

THE HISTORY
OF
THE
HOAGLAND
LABORATORY

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When Frederick Tilney left Brooklyn in 1915, he served for a short time at the New York Post-Graduate Hospital as assistant to Dr. Smith Ely Jelliffe. In that same year he was offered the professorship of nervous anatomy and neurology at the Long Island College Hospital but declined as he had just been appointed professor of nervous diseases at the College of Physicians and Surgeons of Columbia University. The trustees of the Long Island College of Medicine made him a member of their board in 1931 as the first alumni trustee.

In 1935 he became the first director of the New York Neurological Institute. He died in 1938.

CHAPTER XIV

The Department of Bacteriology

The death of Ezra Wilson in 1905 left the department of bacteriology in the hands of Benjamin White. He knew his own competence as a biochemist but he realized that his training in bacteriology was not sufficient for him to assume the responsibility of directing the department and doing bacteriological research. There was no thought of looking elsewhere for an experienced director, for both Charles and Elizabeth Gates knew that White was the man they wanted for the position.

So it was decided that White should have a year of specialized training abroad. The death of Charles Gates did not change this plan since White had already reached an understanding with his sponsors and Elizabeth Gates agreed to carry it out. White was to receive a leave of absence from June 1, 1906, to October 1, 1907. During his absence he was to receive a salary of \$1500 a year to be increased to \$2000 a year upon his return. He would then also be given an assistant director and a laboratory helper.

The board of trustees was very cautious about making financial commitments. Early in 1906 the laboratory received

\$5000 from the estate of Eliza E. Hoagland, (widow of the founder) who had died in October of 1905. It had received donations of \$1000 each from Luella Hoagland, Cora Tange-man and Charles Gates. But the experience of recent years had shown all too clearly that ever increasing deficits were in prospect unless the research program was sharply reduced or unless the Hoagland family made some substantial arrangement. Apparently the trustees never tried to apply pressure on the faculty or board of regents of the Long Island College Hospital to make some contribution to the maintenance and repairs of the laboratory.

In the minutes of the Hoagland board, dated May 25, 1906, it was stated "that a committee of trustees Matheson and Hill was appointed to confer with the family of the late Dr. Hoagland and obtain their wishes as to the filling of the vacancy in the board of trustees caused by the death of President Gates, and as to the future officials of the laboratory; also to consult with them as to the supply of funds to carry out the portions of the plan contained in the communication of Dr. White (concerning his future salary and that of the assistant director.)"

At the June 5 meeting of the trustees, Mr. Matheson reported that he had conferred with Mrs. Gates. She had indicated that the election of Mr. William H. Nichols to the board would be satisfactory, and that she and her two sisters would each agree to contribute \$1000 a year to the laboratory. She also confirmed the agreement with Dr. White as outlined in his letter to the trustees. The Hoagland board thereupon elected Mr. Nichols to the vacant seat and approved the appointment of Dr. White for the year beginning October 1, 1907.

White left for Europe in June and the department of bacteriology was closed down completely until his return. During his stay abroad, White studied bacteriology, protozoology and serology at the Imperial Institute for Infectious Diseases

at Berlin; from there he went to St. Anna's Kinderspital in Vienna where he studied epidemic meningitis under Dr. Jehle. Thence he went to the Royal Hygienic Institute at Munich to investigate the serology of anthrax immunity under Professor Gruber. Finally he took a course on opsonins and vaccine therapy under Sir Almroth Wright at St. Mary's Hospital, London.

Upon White's return, one of his first acts was to nominate Dr. Oswald T. Avery for the position of associate director in the department at a salary of \$1200, which was increased to \$1500 in 1909.

The story of Oswald Avery's coming to the Hoagland Laboratory is best told in his own words:

"I was graduated from the College of Physicians and Surgeons in 1904. The practice of medicine did not appeal to me, for I preferred to work in the laboratory. It happened that at that time Sir Almroth Wright came to New York from England and gave a lecture at the Academy of Medicine on his newly invented opsonic technic. The New York City Health Department was interested in this and arranged to have a colleague of Sir Almroth give a short course of instruction to a small group.

"I was one of those to take this course. At its completion, Dr. William Park gave me a job doing opsonic indices for the Board of Health at a stipend of \$50 per month for part-time work. I also found part-time employment doing milk bacteriology for the Sheffield Company. Pasteurization of milk was just coming in; I made bacterial counts of milk before and after pasteurization at a stipend that was also \$50 per month.

"Benjamin White and I met in this way. While I was a student at the College of Physicians and Surgeons, I roomed with a young law student, William M. Parke, who after admission to the bar practiced for a time in Brooklyn. This young lawyer lived in a rooming house on Remsen Street. It so happened that Benjamin White lived in the same house, and thus we became acquainted. White mentioned to me that

he needed a young doctor to be his assistant director. I responded enthusiastically and so I was invited over to the Hoagland Laboratory."

