

Bibliographical Review on the Academic Achievements of Dr. Hideyo Noguchi

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I. INTRODUCTION

Although Dr. Hideyo Noguchi (1876-1928) was one of the most well known Japanese medical scientists and many biographies of him were published, his academic activities have not been discussed in details from the viewpoints of medicine and microbiology. Moreover, the list of his works has never been published. Consequently, his works as a whole are not well known, even among medical doctors and microbiologists. Therefore, his life and academic achievements have drifted into an abstract legend and he has been idolized.

Noguchi was an excellent medical microbiologist in his time, though he was much criticized, and he should be respected for his great contributions to the medical science. The author would like to introduce his academic achievements with the compilation of a list and classification of his works.



Photo. 1. Dr. Hideyo Noguchi (1876-1928), photographed during the stay in Equador(1918).

First a brief chronology of Noguchi's life is shown as follows:

CHRONOLOGY OF THE LIFE OF HIDEYO NOGUCHI

AD	Age	Matters and Affairs
1876	0	Born in Fukushima prefecture, Japan.
1878	2	Left hand burned and deformed.
1893	17	Graduated from Inawashiro Senior Elementary School.
1897	21	Passed the national examination for medical license.
1898	22	Assistant at the Kitasato Institute for Infectious Disease.
1899	23	Interpreter for Dr. S. Flexner in Tokyo.
1900	24	Emigrated to the United States of America.
1901	25	Private assistant to Dr. Flexner.
1902	26	Assistant at the Department of Pathology, University of Pennsylvania.

1903	27	Studied serology in Denmark.
1904	28	Assistant at the Rockefeller Institute.
1907	31	Received Master of Science degree (Univ. of Pennsylvania), Associate Member of the Rockefeller Institute.
1911	35	Received Dr. of Medical Science degree (Kyoto University).
1913	37	Found <i>Spirochaeta pallida</i> in the brain tissue of the patients of <i>Tabes dorsalis</i> and <i>Dementia paralytica</i> .
1914	38	Member of the Rockefeller Institute. Received Dr. of Science degree (Tokyo University).
1915	39	Awarded the Royal Prize by the Imperial Academy of Japan.
1918	42	Investigation of the agent of yellow fever in Equador.
1923	47	Member of the Imperial Academy of Japan.
1928	52	Died of yellow fever at Accra in Africa.

This chronology was compiled by the author from two biographies^{1),2)} of Dr. Hideyo Noguchi.



Photo. 2. Dr. Hideyo Noguchi together with Dr. S. Flexner, his respected director. (1907?)

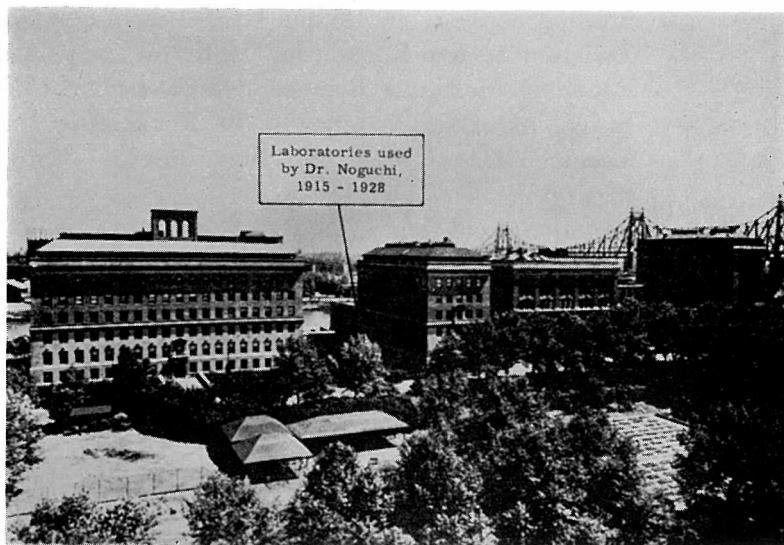


Photo. 3. The whole view of the Rockefeller Institute for Medical Research in those days.

