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PIERRE BRETONNEAU AND THE HISTORY OF DIPHTHERIA IN FRANCE IN THE NINETEENTH CENTURY

by

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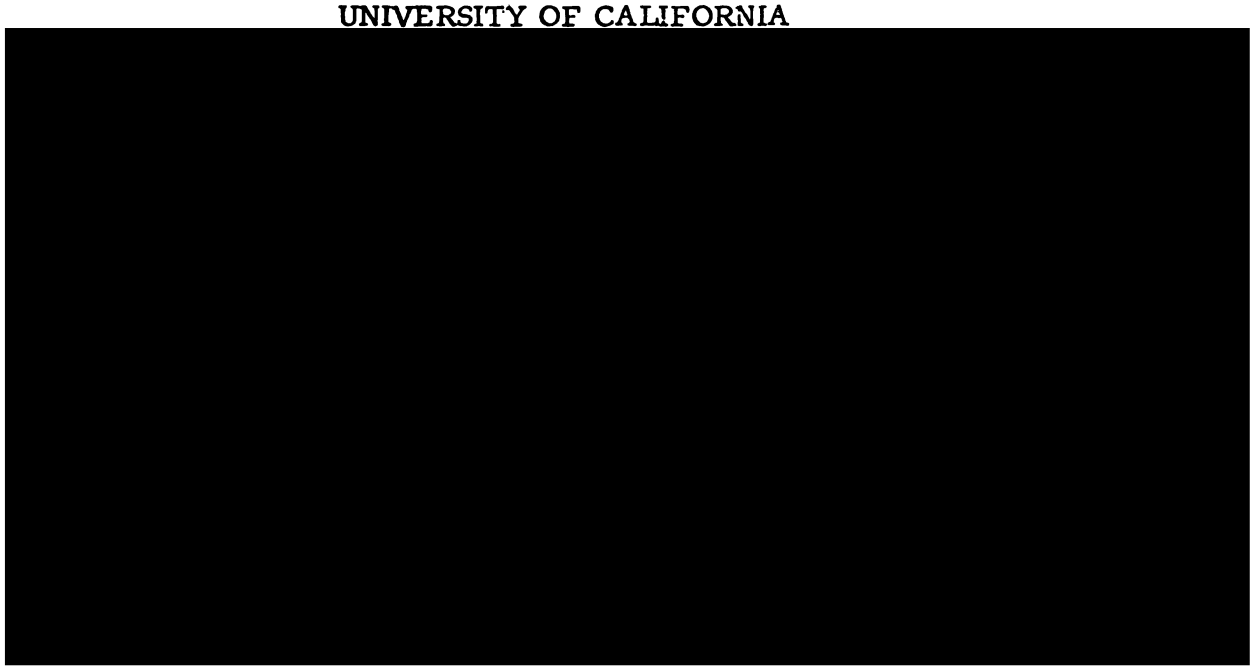

This work is dedicated to

DR. IFOMA BARATUNDE

Fellow Historian and Friend

PIERRE BRETONNEAU AND THE HISTORY OF DIPHTHERIA IN FRANCE IN THE NINETEENTH CENTURY

Zelma L. Dunn, Ph.D.
University of California, San Francisco, 1973

Chairman: Dr. J. B. de C. M. Saunders

This dissertation examines the role of Pierre Bretonneau in clarifying the disease, diphtheria, in France in the nineteenth century. The focus is on his contributions in this regard. Presented also is information on the prevalence of diphtheria in France in the nineteenth century, and the therapeutic procedures used by physicians in France to control it.

Bretonneau's doctrine of diphtheria had widespread influence - extending throughout the world. Particular emphasis is given in this dissertation to two of Bretonneau's pupils - Dr. Armand Trousseau, who popularized the use of tracheotomy as a therapeutic tool in cases of diphtheria in France and to Dr. Victor Fourgeaud, an American physician of French lineage, who wrote the first treatise on diphtheria in California and who notably contributed to controlling diphtheria epidemics in California.

This work is organized into six chapters. Chapter one described early recognition of diphtheria by the Greeks and presents excerpts from major medical writers on the disease, focusing on Aretaeus of Cappadocia and including Hippocrates, the

Father of Medicine, Celsus, Caelius Aurelianus, and Aetius of Amida.

Chapter two examines Bretonneau's doctrine of diphtheria. Explanation is given of the use of the term "diphthera" by the Greeks; Pierre Bretonneau's use of the term "diphtheria"; and the development of Bretonneau's nosography.

Chapter three deals with diphtheria in France in the nineteenth century. Discussion is presented of Bretonneau's writings and five other major writers on diphtheria. Their ideas on the diagnosis, prognosis, etiology, and therapeutics of diphtheria are described.

Chapter four is devoted to Dr. Armand Trousseau's most notable contributions in the popularization of tracheotomy as a therapeutic tool in diphtheria. He was, by far, the most successful tracheotomist in France during his time. Discussion is also given of the role played by other French physicians using tracheotomy in cases of diphtheria.

Chapter five explores the development of the diphtheria antitoxin in the latter part of the nineteenth century - focusing on the contributions of the French, espceically Dr. Emile Roux, who led the French effort.