William M. Parke, mentioned by Avery, had been Avery's classmate at Colgate Academy and his roommate at Colgate University. While studying law at the New York Law School, Parke had roomed at the house of Avery and his mother. Mr. Parke became a trustee of the Hoagland Laboratory in 1940.

The department of bacteriology initiated a most comprehensive and productive program in the fall of 1907. As White outlined it in his annual report to the trustees in May, 1909, the department had "a general plan embracing three specific purposes, i.e., first, to investigate bacteriological problems of a purely scientific nature; second, to prosecute researches upon bacteriological questions related to medical diagnosis and therapeutics; and third, to aid the practitioners in the diagnosis of obscure diseases of bacterial origin, and to prepare and furnish to physicians such therapeutic agents as the laboratory facilities permitted."

White had some very definite ideas concerning the respective function of the scientific staff and the board of trustees. The staff was responsible for the investigative work and it was the responsibility of the trustees to find the means. In other words, when money was needed for worthwhile projects, the trustees were obligated to find it.

This attitude did not make Benjamin White popular with the Hoagland board. Mr. William Hill, who was a trustee at that time, has described him as a "kicker." On some occasions when financial troubles were acute, the secretary of the board rather wistfully pointed out that if White's salary were eliminated there would be no difficulty in balancing the budget. But White had powerful backing by the daughters of Cornelius Hoagland, who saw in him the man who was going to use the laboratory in the way their father had intended it to be used.

The initial plan of White and Avery was to resume the investigation of the toxins of the typhoid bacillus that was begun by Wilson in 1904 and on which White had done some work in 1905. They soon decided that this was too ambitious an undertaking and it was abandoned. As an offshoot of this work, White published a brief account in 1908 of a small ball-mill of his own invention that he had used for grinding the typhoid bacilli for the preparation of toxins. Another abortive effort was a study of the "Pfeiffer phenomenon" which did not yield anything worthy of publication. Two other researches were more productive.

The first was a study of the milk-souring bacteria of the "Bulgaricus" group. Fermented milks (such as yoghurt, leban and others) have long been a staple article of food in the Balkan countries and in the Middle East. They had been recently publicized by the work of Elie Metchnikoff, who believed that their consumption had a favorable effect upon the intestinal flora because they replaced the harmful putrefactive bacteria with the benign lactic acid producing species.

This theory became medically very popular. The lactic acid bacteria were called "the bacilli of long life," and fermented milks were widely used in treating that vague condition called "intestinal auto-intoxication." It so happened that the Hoagland Laboratory was then, as it is now, in a Syrian neighborhood, and the Syrian grocers prepared and sold "leban," the fermented milk of their native country.

White and Avery came to know some of these Syrian grocers and they became acquainted with leban and learned to enjoy it. Their taste for the leban encouraged them to study it bacteriologically and this in turn led to an extensive study of related organisms. Many years later, Avery recalled that he had a "wonderful time" investigating these bacteria that they obtained from all over the world, mostly in commercial preparations of various fermented milks.

When this work was completed in 1909 it was published

as "Observations on Certain Lactic Acid Bacteria of the *Bulgaricus* Type." The authors concluded that there were two distinct types of lactic acid bacilli which they designated as types A and B. The type A stained homogeneously and produced up to 3.7% of optically inactive lactic acid; whereas in type B, intensely staining granules were present and no more than 1.6% of laevo-rotary lactic acid was formed. In the course of this investigation, White and Avery accumulated a great amount of unpublished data on various commercial fermented milks and milk-souring "starters." These data were sent to Dr. Wiley, Chief of the United States Bureau of Chemistry, for use in the federal control of foods.

In the same year, a research on "The *Treponema Pallidum*, Observations on its Occurance and Demonstration in Syphilitic Lesions," was completed and published. Schaudinn had discovered four years before the spiral organism that causes syphilis. Methods for the detection and recognition of the "pale spirochete" were not widely known. Ordinary dyes failed to stain this organism and inspection by transmitted light did not reveal it.

White and Avery investigated several methods then in use abroad. They concluded that "dark field" examination of fresh exudates was most reliable but the apparatus needed was not (at that time) readily available. The principle of the "dark field" is that when minute objects are illuminated from the side by a strong beam of light, these objects appear very bright on a dark background and so are readily visible. They also tested various staining methods and found one devised by Schereschewsky to be most satisfactory.

During this time Avery also did some experimental work with the so-called "Meiostagmin reaction" which was claimed by Ascoli to be of value in the diagnosis of cancer. This was a combined surface tension and viscosity determination, done on the serum of the patient. The claims of Ascoli were not substantiated by this study so the work was dropped.

