *Arch. Phys. Therapy*, 24: 533, 1943.
18. MILEY, G. P., SEIDEL, R. E. and CHRISTENSEN, J. A. Ultraviolet blood irradiation of apparently intractable bronchial asthma. *Arch. Phys. Med.*, 27: 24, 1946.
19. REBBECK, E. W. and WALTHER, R. A. Double septicemia following prostatectomy treated by the Knott technic of ultraviolet blood irradiation. *Am. J. Surg.*, 57: 536, 1942.
20. REBBECK, E. W. Preoperative hemo-irradiations. *Am. J. Surg.*, 61: 259–265, 1943.
21. REBBECK, E. W. Ultraviolet irradiation of blood in the treatment of Escherichia coli septicemia. *Arch. Phys. Therapy*, 24: 158–167, 1943.
22. REBBECK, E. W. Ultraviolet irradiation of auto-transfused blood in the treatment of post-abortional sepsis. *Am. J. Surg.*, 55: 476, 1942.
23. REBBECK, E. W. Ultraviolet irradiation of auto-transfused blood in the treatment of puerperal sepsis. *Am. J. Surg.*, 54: 691, 1941.
24. OLNEY, R. C. Ultraviolet blood irradiation treatment of pelvic cellulitis. *Am. J. Surg.*, 74: 440–443, 1947.
25. OLNEY, R. C. Ultraviolet blood irradiation in biliary disease. *Am. J. Surg.*, 72: 235–237, 1946.
26. HANCOCK, V. K. Treatment of blood stream infections with hemo-irradiation. *Am. J. Surg.*, 58: 336, 1942.
27. DAVIDSON, WM. M. Ultraviolet irradiation relative to anoxia and bends susceptibility. *U. S. Nav. M. Bull.*, 43: 37–38, 1944.
28. SULLIVAN, M. X. and BEROZA, M. The effect of short time ultraviolet irradiation on blood and biochemical compounds. (To be published.)
29. MILEY, G. P. and CHRISTENSEN, J. A. Ultraviolet blood irradiation therapy in acute virus-like infections. *Rev. Gastroenterol.* 15: 271–277, 1948.
30. REBBECK, E. W. and LEWIS, H. T., JR. (To be published.)