Chapter six, the final chapter, described Dr. Victor Fourgeaud's work in California on diphtheria therapeutics connecting and showing Bretonneau's influence upon him. Excerpts were taken from Fourgeaud's treatise on diphtheria and a final discussion is given of other Americans who contributed to diphtheria therapeutics.

224 pages

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CONTENTS

CHAPTER I

THE EARLY RECOGNITION OF DIPHTHERIA

Diphtheria as a disease entity was recognized early by the Greeks. Noteworthy descriptions have been found in the medical literature of the Greek, Graeco-Roman, and early Middle Age Period. The most outstanding description was given by Aretaeus of Cappadocia.

ARETAEUS' CONTRIBUTION TO THE UNDERSTANDING OF DIPHTHERIA

Aretaeus of Cappadocia (81-138 A.D.) is thought to have lived in Alexandria the second half of the first century after Christ or in the second century during the reign of Trajan.

Aretaeus followed the Hippocratic tradition. He adhered to the philosophy of:

> "observation of the patient, to bedside study, and the desire to be useful. He had a clear vision of the duty of the profession...the profession of medicine regarded as the pure and noble performance of an exalted purpose." 1

Aretaeus "published a book of medicine, still extant, which displays a great knowledge of the symptoms of disease very accurately described, and reliable for purposes of diagnosis." 2 He considered it right to check some of the natural actions of the body, which Hippocrates thought were necessary for the restoration of health." 3

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(1) Castiglioni, Arturo, A History of Medicine, tr. from the Italian and ed. by E. B. Krumbhaar, 2nd ed. and enl. New York, Knopf, 1947, p. 215.

(2) Elliot, James Sand, Outlines of Greek and Roman Medicine, London, J. Bale and Sons, Danielson, 1914, p. 87.

(3) Ibid., p. 87.

He was less tied to the opinions of any sect than the physicians of his time, and was both wonderfully accurate in his opinions and reliable in treatment." 4

It is said that "As a clinician, he ranks next to the Father of Medicine in the graphic accuracy and fidelity of his pictures of disease, of which he has given the classic account of... diphtheria (ulcera syriaca)..."5

According to Garrison, "Although not equal to the later Aetius in the accuracy of his transcriptions from Archigenes, Aretaeus is easily the most attractive medical author of his time. He was essentially a stylist, and the character of his Ionic Greek is said to indicate a late period. His work is preserved in the faulty Greek text of 1554 in Wigan's Clarendon Press edition (Oxford, 1723) the Leipzig text of C. G. Kühn, and the Greek text with English translation by Francis Adams (London, 1858)." 6 It is recorded that Aretaeus, "a Greek, was born in Cappadocia, a Roman province in Asia Minor, several centuries after Hippocrates. Although the records are unclear to his precise dates in the chronology of medicine, it is believed that he was a contemporary of Galen, the 2nd or 3rd century after Christ. He studied in Alexandria, whose fame as a medical center was already on the descendency but still recognized as a great school of medicine.

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(4) Ibid., p. 87.

(5) Garrison, Fielding Hudson, An Introduction to the History of Medicine, 3rd ed. rev. and enl. Philadelphia and London, W. B. Saunders Company, 1929, pp. 101 and 102.

(6) Ibid., pp. 101 and 102.

(7) Talbott, John, A Biographical History of Medicine, excerpts and essays on the men and the work, New York, Grune and Stratton, 1970, pp. 15 and 16.

Talbott has stated that "Aretaeus, a sound clinician rejected the idle speculation and superstition and added his personal experiences and observations to the aphorisms of Hippocrates." [8] In Aretaeus' work, "A description and understanding of form and structure of the body preceded a discussion of diagnosis and treatment." [9]

The physicians of ancient time knew of diphtheria and Aretaeus described it as Ulcera Syriaca. His description was as follows:

> "ulcers occur on the tonsils; some indeed, of an ordinary nature, mild and innocuous; but others of an unusual kind, pestilential and fatal. Such as are clean, small, superficial, without inflammation and without pain, are mild; but such as are broad, hollow, foul, and covered with a white, livid, or black concretion, are pestilential. Aphthat is the name given to those ulcers. But if the concretion has depth it is an Eschar and is so called: but around the eschar there is formed a great redness, inflammation, and pain of the veins, as in carbuncle; and small pustules form, at first few in number, but others coming out, they coalesce, and a broad ulcer is produced. And if the disease spread outwardly to the mouth, and reach the columella (uvula) and divide it asunder, and if it extend to the tongue, the gums, and the alveoli, the teeth also become loosened and black; and the inflammation seizes the neck; and these die within a few days from the inflammation, fever, foetid smell, and want food. But, if it spread to the thorax by the windpipe, it occasions death by suffocation within the space of a day. For the lungs and heart can neither endure such smells, nor ulcerations, nor ichorous discharges, but coughs and dyspnoea supervene.
>
> The cause of the mischief in the tonsils is the swallowing of the cold, rough, hot, acid, and astringent substances; for these parts minister to the chest as to purposes of voice and respiration; and to the belly, the stomach, or the chest, as ascent of the mischief by eructations takes place to the isthmus faucium, the tonsils, and the parts there; wherefore children until puberty, especially suffer, for children in particular, have large and cold respiration; for there is most heat in them; moreover, they are intemperate in regard to food; having a longing for varied food and cold drink; and they howl loud both in anger and in sport; and these diseases are familiar to girls until they have their menstrual purgation. The land of Egypt especially engenders it, the