Dr. A. T. Bristow, a surgeon of the Long Island College Hospital, had a patient who was eventually diagnosed as having chronic glanders. Benjamin White recovered and identified the bacillus of glanders from the metastatic abscesses. As the patient remained chronically ill, an autogenous vaccine was prepared and administered. The patient recovered and it was inferred that his recovery was hastened by the vaccine treatment. The report of this case was published in 1910.

Associated with Dr. Louis C. Ager, by now a prominent pediatrician, Oswald Avery wrote a report on "A Case of Influenzal Meningitis." The importance and common occurrence of the Pfeiffer bacillus (*Hemophilus influenzae*) as a cause of meningitis in children was not realized at that time because the best methods of cultivating this germ were not yet known and only two or three cases of this kind had ever been reported.

White and Avery published in 1910 an important study entitled "Concerning the Bacteriemic Theory of Tuberculosis." This work was inspired by the claims of Dr. Randle C. Rosenberger who had said that tubercle bacilli could be demonstrated in stained smears of the blood of tuberculosis patients in all stages of the disease. This, if verified, would be a most important finding. White and Avery examined the bloods of fifty-one tuberculosis patients by various technics and were unable to find tubercle bacilli in any of them. They concluded that the acid-fast bacilli seen by Rosenberger were not tubercle bacilli but accidental contaminants probably coming from the distilled water.

Both White and Avery were greatly interested in the therapeutic and prophylactic use of vaccines, and especially in autogenous vaccines. Among others, they prepared gonococcal vaccines for Dr. J. Sturdivant Read to use clinically. It was concluded that they had no beneficial effect on acute early cases of gonorrhea, but apparently had some value in chronic infections. They also prepared typhoid vaccines and ad-

ministered them to hospital personnel at the time Major Russell of the United States Army began using them.

Because of his extensive knowledge of the subject, Avery was asked to write the chapter on "Opsonins and Vaccine Therapy" (with Dr. N. B. Potter) for Hare's "Modern Treatment," a widely used text on clinical medicine of the time.

Another field of interest was the bacteriology of post-surgical infections, and White and Avery hoped eventually to write a monograph on that subject. Partly to obtain material for this projected work, clinicians from the various hospitals of Brooklyn, and especially from the Long Island College Hospital, were encouraged to bring their bacteriological problems to these men, and many did. Both men were very approachable and Avery was especially so. He loved to teach and was always ready to give individual lectures to any who came to him for information. It was a twist of fate that Avery, the superlative teacher, never held an academic position and never regularly taught a class of medical students.

PART 2

The Department of Bacteriology

Benjamin White suffered a severe hemorrhage from the lungs in July of 1909. Avery found the characteristic "acid-fast" bacilli in his sputum, which made certain the diagnosis of tuberculosis. In August, White was sent to the Trudeau Sanitarium at Saranac Lake on a stretcher. It was at first thought that he had tuberculous pneumonia and the prognosis appeared very grave.

Fortunately it turned out to be less serious than at first feared. By the end of September, White reported to the Hoagland trustees that he was already convalescent and feeling better than he had felt for years. Dr. Edward R. Baldwin had assured him that his troubles were over though he would still need rest and care. So White asked for a leave of absence

until October 1910; in the following year he asked to have that leave extended to October of 1911.

Though White was at Saranac Lake because he was ill with tuberculosis, nevertheless he was soon able to do a considerable amount of research. Most of the workers in the sanitarium and in the laboratory had come there because they themselves had had tuberculosis; this was true of Dr. Trudeau himself as well as of Baldwin, Gardner and others. They learned to live with their disease and would work for two or three hours a day, adjusting everything to that pace.

During 1910 and 1911, White actually accomplished a great deal of research. He studied the chemistry of the tubercle bacillus and especially its fatty constituents, and the action of normal and tuberculous body fluids upon these lipids. Some of the early part of 1911 was spent in Brooklyn but in the summer months he returned to Saranac Lake where Avery accompanied him to participate in the work.

Benjamin White, however, did not devote all of his time to "curing" and to experimental work, for it was during this period that he met the young lady who was later to become his wife. This was Laura Genoa Solari, who lived at Saranac Lake at that time because she had a sister there who was suffering from tuberculosis.

While convalescing, White still directed the department of bacteriology in Brooklyn. This he did, partly by letter, partly by occasional visits.

In October, 1909, White secured the appointment of Dr. Charles Z. Garside, late chief of the department of bacteriology at the Lederle Laboratories, to be Avery's assistant. Dr. Garside was actually on a part-time basis for he was also on the staff of the medical department of Fordham University where he was adjunct professor of bacteriology. On coming to the Hoagland Laboratory, he began an investigation of the biology of the diphtheria group of organisms. This work was reported before the County Medical Society but

never published. He also participated in the preparation and evaluation of bacterial vaccines, a research that was summarized in an article published in 1911. Dr. Garside resigned in 1912 to devote full time to his duties at Fordham. He died soon after while still a young man.