Noguchi began his research work in 1901 and continued his super-human efforts until his death in 1928.

The first project was a study of snake venom under the direction of Dr. Flexner, and the first report of his research work was published in 1902 (See Article No. 1 in the list).

The last report was made by his coworkers in 1929, the year after he died. It was entitled "Etiology of Oroya Fever" (See Article No. 204 in the list).

All of the articles from his working period (1901-1928), including those written with coworkers, are listed chronologically in the following section.

II. THE LIST OF ARTICLES OF NOGUCHI AND WITH COWORKERS.

1) Flexner, S., and Noguchi, H.:

Snake venom in relation to haemolysis, bacteriolysis, and toxicity.

J. Exp. Med., 6, 277-301, 1902.

2) Noguchi, H.:

The anti-haemolytic action of blood sera, milk, and cholesterol upon agaricin, saponin, and tetanolysin, together with observations, upon the agglutination of hardened red corpuscles.

Univ. Pennsylvania Med. Bull., Nov., 1-12, 1902.

- 3) Noguchi, H.:
A study of immunization haemolysins, agglutinins, precipitins, and coagulins, in cold-blooded animals.
Univ. of Pennsylvania Med. Bull., Nov., 1-18, 1902.
- 4) Noguchi, H.:
The interaction of the blood of cold-blooded animals, with reference to haemolysis, agglutination, and precipitation.
Univ. of Pennsylvania Med. Bull., Nov., 1-18, 1902.
- 5) Flexner, S., and Noguchi, H.:
The constitution of snake venom and snake sera.
J. Path. and Bact., 8, 379-410, 1903.
- 6) Flexner, S., and Noguchi, H.:
On the plurality of cytolytins in snake venom.
Univ. of Pennsylvania Med. Bull., July-August, 1-32, 1903.
- 7) Flexner, S., and Noguchi, H.:
On the plurality of cytolytins in normal blood serum.
Univ. of Pennsylvania Med. Bull., July-August, 1-15, 1903.
- 8) Noguchi, H.:
The effects of venom upon the blood corpuscles of cold-blooded animals.
Univ. of Pennsylvania Med. Bull., July-August, 1-7, 1903.
- 9) Noguchi, H.:
The multiplicity of the haemagglutinins and the heat lability of the complements of cold-blooded animals.
Univ. of Pennsylvania Med. Bull., July-August, 1-8, 1903.
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Upon the production and properties of anticrotalus venom.
J. Med. Res., 11, 363-376, 1904.
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Toxines et antitoxines. L' influence de la temperature sur la vitesse de reaction. I.
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Toxines et antitoxines. Saponine-cholestering.
Oversigt over det kgl. danske videnskabernes selskabs forhandling, No. 6, 457-464, 1904.
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A study of the protective action of snake venom upon blood corpuscles.
J. Exp. Med., 7, 191-222, 1905.
- 15) Flexner, S., and Noguchi, H.:
On the occurrence of *Spirochaeta pallida* Schaudinn, in syphilis.
Medical News, June, 1-4, 1905.
- 16) Madsen, Th., and Noguchi, H.:
Toxines et antitoxines. Venis-antivenins. (*Crotalus adamanteus*, *Naja tripudians*, *Ancistrodon piscivorus*).
Oversigt over det kgl. danske videnskabernes selskabs forhandling, No. 4, 233-268, 1906.