(8) Ibid., p. 16.
(9) Ibid., p. 16.

air thereof being dry for respiratiion, and the food diversified, consisting of roots, herbs of many kinds, acrid seeds, and thick drink; namely, the water of the Nile, and the sort of ale prepared from barley. Syria, also, and more especially Coelosyria, engenders these diseases, and hence they have been named Egyptian and Syrian ulcers.

The manner of death is most piteous; pain sharp and hot as from carbuncle; respiration, bad, for their breath smells strongly of putrefaction, as they constantly inhale the same again into their chest; they are in so loathsome a state that they cannot endure the smell of themselves; countenance pale or livid; fever acute, thirst is if from fire, and yet they do not desire drink for fear of the pains it would occasion; for they become sick if it compress the tonsils, or if it return by the nostrils; and if they lie down they rise up again as not being able to endure the recumbent position, and if they rise up, they are forced in their distress to lie down again; they mostly walk about erect, for in their inability to obtain relief they flee from rest, as if wishing to dispel one pain by another. Inspiration large, as desiring cold air for the purpose of refrigeration, but expiration small, for the ulceration, as if produced by burning, is inflamed by the heat of respiration. Hoarseness, loss of speech supervene; and these symptoms hurry on from bad to worse, until suddenly falling to the ground they expire." 10

This is a masterly description of diphtheria and its symptomatology.

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(10) Major, Ralph Hermon, Classic Descriptions of Disease, 3rd ed. Springfield, Ill., C. C. Thomas, 1945, pp. 150-151, (see The Extant Works of Aretaeus, the Cappodocian, Edited and translated by Francis Adams L.L.D. London: Sydenham Society, 1856, p. 253).

THE ORIGINS OF ARETAEUS' MEDICAL PHILOSOPHY -- ATHENAEUS OF ATTALEIA AND THE PNEUMATIC SCHOOL

The medical philosophy to which Aretaeus adhered was an outgrowth from the Pneumatic School which existed during the Graeco-Roman Period (156-576 A.D.). This school may be traced from Diogenes of Apollonia (c. 450 B.C.) to Plato (428-347 B.C.) to Athenaeus of Attaleia (c. 2nd C. A.D.) who is known as the founder of the Pneumatic Sect. Athenaeus was the teacher of Agathinus (c. 2nd C. A.D.) of Sparta who in turn taught Archigenes (c. 54-117 A.D.) of Apameia. Archigenes combined Pneumatic ideas with others and started a new sect.

"Pneuma in Greek originally meant breath and was easily identified with the life principle. For Anaximenes of Miletus (570-500 B.C.) air both surrounds and controls the universe and is the source of individual life." 11

One particular concept of Pneumatism was adopted from Hippocrates' (460-377 B.C.) humoral pathology. This was the idea that..."Disease consisted in an abnormal state of the elements." 12

"According to the Pneumatists, perfect health consisted in the perfect condition of the pneuma, and of the tonus that is maintained, as recognizable by the pulse. In the diagnosis and therapeutics of the Pneumatic school this concept predominated, hence the great importance of the pulse and dietetic and physical therapy." 13

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(11) The Encyclopedia of Philosophy, Volume Six, Paul Edwards, Editor-in-Chief, The Macmillan Co., and The Free Press, New York-Collier Macmillan Ltd., London, 1967, p. 360.

(12) Castiglioni, Arturo, op. cit., p. 214.

(13) Ibid., p. 215.

In his utilization of the pneuma concept, Empedocles (c. 490-430 B.C.) described the embryo as alive but non-breathing.

Diogenes of Apollonia made "pneuma the source of a whole series of biological functions." [14] It is said that he lived in Athens most of his life. "Following Anaximenes, he proposed the physical theory that all things in thw world are modifications (heterioseis) of the same basic stuff, air (aer)." [15] He wrote a book called On Nature.

Diogenes boldly asserted that air is the basic cosmic substance since it is the life principle and intelligence of the whole animate world. Air is the source and guiding power of every physical change. It is the most versatile and adaptable substance. Its capacity to manifest itself in a wide variety of forms, and under every conceivable condition - as hot, as cold, as wet and then as dry - is evidence of its rationality and divinity. To the extent that there is air in all animation, a part of God is in every living creature." [16]

Aristotle (384-322 B.C.) believed in a connate pneuma. "Some derived Aristotle's famous connate pneuma from" [17] the concept of the pneuma as that of the Pneumatic School. "For Aristotle this is the material cause of soul in semen, and its association with heat makes it analogous to ether. In the living creature it is centered in the heart and is fundamental to the mechanism of sensation." [18]

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(14) The Encyclopedia of Philosophy, Volume Six, Paul Edwards, Editor-in-Chief, The Macmillan Co. and The Free Press, New York, Collier-Macmillan Ltd., London, 1967, p. 360.
(15) Ibid., Volume Two, p. 409.
(16) Ibid., p. 409.
(17) Ibid., p. 360.
(18) Ibid., p. 360.