At a meeting of the hospital staff held on May 11, 1910, it was moved by Dr. Van Cott and carried that "the board of trustees of the Hoagland Laboratory be asked to furnish a special assistant from the department of bacteriology of the Hoagland Laboratory to be at the service of the staff of the Long Island College Hospital for bacteriological work in the hospital and the making of vaccines, and that he be at the call of the attending staff and receive the title of 'Bacteriologist to the Hospital' the salary of said bacteriologist and expenses of the work to be borne by the Hoagland Laboratory."

There had already been several unofficial conferences between White and the hospital staff, and White was strongly in favor of such an appointment. It is very possible that he himself originated the idea, for it was a part of the general program for his department as outlined in his 1909 report to the trustees. He had especially in mind two different lines of research, both of which required abundant clinical material: the preparation and improvement of autogenous vaccines, and the investigation of post-surgical infections.

White was asked to find a suitable man. He appointed Harold W. Lyall with the title of clinical assistant in bacteriology at a salary of \$1200 a year. The appointment became effective October 1, 1910. Mr. Lyall was a graduate of Brown University with the degrees of A. B. and M. A. He had some experience as bacteriologist doing part-time work for the Rhode Island State Board of Health.

Lyall very soon established an efficient bacteriological service for the Long Island College Hospital. He was warmly praised by Dr. White for this and for his ability to maintain

cordial relations with the hospital staff. The preparation and evaluation of autogenous vaccines was under Avery's supervision. Referring to these vaccines in his 1912 report to the trustees, White commented that "most gratifying results in many cases were being obtained."

Parts of Lyall's work were reported in two different publications in 1912. One was on the blood culture findings in 45 cases of pneumonia and the other was on a rare case of meningitis caused by the typhoid bacillus.

The department was further enlarged in 1911 by the addition of a stenographer and librarian, Miss Barbara M. Bradford. Among her duties was that of establishing a filing system for the cataloging of scientific articles.

The first portion of their work on the chemistry of the tubercle bacillus was completed by White and Avery during 1911. This was published in 1912 under the title of "The Action of Certain Products Obtained from the Tubercle Bacillus. A. Cleavage Products of Tuberculo-Protein Obtained by the Method of Vaughn. The Poisonous Substance." The experimental work for this paper was done in part at the Saranac Laboratory for the Study of Tuberculosis and in part at the Hoagland Laboratory.

In pursuing and interpreting this work, White and Avery were rather carried away by a theory originated by Victor Vaughn. This theory held that the toxic effect of certain bacteria was due to a poisonous fraction that was split off from the bacterial protein. Experimentally this was conveniently done by the action of hot alkaline alcohol. True, similar toxic fraction could be split off from other proteins such as egg albumen or serum protein. But in an infection it was the bacterial protein that was at the spot. The Vaughn theory was in vogue at that time. In the same year, 1912, White presented a paper before the annual meeting of the National Association for the Study and Prevention of Tuberculosis, in which he elaborated on some theoretical implications.

During the early part of 1911 the outlook for the department seemed bright indeed. White had recovered his health and was working enthusiastically as was Avery. Garside and Lyall were eager and doing excellent work. The department rated very high in scientific circles for its research had been of first quality. Even more interesting and important problems were contemplated. Yet in July of 1911 the staff became uneasy and disheartened. The reason was entirely one of Hoagland Laboratory finances.

PART 3

The Department of Bacteriology

Ever since 1903 the expenses of running the Hoagland Laboratory had been greater than the income from endowments and the fees paid by the college. The Hoagland family had made annual donations averaging \$3662 over the eight year period from 1903 to April 30, 1911. Up to that point, these donations had been sufficient to wipe out the deficits.

In the year 1910-1911, there was an unusually large expenditure for repairs and improvement of the building (\$3762.02 had been required for this purpose). At the same time, the only contribution received was \$3000 from Ella Hoagland. Dr. Raymond's report to the board, made on May 26, stated that the income for the preceding year had been \$9630.12, including Ella Hoagland's contribution, but total expenditures were \$13,926.82, leaving a deficit of \$4296.70. Dr. Raymond estimated that the total deficit for 1911-1912 would be \$6354.40. Further repairs to the building were still needed and two new workers had been added to the payroll—Lyall and Miss Bradford. Obviously the endowment could not be invaded every year for such sums as this.

The crisis in 1911 was due to the fact that up until May 26 nothing had been heard from the Hoagland sisters. On this date, the board of trustees directed the secretary to describe the

plight of the laboratory to Mrs. Gates, Mrs. Tangeman and Miss Hoagland and "to ask from each, for the guidance of the board, an expression as to their opinion and wishes as to the future work of the laboratory," and to inform them that no appropriations would be made until the board learned the view of the ladies.