- 17) Noguchi, H.:
Toxines et antitoxines. Expériences thérapeutiques avec les antivenins (Crotalus adamanteus et Ancistrodon piscivorus).
Oversigt over det kgl. danske videnskabernes selskabs forhandling, No. 4, 269-280, 1906.
- 18) Flexner, S., and Noguchi, H.:
The effect of eosin upon tetanus toxin and upon tetanus in rats and guinea pigs.
J. Exp. Med., 8, 1-7, 1906.
- 19) Noguchi, H.:
On certain thermostabile venom activators.
J. Exp. Med., 8, 87-102, 1906.
- 20) Noguchi, H.:
The photodynamic action of eosin and erythrosin upon snake venom.
J. Exp. Med., 8, 252-267, 1906.
- 21) Madsen, Th., Noguchi, H., and Walbum, L.:
The influence of temperature upon the rate of reaction (haemolysis, agglutination, precipitation).
J. Exp. Med., 8, 337-364, 1906.
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The effect of eosin and erythrosin upon the haemolytic power of saponin.
J. Exp. Med., 8, 268-270, 1906.
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The influence of colloids upon the diffusion of haemolysins.
J. Exp. Med., 8, 547-563, 1906.
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Therapeutic experiments with anticrotalus and antimoccasin sera.
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The thermostabile anticomplementary constituents of the blood.
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Ueber eine lipolytische Form der Haemolyse.
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Ueber die chemische Inaktivierung und Regeneration der Komplemente.
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Ueber gewisse chemische Komplementsubstanzen.
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The nature of the antitetanic action of eosin.
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Local immunity to tetanus in inoculated rats treated with eosin.
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On extracellular and intracellular venom activators of the blood, with especial reference to lecithin and fatty acids and their compounds.
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On the influence of the reaction and of desiccation upon opsonins.
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International Congress on Tuberculosis, 235-246, 1908.
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Ueber die Einwirkung von Seifen auf die Lebensfähigkeit und immunisierende Eigenschaft des Tuberkelbacillus.
Zentralb. f. Bakt. u. Infektionsk., I Abt., Orig., 52, 85-92, 1909.
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Pure cultivation of *Spirochaeta phagedenis* (new species), a spiral organism found in phagedenic lesions on human external genitalia.
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Experimental research in syphilis, with special reference to *Spirochaeta pallida* (*Treponema pallidum*).
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Reinzüchtung der Spirochäten des europäischen, des amerikanischen und des afrikanischen Rückfallfiebers.
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Experiments on the cultivation of the microorganism causing epidemic poliomyelitis.
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Kultivierung des Mikroorganismus der Poliomyelitis epidemica.
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III. CLASSIFICATION AND DISCUSSION ON THE LIST OF ARTICLES.

(A) Chronological distribution.

Noguchi's first article was published in 1902 and at least one article was published every year thereafter until 1929, the next year of his death. A chronological distribution is as follows (Table 1).

Table 1. Chronological distribution of Noguchi's articles

Year (AD)	Number of papers	By single name	With coworker(s)
1902	4	3	1
1903	5	2	3
1904	4	0	4
1905	2	1	1
1906	10	6	4
1907	11	10	1
1908	2	2	0
1909	13	13	0
1910	6	6	0
1911	15	7	8
1912	15	13	2
1913	19	14	5
1914	3	3	0
1915	3	2	1
1916	1	1	0
1917	6	2	4
1918	11	9	2
1919	10	10	0
1920	5	3	2
1921	9	5	4
1922	4	4	0
1923	5	4	1
1924	6	5	1
1925	3	2	1
1926	14	10	4
1927	7	7	0
1928	8	7	1
1929	3	0	3
28 years	204	150	54

Noguchi published 204 articles; the most in one year was 19 (in 1913), while the minimum was 1 paper in 1916. He averaged 7.3 papers per year during his working period of 28 years. About three fourths of them were written by Noguchi alone. The quantity of Noguchi's publications is amazing.

His reasons for writing so many papers are worthy of discussion. The author believes that there were at least two factors; one was the situation of the environment (USA) in which he lived and worked; and another was his own personality. The former can be explained by the fact that academic activities in the USA are generally supported by the grant system.