"The principles of theory and practice of the Pneumatic School...possessed an eclectic character, since they combined Methodism with a rejuvenated Dogmatism." 19 "Athenaeus combined with a remarkable knowledge of medical and philosophical literature, great practical skill in his profession. He published a work in at least thirty volumes; a clear and competent exposition of the entire art of medicine. He believed that not only physicians, but laymen should acquire a medical education. With the principle of qualities for the criterion he analyzed foodstuffs (cereals, bread) and drinking water, taking into consideration the influence of sun, shade, filtration through the soil, and the character of the region from which it was the importance of the simultaneous development of the body and soul, and thought the earliest instruction of young children should be imparted as far as possible by play. None of his writings have survived, but he is extensively quoted and criticized by Galen." 20

Agathinus..."named the school"...to which he belonged... "Eclectic and strove to bring it in closer touch with the Empirics and the Methodists. He further elaborated the favorite subjects of his master, especially the study of the pulse, experimented on dogs regarding the action of hellebore and was a great advocate of the use of cold baths, following Asclepiades and Antonius Musa." 21

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(19) Lund, Fred B., Greek Medicine, Paul B. Hoeber, Inc., New York, 1936, p. 84.
(20) Ibid., p. 84.
(21) Ibid., p. 85.

Archigenes..."added much to the reputation of this, the Eclectic School. The great Galen, himself an Eclectic, quoted extensively from his writings. He was the author of many medical works, on the pneumatic theory, on the pulse, fevers, local affections, on surgery (especially the determination of the right time to operate), drugs (hellebore in particular), and general therapeutics. He was an exceptional therapeutist, a highly gifted surgeon, and raised the study of the pulse to the highest level which it attained in antiquity. He endeavored to separate the primary phenomena of disease from those which were secondary and sympathetic. He was the son of a physician, Philippos, a renowned pathologist, and was among the best authors of his time. Although he was a fashionable physician, and went to the extent of preparing hair-dyes for his lady patients, he never descended to quackery." 22

"He brought back from Hippocrates the discarded belief in critical days. He classified the pulse according to size, rapidity, strength, fullness, tension, frequency, rhythm, and regularity. He described leprosy, and knew diphtheria." 23 Archigenes, Leonidas and Heliodorus were all members of the Eclectic School. Antyllus, one of the most outstanding surgeons of his time, was also a member.

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(22) Ibid., p. 85.
(23) Ibid., p. 86.

The Pneumatic philosophy has been ably described by Henry Osborn Taylor and James S. Elliott. Taylor stated: [24]

> "Theories sat rather lightly on these excellent practitioners of the Graeco-Roman time, who might call themselves by one name or another. This remark applies to members of the so-called Pneumatic School, who were generally eclectic, adopting the best features of medical practice in the second half of the first century. They were affected by the Stoic physics, in which borrowed materials filled out a system novel in form. Accepting the old working elements, they found the life-giving principles to be the 'Pneuma', like unto air and breath. It is innate, yet constantly with the blood through the arteries conveying more Pneuma, and the veins more blood. Pneuma vivifies the body, and makes it a living unity, carries on the energies of growth and reproduction, as well as sensation, desire, and thought. The normal condition and proper TONOS or tension of the Pneuma means health and this is indicated by the pulse; while sickness springs from disorder of the Pneuma, due to irregularities of the warm and cold or dry and moist elements, and the consequent morbid excess of one or the other of the humors." 25

Taylor continued with the observations:

> "While the 'Pneumatists' rejected the fundamental theory of the Methodists, they availed themselves of their treatment of disease, and drew upon all the best medical knowledge of the time. They were wise physicians, following many a precept of Hippocrates, and efficient surgeons." 26 "Pneumatology became increasingly important in medical theory, and in Galen's physiology blood and pneuma joins with blood in the left ventricle to form 'zotic' pneuma (vital spirit). From the brain psychic pneuma (animal spirit) is distributed by the nerves. Others added physical pneuma (natural spirits), located in the liver." "For the Stoics pneuma is one manifestation of the divine active principle in the universe, but early Christians distinguished a transcendent divine pneuma in addition to this immanent, essentially material cosmic pneuma." 27
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> "The pneuma, or spirit, was in their opinion the cause of health and disease. They believed that dilatation of

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(24) Taylor, Henry Osborn, Greek Biology and Medicine, Marshall Jones Co., Boston, Mass., 1922, p. 94.
(25) Ibid., pp. 94-96.
(26) Ibid., p. 95.
(27) The Encyclopedia of Philosophy, Volume Six, loc. cit., p. 360.