No word had been received by June 8 from the "benefactors," as they were called by the board. But on June 17, Mrs. Gates sent a check for \$1000, so the trustees appropriated money for salaries of the whole staff but only to October.

The members of the department of bacteriology were quite shaken by this turn of events. What steps were taken by Benjamin White, if any, are not known. But Oswald Avery spent his vacation at the biological laboratories of the H. K. Mulford Company, instructing its staff in bacteriological technic and at the same time learning their methods of preparing antitoxins, tuberculin and vaccines. Garside arranged to return to the medical department of Fordham University on a full-time basis. Lyall alone appeared to be secure in his position since he would probably be retained to do the bacteriological work for the hospital.

In order to understand the financial situation thoroughly, it is necessary to appreciate the fact that there was a fundamental difference in the point of view of the board of trustees and that of the Hoagland daughters.

The board believed that the laboratory should help the Long Island College Hospital and cooperate with it as much as possible. This view was reflected by Mr. Matheson, president of the board, in a letter to Mrs. Gates dated June 20, 1911. Mr. Matheson here stated that the "trustees have always encouraged Dr. White in any definite practical proposition he had to make that was within our means. While I am the last in any way to complain or delay the highest ideals, I do not sympathize with the idea that we can best serve the needs of the community by concluding that the cause of the medical

school is hopeless. I cannot escape the conviction that it is our duty to elevate it and that we can do this best by cooperation, and I have amply proved that both the college and hospital and the Polhemus Clinic are agreed for cooperation."

Ella Hoagland and Mrs. Gates were far less friendly to the college and the hospital. Miss Hoagland, who had given \$3000 the year before, made no reply to the secretary's urgent letter. Mr. Matheson then cabled her, since she was abroad at that time, "Must decide on laboratory's future. Can you assist?" Miss Hoagland cabled Mrs. Gates. "Matheson's address lost. Tell him will assist laboratory if it is kept from hospital."

At the time Mr. Matheson wrote his letter, the recommendations of the Flexner Report had not been adopted and the system of paying "dividends" to the faculty of the college was still in effect. The Hoagland daughters may have been aware of this practice, and of the contents of the Flexner Report, and this may have affected their thinking on the subject of further financial support.

Mrs. Elizabeth Gates was even more outspoken. In a letter written to Mr. Matheson on June 17, 1911, she said, "I do not think it necessary for me to tell you that I have not been in sympathy with things as they have gone at the laboratory these last five years. But Dr. White has been good enough to tell me all the good things which seem to be ahead of them in their work there, and of the broadening they hope to reach under the new work planned for next year. As things have been there, I have felt that I could not agree to any further support, consequently I withheld my check last autumn.

"I think Dr. White is entirely right in what he has been trying to do in the way of 'housecleaning.' From what he tells me there has been a change of view among some of the people there, in whom I have no confidence. I want to be sure that they will stick to their word. I am quite sure that both my

father and Mr. Gates would have approved of Dr. White's course, and it will be a great pleasure to me if things could be arranged according to his plan. Anything but have the laboratory used as a classroom for a second-rate medical institution.

"I am quite ready to adopt the report as Dr. White sent it to me. Rather than curtail any of the actual work of the laboratory, I am enclosing my check for \$1000 which I did not send last September."

Mrs. Gates' reference to 'housecleaning' may be taken literally, because in his annual report of May, 1911, White commented on the poor janitor service and the general dilapidation and lack of cleanliness of the building, and suggested that the college, which used three of the four floors of the laboratory, might render some assistance.

Mrs. Gates' bitter words were no more caustic than those of Abraham Flexner when he made his devastating report in 1911. Her feeling was well expressed in a letter she wrote to Mr. Hill some years later (1922): "I always felt that if the laboratory were being used for the purpose my father intended, there would not be such a drain on its funds for repairs, etc., and I surely would have been willing to help more. However, since the trustees decided to make it a part of the Long Island College, they must find funds for such expenditures."

Nevertheless, in October of 1911, Mrs. Gates sent Mr. Matheson another check for \$2000. In her accompanying letter she said, "It seems to me the trustees should make some plan to help carry on the work there . . . I do not feel that it is up to my sisters and myself to make good such a large deficit every year. The endowment fund should be raised . . . I am ready to contribute \$10,000 to such a fund."

At a special meeting of the trustees held September 15, 1911, Drs. Avery and Garside and Mr. Lyall were reappointed for the ensuing year and appropriations made for their salaries, with a modest increase for Dr. Avery. These men had

spent all summer not knowing if they would have places after October 1. Dr. White was reappointed provided funds would become available. Dr. Raymond, in a statement to the board, made the delicate suggestion that "if Dr. White is not re-engaged, there will be a surplus of \$1446.10." When Ella Hoagland sent her check for \$3000 later in the year, Dr. White was reappointed unconditionally.