Financial support will be given by a foundation only to an enthusiastic researcher who is recognized by the quality of his publications, to be qualified. Little can be done without money in the USA. One who wishes to continue his research activity must work hard and publish often. Because Noguchi did this, he was supported financially by many foundations.

As for Noguchi's personality, he was not a man of quiet, but was full of fighting spirit. He also had a limitless passion for the medical science, continuing his research work almost without stop. Moreover, he had hard feelings against the medical society of his mother country. He had to prove himself by his brilliant works, because he had left his conservative homeland due to his poor school career. Japan would not give him the position he deserved, so he had to work in the USA. He also might have wanted to demonstrate his international success in medical research to the people of Japan.

In spite of his success and hard work, many of his papers were criticized, and in later years many errors were pointed out.

(B) Journals in which the articles were published.

Noguchi's works were published in many journals and magazines. They are listed in Table 2.

Table 2. Journals in which the articles of Noguchi and with coworkers were published.

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- 1). American Journal of Hygiene: (1) 149.
 - 2). American Journal of Syphilis: (1) 114.
 - 3). American Journal of Tropical Medicine: (2) 165, 170.
 - 4). Annales de L'Institut Pasteur: (1) 113.
 - 5). Archives of Diagnose: (1) 46.
 - 6). Archivvers Ophthalmology: (1) 60.
 - 7). Berlin Klinische Wochenschrifts: (5) 87, 92, 97, 101, 108.
 - 8). Biochemische Zeitschrift: (2) 26, 27.
 - 9). Bulletin of New York Academy of Medicine: (1) 192.
 - 10). Bulletin of Pennsylvania University: (7) 2, 3, 4, 6, 7, 8, 9.

- 11). Comptes Rendus des Seances de la Souiete de Biologie et des ses Filiales: (1) 106.
- 12). Internal Clinics: (1) 55.
- 13). Interstate Medical Journal: (1) 59.
- 14). Journal of American Medical Association: (16) 47, 48, 52, 69, 84, 89, 96, 124, 131, 150, 151, 152, 163, 164, 176, 193.
- 15). Journal of Cutaneous Disease: (1) 99.
- 16). Journal of Experimental Medicine: (104) 1, 14, 18, 19, 20, 21, 22, 23, 24, 28, 30, 31, 32, 33, 37, 45, 49, 50, 54, 61, 62, 63, 64, 65, 66, 67, 70, 71, 73, 74, 75, 76, 77, 78, 79, 80, 81, 83, 88, 90, 91, 93, 94, 111, 112, 115, 116, 117, 118, 119, 120, 121, 122, 123, 126, 127, 128, 129, 130, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 153, 155, 157, 159, 161, 173, 175, 178, 180, 181, 182, 184, 185, 188, 189, 190, 191, 194, 195, 195, 196, 197, 199, 200, 202, 203, 204.
- 17). Journal of Medical Reserach: (1) 10.
- 18). Journal of Pathology and Bacteriology: (1) 5.
- 19). Journal of Pharmacology and Experimental Therapy: (1) 95.
- 20). Journal of Tropical Medicine and Hygiene: (1) 171.
- 21). Lancet: (1) 156.
- 22). Medical News: (1) 15.
- 23). Medical Record: (1) 110.
- 24). Montana State Bd. of Health, Special Bulletin of North-West Medicine: (1) 160.
- 25). München Medizinische Wochenschrift: (6) 51, 56, 68, 72, 86, 100.
- 26). New York Medical Journal: (1) 109.
- 27). New York State Journal of Medicine: (1) 158.
- 28). Oversigt over det Kgl. danske videnskabernes selskabs forhandling: (5) 11, 12, 13, 16, 17.
- 29). Presse Médicale: (4) 98, 102, 103, 104.
- 30). Proceeding of the International Conference of Health in Tropical America: (2) 167, 169.
- 31). Proceeding of New York Pathological Society: (3) 34, 35, 57.
- 32). Proceeding of Royal Society of Medicine: (1) 107.
- 33). Proceeding of the Society for Experimental Biology and Medicine: (5) 40, 41, 42, 43, 44.
- 34). Science: (4) 172, 177, 179, 201.
- 35). System of Medicine: (1) 36.
- 36). Sixth International Congress on Tuberculosis: (1) 38.
- 37). Transactions of the Associations of American Physicians: (1) 174.
- 38). Wiener Medizinische Wochenschrift: (1) 105.
- 39). Zentralblatt für Bakteriologie und Infektionskrankheits: (1) 39.
- 40). Zeitschrift für Immunitätforschung: (3) 53, 58, 85.