> the arteries drives onward the pneuma, and contraction of the arteries drives it in a contrary direction. The pneuma passes from the heart to the arteries. Their theories also had reference to the elements. Thus, the union of heat and moisture maintains health, heat and dryness cause acute diseases; cold and moisture cause chronic diseases; cold and dryness cause mental depression, and at death there are both dryness and coldness. In spite of these strange opinions the Pneumatists made some scientific progress, and recognized some diseases hitherto unknown. Galen wrote of the Pneumatists: "They would rather betray their country than abjure their opinions." 28

One other opinion is that of Charles Cumston:

> "The theory of the Pneuma, the igneous spirit which animates alike the universe and each particular body- that which is called the universal soul -- furnished an excellent means for avoiding collision with solidism or Humorism, and it was this theory that gave the name of the Pneumatic School to the partisans of Athenaeus..." 29

The Pneumatic School of Medicine was of major importance in the development of Aretaeus' attitudes towards medicine.

Hence, it can be safely said that, "Although Aretaeus lived nearly 2,000 years ago, his writings have meaning in relation to the practice of medicine today. He was a critical observer at the bedside; he reported the natural history of morbid processes and refused to dissipate his talents in useless speculation -- a sound procedure for ancient Cappadocia or contemporary clinical medicine." 30

Although, it can also be stated that Aretaeus' description of diphtheria was the most outstanding in early times, there were others who described diphtheria.

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(28) Elliott, James Sands, op. cit., p. 86.

(29) Cumston, Charles Greene, An Introduction to the History of Medicine, Kegan Paul, Trench, Trubner and Co., Ltd., New York: Alfred A. Knopf, 1926, p. 129.

(30) Talbott, John, op. cit., p. 16.

OTHER OUTSTANDING DESCRIPTIONS OF DIPHTHERIA

HIPPOCRATES. Hippocrates (460-377 B.C.) the renowned Father of Medicine, was born on the island of Cos. He descrnded from a long line of physicians. He clarified medicine by separating it from philosophy. His contributions to medicine were made during one of the most stimulating periods in human history. Some of his contemporaries were: the philosopher Democritus, the statesman Pericles, the sculptors Polycletus and Phidias, the historians Herodotus and Thucydides, the poet Pindar, and the dramatists Aeschylus, Sophocles, Euripides, and Aristophanes.

It is said that hsi verified medical writings comprise some 300 or more works. It is generally agreed that the works included in the Hippocratic Corpus were more than likely the works of many scholars. The "current compilation in The Genuine Works of Hippocrates, proceeds from the "Prognostics" and the "Aphorisms" to the "First and Third Books of the Epidemics," to the "Regimen in Acute Diseases," "On the Articulations," "On Fractures," "On Wounds of the Head," and concludes with "The Oath" and "The Law," each, prepared in a precise but simple style of composition." 31

Hippocrates was noted for his initiation of the method of bedside study of the patient. He "placed the dignity of the physician on the highest plane of social intercourse and gave Greek medicine its ethical ideas." 32

(31) Talbott, John, op. cit., pp. 4-5. (see Adams, F., The Genuine Works of Hippocrates, New York: William Wood & Co., 1929.

(32) Ibid., pp. 4-5.

Several references in the Hippocratic works appear which are undoubtedly diphtheria. A description is found of a female patient who had diphtheria; which is called angina:

> "The woman suffering from angina who lay sick in the house of Aristion began her complaint with indistinctness of speech. Tongue red, and grew parched.
>
> First day. Shivered and grew hot.
>
> Third day. Rigor: acute fever; a reddish, hard swelling in the neck, extending to the breast on either side; extremities cold and livid, breathing elevated; drink returned through the nostrils -- she could not swallow -- stools and urine ceased.
>
> Fourth day. General exacerbation.
>
> Fifth day. Death." 33

In the Hippocratic Aphorisms is found mention of diphtheria. Seven of the aphorisms are worthy of mention in this connection. These either mention angina or aphtha, which are two designations given to diphtheritic maladies.

Aphorism number 20, Section III, refers to angina:

> "In the spring occur melancholia, madness, epilepsy, bloody flux, angina, colds, sore throats, coughs, skin eruptions and diseases, eruptions turning generally to ulcers, tumours and affections of the joints." 34

Aphorism number 22, Section III, states, in reference to anginas:

> "In the autumn occur most summer disease, with quartans,

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(33) Hippocrates, with an English translation by W. H. S. Jones, Volume I, London, Wm. Heinemann, N. Y., G. P. Putnam's Sons, 1923, p. 231.

(34) Hippocrates, Aphorisms, tr. W. H. S. Jones, Volume IV, p. 129.

irregular fevers, enlarged spleen, dropsy, consumption, strangury, lientery, dysentery, sciatica, angina, asthma, ileus, epilepsy, madness, and melancholia." 35

Aphorism number 24, Section III, mentions aphthae:

"In the different ages the following complaints occur: to the little children and babies, aphthae, vomiting, coughs, sleeplessness, terrors, inflammation of the navel, watery discharges from the ears." 36

Aphorism number 34, Section IV, states:

"If a patient suffering from fever, with no swelling in the throat, be suddenly seized with suffocation, it is a deadly symptom." 37

Aphorism number 10, Section V, is a statement which refers to angina:

"Those who survive angina, should the disease turn to the lungs, die within seven days, or should they survive these, develop empyema." 38