Dr. Raymond's estimate had been that \$6354 would be needed in 1911-1912 over and above the probable income of \$6732.50. Ella Hoagland and Mrs. Gates had just contributed \$6000, so it was felt that the research program could proceed.

PART 4

The Department of Bacteriology

It was completely characteristic of Benjamin White that he promptly asked for an increased appropriation for salaries, apparatus, supplies and current expenses. He also asked for an increased staff including another assistant, another laboratory helper, a pathologist and a chemist (presumably part-time). The pathologist was needed to prepare and study tissue sections from animals injected with different chemical fractions of the tubercle bacillus. Dr. Frederick Tilney was temporarily doing this work for him at the College of Physicians and Surgeons.

White also suggested that it would be desirable to establish four Research Fellowships paying \$500 to \$900 yearly for the training of laboratory workers and the prosecution of current investigations.

New bacteriological research was under way even before it was settled that the program would go on. During the summer of 1911, Dr. Charles E. North of New York City, had investigated an outbreak of typhoid fever in an Adirondack camp. Most of the laboratory examinations of blood and feces were made at the Hoagland Laboratory by Avery and Garside

and the epidemic was thereby traced to a healthy typhoid carrier.

Avery and Lyall were also conducting an investigation which was published as "Secondary Infection in Pulmonary Tuberculosis." This work was important because the medical literature was full of conflicting claims as to the occurrence of secondary infection in this disease as established by sputum cultures and more especially by blood cultures. Avery and Lyall made careful cultures from the sputa of fifteen cases and found that the flora did not differ in any significant way from cases of non-tuberculous diseases of the respiratory tract. Blood cultures made on five cases of bronchiectasis and 110 cases of pulmonary tuberculosis were uniformly negative.

The authors ascribed the previously reported positive results to faulty technics, which often resulted in bacterial contamination of the patient's blood while withdrawing a sample for culture. To prevent this, they made a small cut through the skin after treating it with iodine solution, thus permitting the vein to be entered directly with the needle without passing through the skin (which can never be completely sterilized). This work was done at the Ray Brook Hospital for Incipient Tuberculosis, the Brooklyn Home for Consumptives, and the Hoagland Laboratory.

During this time White and Avery made a study of the immunity reactions to a pure substance—the crystalline vegetable protein edestin, which is derived from hemp seed. This they obtained in a highly purified state from Dr. Thomas B. Osborne of Yale University. The work, when completed, was published as Part III of a series of papers on "The Biological Reactions of Vegetable Proteins." Parts I and II of this series were contributed by Drs. H. Gideon Wells and Thomas B. Osborne.

White and Avery were able to produce in animals specific antibodies to edestin with which they could demonstrate the immune phenomena of precipitation, complement deviation

and guinea pig anaphylaxis. Edestin, like many plant proteins, will agglutinate the red blood cells of the sheep and man and they showed that the antiserum to edestin would inhibit the hemagglutination.

They also found that when the edestin-antibody precipitate was washed and then incubated with fresh normal guinea pig serum, it yielded a substance or substances that, when injected intravenously into guinea pigs, produced a fatal anaphylactic-like intoxication, similar to that of the anaphylatoxin of Friedburger. This field of investigation was still unexplored ground at that time.

White had a clear concept that antibodies were responsible for many of the manifestations of disease, a very modern point of view that was brought out in a paper read before the annual meeting of the Medical Society of the State of New York in April of 1912.

An extensive epidemic of severe sore throat occurred in the city of Cortland and the village of Homer early in 1913. This epidemic was thoroughly studied by Drs. Charles E. North, Benjamin White and Oswald Avery. A beta hemolytic streptococcus was recovered from patients. It was found that over 70% of the cases occurred among the patrons of a single dairy. In this dairy two cows were found that had acute streptococcal inflammation of the udder (garget). A streptococcus isolated from their milk appeared identical with the epidemic strain. Similar milk-borne epidemics due to streptococci had been reported in Boston in 1910-1911 and in Baltimore in 1912. This study was published in January, 1914.

Oswald T. Avery resigned as associate director of the department of bacteriology on September 4, 1913, to go to the Rockefeller Institute for Medical Research, where his contributions have made scientific history. In later years, Dr. Avery told the full story of events leading to this step.

In the spring of 1913, Dr. Rufus Cole, director of the Rockefeller Institute Hospital, paid a visit to the Hoagland

Laboratory. He found Avery at his laboratory bench adding bile to a broth culture of pneumococci in order to dissolve them. Cole explained that at the Institute they did not use crude bile for this purpose, but bile salts dissolved in a buffered solution. Avery was much impressed. He wondered at the time why Cole had come to Brooklyn on a seemingly casual visit. White guessed correctly that his purpose was to secure Avery for the Institute.