Reviews and Textbooks

- A manual for Students and Physicians: 162.
 A table: 166.
 Billings-Forscheimer's Therapeusis of Infectious Diseases: 168.
 Cecil's Textbook of Medicine: 187.
 Encyclopaedia Britanica: 186.
 Newer Knowledges of Bacteriology and Immunology: 198.

Numerals in parenthesis show the number of articles published.
 Numerals without parenthesis show the article number.

Noguchi published in more than forty journals but more than half of his articles were in the "Journal of Experimental Medicine" (J. Exp. Med.). This journal was issued from the Rockefeller Institute at that time, so he published in it because he was acquainted with it and relied on its prestige. This Journal is still continuing of publication today.

Next was the "Journal of American Medical Association" (J. Am. Med. Assoc.), in which he published 16 articles. In none of the other 38 journals or magazines did he publish more than seven articles.

(C) Classification of the articles by language.

Most of the articles (188 out of 204) were written in English, but some were in other languages, including French, German and Spanish. None were written in Japanese. Table 3 shows a classification of articles by language.

Table 3. Classification of Noguchi's articles based upon the languages.

English	188
French	9
German	6
Spanish	1
	204

Noguchi had an aptitude for language. He could read, speak and write English like a native speaker. His style of English was very smooth and elegant. He usually wrote his manuscripts in English. As Japanese was not an international language, and he wanted his research works to be read all over the world. In this point, his linguistic talent and working environment were beneficial for the publication of his works.

(D) Noguchi's coworkers in the list.

Noguchi had many friends and coworkers. More than thirty people are well known from his biography, but in his writings he collaborated with a total of 26 researchers, as listed in Table 4.

Among Noguchi's coworkers S. Flexner and J. Bronfenbrenner are most remarkable, as their names commonly appear in the articles. Flexner was a benefactor and a director for Noguchi. He gave Noguchi a project of the study of snake venom and supported him financially soon after his arrival in Pennsylvania. Noguchi was also given positions as an assistant at the University of Pennsylvania and later at the Rockefeller Institute through the kindness of Flexner. Their cooperation

Table 4. Coworkers and numbers of their articles in the list.

1.	Akatsu, S.: 116, 118.
2.	Bronfenbrenner, J.: 61, 62, 63, 64, 65, 66, 67, 77, 78, 95.
3.	Cohen, M.: 57, 60, 94, 112, 125, 144.
4.	Collins, J.: 163.
5.	Flexner, S.: 1, 5, 6, 7, 10, 15, 18, 23, 89, 91, 92.
6.	Hercelles, O.: 179.
7.	Kaliski, D.J.: 129.
8.	Kligler, I.J.: 145, 146, 147, 148.
9.	Kudo, R.: 119.
10.	Lindenberg, A.: 170.
11.	Madsen, Th.: 11, 12, 16, 21, 29.
12.	Madsen, Th., and Walbum, L.: 13.
13.	Moore, J.W.: 50.
14.	Müller, H.R., Tilden, E.B., Tyler J.R.: 203, 204.
15.	Müller, H.R., Torres, O., Silva, F., Martins, H., Riberro dos Santos, Vianna, G., and Biao, M.: 167.
16.	Ohira, T.: 115.
17.	Pareja, W.: 150.
18.	Shannon, R.C., Tilden, E.B., and Tyler, J.R.: 202.
19.	Tilden, E.B.: 180.

yielded good results over a wide range including studies of snake venom, bacterial toxin, serology, *Spirochaeta pallida* and poliomyelitis virus.