Aphorism number 37, Section VI, states:

"In case of angina, it is a good thing when a swelling appears on the outside of the trachea: 39

Aphorism number 49, Section VII, there is the statement:

"In cases of angina, if swelling or redness appear on the breast, it is a good sign, for the disease is diverted outwards." 40

Hippocrates, in his chapter, On the Prognostics, described an affection which has all the symptoms of diphtheria:

"Ulceration of the throat with fever is a serious affection and if any other of the symptoms formerly described as being bad is present, the physician ought to announce that his patient is in danger. Those quincies are most dangerous and most generally fatal which make no appearance in the fauces

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(36) Ibid., p. 131.
(37) Ibid., p. 143.
(38) Ibid., p. 159.
(39) Ibid., p. 187.
(40) Ibid., p. 205.

nor in the neck but occasion very great pain and difficulty of breathing. These induce suffocation on the first day, the second day, the third day or the fourth day." 41

CELSUS. Very little is known about the life of Celsus (25 B.C. - 50 A.D.) who authored the medical treatise, De Medicina. Further... "it appears likely that this medical book was but the second part of a large treatise containing six parts, the other five being:

(1) Agriculture;

(2) Military Arts;

(4) Rhetoric;

(5) Philosophy;

(6) Jurisprudence." 42

Two authors of that time refer to Celsus in their writings, Pliny the Elder and Quintilian. It is thought that, "the complete name of the author was probably Aulus Cornelius Celsus. The tradition that A stands for Aurelius must be wrong, as Aurelius is not a praenomen." 43

It is still a question for dispute as to whether Celsus was a practising physician. Nevertheless, one must admit that the author of the De Medicina possessed a remarkable knowledge of the medical arts. Pliny classified Celsus as a medical amateur. 44

The prooemium to the De Medicina is a most fair and judicious summary of the history of medicine, and deals at some length with the Dogmatic, the Methodic and the Empiric Schools." 45 "The work recognizes the importance of anatomy as a basis of medicine,

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(42) Celsus, De Medicina, tr. W. G. Spencer, Cambridge, Harvard Univ. Press, 1935, p. vii., Introd., by W. H. S. Jones.
(43) Ibid., p. viii.
(44) Ibid., p. viii.
(45) Ibid., p. ix.

and the anatomical knowledge displayed is sound. Stress is laid on diagnosis and prognosis, which it is said must precede treatment - a true Hippocratic touch. Drugs are recommended more than they are by Greek writers on medicine. On the other hand, all due importance is attached to general hygiene and to physical exercises. Scholars have noticed that sport is preferred to gymnastics, wherein the writer agrees with both (px) Roman feeling and Roman practice. In the treatment of fevers the De Medicina is more empirical than usual. It "regards exclusively the clinical picture and the empirical remedy." 46

The work is praised by Latinists for its "strong, lucid and elegant" 47 language.

Celsus, in referring to diphtheria in the De Medicina thought it "by far the most dangerous" of the ulcers of the Greeks. In Book VI, he wrote:

> "But by far the most dangerous are those ulcers which the Greeks call aphthae, certainly in children; in them they often cause death, but there is not the same danger for men and women. These ulcers begin from the gums; next they invade the palate and the whole mouth; then they pass downwards to the uvula and throat, and if these are involved, it is not easy for the child to recover. But the disease is even worse in a suckling, for there is then less possibility of its conquest by any remedy. But is most important that the nurse should be made to take exercise both by walking and by doing work which moves her arms; she should have bland, easily digestible food: and for drink, if the infant is feverish, water; if free from fever, diluted wine. And is the nurse is constipated, her bowels are to be moved by a clyster. If there is clotted phlegm in her mouth, she must vomit. Then the child's ulcers are to be anointed with honey, to which is added sumach, which they call Syrian or bitter almonds; or a mixture of dried rose leaves, pinecone seeds, mint, young stalks, and honey, or that medicament which is made of mulberries, the juice of which

(46) Ibid., pp. 257-259.
(47) Ibid., pp. 257-259.

is concentrated in the same way as pomegranate juice to the consistency of honey; similarly too there is mixed with it saffron, myrrh, alum, wine and honey; nothing should be given which provoke spittle. If it is an older child he should generally gargle as described above. If the milder medicaments do little good, the caustic materials which induce crusts upon the ulcers should be applied such as split alum or copper ore or blacking. Even hunger is beneficial and the greatest possible abstinence is to be ordered. The food ought to be bland; for cleansing the ulcers, however, sometimes cheese with honey is appropriately given." 48

(48) Ibid., pp. 257-259.