In a few days Avery was asked to come to the Institute and look it over. At luncheon he found himself seated next to Dr. Simon Flexner, the head of the Institute. Flexner was full of questions about his work, his training, his interests. Later in the day, Cole suggested that there might be an opening for him there. That summer, while Avery was working at Saranac Lake, he received a letter from Cole offering him a position.

Avery was not then fully aware of the gloomy outlook at the Hoagland Laboratory, for he first declined Cole's offer. He said he felt happy at the Hoagland Laboratory; the work was interesting; he liked his colleagues. He liked his complete freedom to work at what he wanted to do without being put under pressure.

Cole, however, did not give up. He had been greatly impressed by the article on "Secondary Infections in Pulmonary Tuberculosis" done with Lyall. By the end of the summer, Avery was persuaded to come to the Rockefeller Institute.

Thus ended six years of service at the Hoagland Laboratory. As he himself said at a later time, it was here that he learned bacteriology and here that he learned research. To him it was "a wonderful place for a young man to get his start." His scientific accomplishments at the Rockefeller Institute are too extensive and too well known to be mentioned here.

Now working without Avery, White continued alone with his studies of the lipids of the tubercle bacillus and their possible role in anaphylaxis. Previous reports in the literature

concerning the antigenicity of these lipids were contradictory. It would be of the highest importance to learn of their true role in tubercular infection. In this investigation White carefully freed the fatty constituents from all associated protein and found that they then had no antigenicity whatever when

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and an indifferent group.
into smaller groups on
acid from the carbohy-
inulin. This paper was

the same time—"Observa-
the Streptococci"—Lyll
e production and nature
known that there are two
nolytic streptococci; the
'streptolysin S.' He con-
with the bacterial bodies

periments in Anaphylaxis with the L
Bacillus" was published in 1914. It wa
the Tenth Annual Meeting of the As
and Prevention of Tuberculosis.

Harold W. Lyall succeeded Osw
director of the department of bacteriol
was on the classification of the streptoco
methods for classifying these impor
basis of their antigenic constitution we
Classification on the basis of biological
be the only choice.

Lyall divided the streptococci in
according to their reaction on sheep
made on blood agar plates were su
Lyall devised a more accurate method
were incubated with washed sheep ery
Three clear-cut groups were distinguis
a methemoglobin-producing group, an
Each of these was in turn subdivided
the basis of their ability to produce
drates salicin, raffinose, mannitol and
published in 1914.

In a second paper published at th
tions on Hemolysin Production by
studied the factors that influenced the
of streptococcal hemolysin. It is now k
distinct hemolysins produced by hem
one he studied is now designated as '
cluded that it was closely associated v

and was not in solution. He also noted the marked heat-ability of this hemolysin. These two papers were submitted as his thesis for the Ph. D. degree, which was conferred upon him by Brown University.

The entire staff of the bacteriology department, including Avery, was invited to spend the summer of 1913 at the State Hospital for Tuberculosis at Ray Brook. There it began an intensive investigation of complement fixation as a diagnostic method in tuberculosis and syphilis. The loss of Dr. Avery at the end of August caused the staff to abandon the tuberculosis part of this work upon their return to Brooklyn but the study of the Wasserman reaction in syphilis was continued.

Dr. White reported to the trustees that the Wasserman test as done in Brooklyn at that time was most unrealistic and unsatisfactory. This was because the hospitals and laboratories had been using a modified method which was quite worthless. The staff introduced the original and more difficult technic with such good results that it was adopted by other institutions. A course of instruction was given by White and Lyall to laboratory workers from Brooklyn, New York, and Providence. When the department of bacteriology was broken up, Dr. Archibald Murray took over this work in which he had become greatly interested, for he had been studying the relation of the Wasserman reaction to the treatment of syphilis and tabes.

PART 5

The Department of Bacteriology

The financial crisis of 1911 was repeated in 1912 and again in 1913; if anything the situation had become worse. The trustees became increasingly pessimistic as shown by a letter dated November 1, 1912, sent to Mrs. Gates and Ella Hoagland.

"To the Benefactors of the Hoagland Laboratory:

At a meeting of the Board of Trustees, held this day, the financial affairs of the Hoagland Laboratory and its future constituted the sole object of consideration. It was resolved that the Secretary communicate to the Benefactors the opinion of the Board that the time has arrived when the work of the Laboratory should be established on a firm foundation for all time. That it is unwise to continue the work from year to year depending on donations, but that if it is to be continued as at present conducted, it will be necessary to add to the present endowment at least \$125,000. The present Board feel that they would be unable to effect this increase, but are not willing to stand in the way of having the affairs of the Laboratory administered by other Trustees, if such Trustees can bring about the desired result. If this increased endowment cannot be obtained the Board sees no other way than to curtail the work to the amount of the income. This would necessitate the cessation of the research work as it is now being carried on, and the continuance of the services of the Director of Bacteriology and his associates. In justice, however, to them the Board desire to continue their services for another year to give them time to adjust themselves to the new conditions, but to do this must have additional financial assistance to the amount of \$3000."