Bronfenbrenner was an excellent coworker for Noguchi and they cooperated mainly in serology, particularly in the study of complement.

Other coworkers all seemed from their works to be enthusiastic researchers in their projects, and valuable articles were published by them.

(E) Classification of the articles by subject.

Noguchi's projects covered many fields including medical microbiology, serology and immunology, bacterial toxin and snake venom, and others. They are classified in Tables 5-A and 5-B.

The largest groups are syphilology and spirochaetology, each including 36 papers. Etiology of yellow fever, immunological study, etiology of Oroya fever, bacterial toxin and snake venom follow in decreasing number of articles. The other groups of articles contain less than 10 papers each.

Noguchi is consequently considered to be an experimental syphilologist, spirochaetologist, and etiologist of other infectious diseases. There have been severe criticisms on some articles by Noguchi, such those on cultivation of *Treponema pallidum*, his descriptions of the causative agent of yellow fever, the etiology of trachoma, and others. Most of those are valid, but Noguchi's errors should be understood in the context of

Table 5-B. Classification of Noguchi's articles based upon the subjects.

2) Subjects and numbers of the articles	
Syphilis.....	(36)
Experimental syphilis	5
Serological diagnosis	20
Tabes dorsalis	7
Luetin reaction	4
Spirochetes.....	(36)
Cultivation	25
Leptospira	5
Genital spirochetes	2
Saprophytic spirochetes	2
Review	2
Yellow fever.....	(30)
Immunology.....	(21)
Oroya fever.....	(20)
Verruga peruviana	(2)
Bacterial toxin	(11)
Snake venom	(10)
General Bacteriology	(6)
Trachoma.....	(6)
Protozoology	(6)
Rockey Mountain Spotted Fever.....	(4)
Vaccinia virus	(4)
Poliomyelitis.....	(3)
Others	(7)

Numeral of each round bracket shows the number of articles published.

IV. SUMMARY

A complete list of articles by Dr. Hideyo Noguchi was compiled by the author. The articles are classified and discussed. The quantity and range of the articles were impressive. The author expresses his great respect for Dr. Hideyo Noguchi, who was an excellent scientist and dedicated researcher.

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POST SCRIPT

This article was published to commemorate the centenary of the birth of Dr. Hideyo Noguchi.

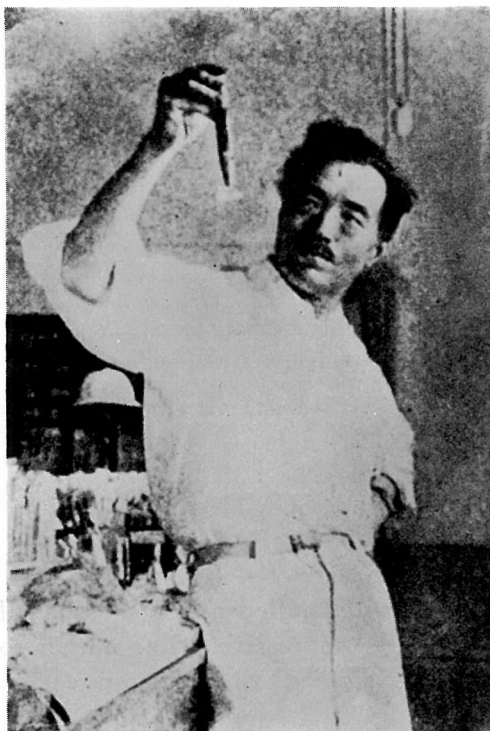


Photo. 4. Dr. Hideyo Noguchi, his last portrait at the laboratory in Accra (1928).