CAELIUS AURELIANUS. Caelius Aurelianus (c. 5th C. A.D.) was "the foremost of Soranus' translators." 49 He prepared Latin versions of all his books. "Little is known of Caelius apart from his writings. He was of African birth, and like Soranus, was a member of the Methodist Sect. He probably lived in the fifth century, though the date cannot be objectively demonstrated and is based chiefly on considerations of style." 50

Caelius translated Soranus' Acute Diseases (three books) and his Chronic Diseases (five books). In these two works, "the various diseases are taken up in an order which, roughly speaking, proceeds a capite ad calcem. The scope of the discussion varies widely, some diseases being dismissed in a few paragraphs, while others are treated in great detail. But a typical account of a disease includes (1) the etymology of the name of the disease, (2) the difinition of the disease, (3) the symptoms, (4) the method of distinguishing other similar diseases, (5) the part affected, (6) the treatment as practiced by the Methodists, and (7) the treatment as practiced by others, with a refutation thereof." 51

The term applied to diphtheria by Caelius Aurelianus was Synanche. Book Three of his version of the work On Acute and Chronic Diseases gives a clear description of diphtheria:

> "In the preceding books we set forth the treatment of acute diseases accompanied by fever. We shall now lay down rules

(49) Caelius Aurelianus, On Acute Diseases and on Chronic Diseases, Edited and Translated by I. E. Drabkin, The Univ. of Chicago Press, 1950, p. xi.
(50) Ibid., p. xi.
(51) Ibid., pp. xi-xii.

for those known to occur without fever, thereby completing our account of the different kinds of acute diseases. And we shall begin with the disease of synanche, which gets its name from its similarity to hanging, for when it is fatal its effect is like that of choking by a hangman's noose, the Greek word for hanging, being anchone. Or synanche may get its name from the fact that it cuts off respiration by constraining the breath, the Greek word for constrain being synechein. But others have called this disease 'cynanche' or 'lycanche'. since it frequently attacks dogs and wolves, the Greek word for 'dogs' being cynes and for wolves' lycoe; moreover, when humans who have the disease begin to choke, they emit sounds or howls like those made by these animals.

Now one form of synanche occurs without visible sign, another gives a clear and visible indication; again, one form occurs inside the cavity of the mouth 9and throat), another outside it, and still another both inside and outside; and (the affection) may be found on the right side, on the left, or on both. Some writers, e.g. Valens the Naturalist in Book III of his work On Treatments, use specific terms to distinguish these types of disease. They leave without special designations that type which occurs without any visible inflammation. But that which occurs with a visible inflammation of the inner parts on both sides they call 'cynanche'. Their reason is that this type causes difficult breathing, bulging eyes, and hanging tongue; and something of the same sort often occurs in the cases of voracious dogs, when goaded on by their nature, they disregard our threats and, with fearless greed, seize far more than they can swallow. The prey often sticks in their throat and is checked by a wavering retentive action, so that they can neither swallow it nor give it up. Again, when (this form of) the disease occur on one side only, these writers call 'parasynanche'. And when the inflammation occurs in the outer parts and on both sides they call the disease 'hyanche'. For the necks of swine (Greek hyes) are often affected by swelling of this type. But if the inflammation is in both the inner and the outer parts and on both sides, they assert that the disease is then properly called 'synanche'. And if this form occurs on one side only, they call it 'parasynanche'. But there is no advantage in distinguishing the various forms of the disease by special names.

Of the antecedent causes by which this disease is produced, some are hidden, while others are obvious and are common to other diseases too. These latter causes include,

in particular, difficult and labored vomiting, especially if the food has already decomposed, excessive drinking of wine, swallowing of snow, violent screaming that persists on the same note (Greek monotonos), catarrh, the eating of acrid foods contrary to one's custom, the drinking of burning and fiery drugs, a purge, produced by hellebore, and, in the case of some women, the retention of the menstrual flow. Men are more often attacked by this disease than women, and young and middle-aged men more often than boys and old men.

Defining this disease in Book II of his commentary on Hippocrates' Aphorisms, Asclepiades says that synanche is a moistening of, or a flow of moisture to, the throat, especially to its highest part, this flow more often coming down from the head. But this definition is wrong. For every flow of moisture (Greek rheumatismos) is a running or discharge of a considerable amount of liquid matter. In synanche, however, there is an inflammation but no such discharge of large quantity of fluid, unless this is occasionally brought about by the patient's distress.

We, however, following Soranus' view, apply the term 'synanche' to difficulty in swallowing and acute choking occasioned by a severe inflammation of the throat, of those parts which are used in swallowing food and drink. In addition to 'difficulty in swallowing' we include 'swift and acute choking' to distinguish this disease from inflammation of the tonsils or the uvula. For, while it is true that in synanche there is always an inflammation of the tonsils, and uvula, it is not true that whenever there is an inflammation of these parts we have a case of synanche. For we take it that the essence of synanche is its severe inflammation. And this also serves, to distinguish synanche from choking accomplished by a noose. For while this form of choking is also very swift and acute, it does not originate in an inflammation.

II. The Symptoms of Synanche

Those who are beginning to suffer from this disease show the following symptoms. They complain without any apparent reason and find it painful to move their neck and throat; there is copious saliva but no inflammation, a slightly painful

sensation in the throat, together with a feeling of roughness, difficulty in swallowing the regular flow of saliva that collect in the mouth, and, in addition, a kind of difficulty in breathing, as if a thick fluid impeded.