Early in 1913, White prepared an elaborate statement for the consideration of the trustees. In it he pointed out that the yearly expense of operating the Hoagland Laboratory was \$10,749, while the income was only \$5020. As the building was deteriorating for lack of maintenance funds, an annual budget of at least \$14,562 was actually required. This would be made possible by an addition of \$200,000 to the present endowment. In his Annual Report to the trustees on May 1, 1913, White concluded with these words, "As Director, I beseech the members of your Board, a more interested

cooperation and a support which will enable us to continue the work at the Hoagland Laboratory."

In the fall of 1913, White revised his estimate of expenses for the coming year. It was the last desperate effort to keep the ship afloat. By omitting a successor to Dr. Avery, by eliminating salary increases for Lyall and himself, by leaving out all repairs for the building, he cut the estimated expenses for the following year to \$9920. The estimated income was \$4910. The usual Hoagland donation of \$5000 would make up the difference.

Ella Hoagland had contributed \$3000 in 1911-1912 and again in 1912-1913. Elizabeth Gates had given \$2000 in each of those years. The sisters were becoming more and more loath to make up the constant deficits. Mrs. Tangeman had made no contributions for several years. Mrs. Gates made it very clear that she was contributing only because of Dr. White.

The fall of 1913 was the beginning of the end for the department of bacteriology. Ella Hoagland contributed only \$2000, and an unnamed donor (surely Mrs. Gates) had promised \$2010 which was to be ear-marked for White's salary. The department limped along throughout the winter. In the spring Elizabeth Gates gave up the fight to continue the research program for which her father had founded the laboratory.

Benjamin White resigned as director of the department of bacteriology on May 28, 1914; Harold Lyall also resigned, as did Barbara Bradford. Miss Bradford was to remain until September to attend to the mailing of reprints of three forthcoming publications. The department of bacteriology was placed in charge of Dr. Van Cott, who was not dismayed at the turn of events, but predicted that "there is a growing opportunity for constructive work in the harmonious relation with the college, the hospital, and the medical profession of Brooklyn which will weld all interests together and realize in large measure the ideals of its generous founder."

After leaving the Hoagland Laboratory, Dr. White became assistant director of the Bacteriological Laboratories of the New York City Department of Health. He was in charge of the Antitoxin Laboratories at Otisville, New York, until 1918. After an interlude in the Army during World War I, he became director of the Biologic Laboratories of the Massachusetts State Department of Health and assistant professor of bacteriology and immunology in the Harvard Medical School. He died on March 28, 1938.

Dr. Harold W. Lyall accompanied White to Otisville. In later years he became assistant director in the Division of Laboratories and Research of the New York State Department of Health.

One may well wonder why Benjamin White remained at the Hoagland Laboratory as long as he did. He had no increase in salary after 1907. Because of friction with the board of trustees, his situation was not always one of comfort. On the other hand his standing in his profession was such that he could have found a better position at any time.

But White was both a sentimentalist and a man of intense loyalties. While still a student at Yale he had been indoctrinated with the idea that the Hoagland Laboratory was everything that was fine and wonderful in scientific ideals and research. He never wavered in the thought that his department must remain a beacon light in medical science as it had been in the days of Sternberg and Ezra Wilson. Then too there was a debt of loyalty to the Hoagland sisters, especially to Elizabeth Gates who had backed him up for years. As long as they were fighting for his program, how could he give up the struggle?

Oswald Avery, who felt very deeply about the matter, spoke of Benjamin White as the ideal department head, who felt a responsibility to his people to provide them with equipment, supplies and opportunity for research; the rest was left to them. The only pressure he ever exerted was that of his own

example. His staff responded by giving him their complete loyalty and by out-doing themselves in turning out good work. Avery himself became that kind of a department head.

After the departure of White and Lyall, no more research was ever done with the funds of the Hoagland Laboratory save that of the Van Cott Fellowship which had a special endowment for that purpose.

The life-span of the Hoagland Laboratory as a research institution was just twenty-five years, most of them years of great accomplishment. There had been triumphs and there had been failures. The great triumph had been the blazing of a trail, the setting of a pattern at a time when the independently endowed research laboratory was unknown. Other triumphs were the many positive contributions made to medical science and to public health.

The great failure was that of missed opportunities—the opportunity to become a school of advanced education in biologic science; the opportunity to secure permanently such men as Sternberg, Kemp, Mall, White, Avery, Lyall and others; the opportunity to continue its tradition through the ensuing critical period; the opportunity to assure its own survival as an independent research institution similar to the Rockefeller Institute.