And as the disease emerges and gains strength, in cases with visible inflammation the redness of this inflammation can now be seen in the fauces, the uvula, the parts above the tongue, and the upper parts of the throat. And there is difficulty in swallowing any food or drink. There is, in addition, a choking sensation, increasing as the inflammation increases, difficulty in breathing, and nausea. And if one opens the patient's mouth and depresses his tongue with a finger, the parts will be found to be dry and tense.

As the disease becomes even more severe, all the parts become inflamed, including the neck and face; there is a flow of thick fluid and saliva; the eyes bulge and are bloodshot; and the blood bessels are distended. And if the disease grows still worse, the tongue hangs out of the mouth, the throat is parched and dry, limbs cold and numb, and pulse rapid and thick. The patient finds it hard to live, especially on his back or side, and frequently, too, he wants to sit up; his speech is indistinct, confused, and accompanied by pain. And if the disease begins to move toward a fatal conclusion, the face turns blue, the voice is lost, there is a wheezing sound in the throat and the chest, and liquid taken is returned, there is a failure of the pulse (Greek asphygmia), in some cases there is foaming at the mouth. Death then inevitably follows.

But if the disease is without any visible inflammation, there are the following symptoms: neck attenuated, stretched, and inflexibly erect; face and eyes hollow; forehead drawn; complexion leaden; much difficulty in breathing; absence of any obvious inflammation or visible swelling, either in the internal or in the external parts, as has been indicated; extreme blunting of the senses; weakness; and swift death with choking.

But if erysipelas spread about the patient's neck or appears on his chest and persists, it is often a good sign, for the inflammation is then apparently arising from the depth of the body to the surface. If, on the other hand, the erysipelas suddenly vanishes without the application of any medical remedy, it is a deadly sign; for it means that the inflammation is descending from the surface of the body to the depths. And if it happens that the erysipelas is not a subsequent development, i.e., does not represent the bringing of the inflammation from the depths to the surface, but either precedes synanche or emerges together with it this is in all respects an unfavorable sign.

Again, if considerable liquid matter or flow of thickly condensed saliva appears at the highest stage of the disease, it is a bad sign; but if it appears after that stage, it presages recovery. For in the former case it indicates extreme suffocation, in the latter loosening of the body. In some cases of synanche the inflammation becomes so intense that it produces constriction of the fauces, throat, and chin. And the disease itself involves a state of stricture and is acute, swift, severe, and usually continues, though sometimes intermittent." 52

(52) Ibid., pp. 299-305.

AETIUS OF AMIDA. Aetius of Amida (502-574) was royal physician to Justinian I, 527-65. He was also lord high chamberlain at the court of Byzantium. He "left an extensive compilation, usually called the Tetrabiblion, which is a principle authority for what we know of the work of Rufus of Ephesus and Leonides in surgery, Soranus and Philumenus in gynecology and obstetrics." 53

He, "gives a description of epidemic diphtheria not unlike that of Aretaeus, mentioning paralysis of the palate as a sequel, and his work contains the best account of diseases of the eye, ear, nose, throat and teeth in the literature of antiquity. He had also interesting chapters on goitre and hydrophobia." 54

Aetius, "had a good idea of diphtheria. He speaks of it in connection with other throat manifestations under the heading of "crusty and pestilent ulcers of the tonsils." He divides the anginas generally into four kinds. The first consists of inflammation of the fauces with the classic symptoms; the second presents no inflammation of the mouth nor of the fauces, but is complicated by a sense of suffocation -- apparently our neurotic croup. The third consists of external and internal inflammation of the mouth and throat, extending towards the chin. The fourth is an affection rather of the neck, due to an inflammation of the vertebrae - retropharyngeal abscess - which may be followed by

(53) Garrison, Fielding H., Introduction to the History of Medicine, W. B. Saunders Co., Phila. and London, 1921, p. 112.
(54) Ibid., p. 112.

luxation, and is complicated by great difficulty of respiration. All of these have as a common symptom difficulty of swallowing. This is greater in one variety than in another at different times. In certain affections he remarks that even drinks when taken are returned through the nose." 55

He gave a description of epidemic diphtheria:

> "In children the complaint is developed almost constantly from previously existing aphthae. The ulcers are at times white and patchy, at others of an ashen-grey colour, or they resemble the scabs caused by the use of the cautery. The patient is seized with dryness of the throat, to which is added great difficulty in breathing, particularly when redness is seen under the chin, or if, after the acute stage is over, nome and gangrene ensue...care should also be taken of the fever, which usually sets in with severity. In many cases the uvula is destroyed and, if after a long time the ulceration stops and cicatrization begins, children speak distinctly and swallowing, fluid returns through the nose. Thus, I have seen a girl die after forty days, who was already in convalescence. Most cases, however, are in danger till the seventh day." 55

During early antiquity several writers discussed diphtheria. Ths most interesting and outstanding description was given by Aretaeus of Cappadocia. Others describing it were: Hippocrates, Celsus, Caelius Aurelianus, and Aetius of Amida.

During antiquity, the term diphtheria was used to denote parchment or leather -- hence, when, Pierre Bretonneau, in the nineteenth century, gave the name to the disease, he called it diphtheria because of the false membrane which develops in the throat and other areas where the bacilli localize in the body.

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(55) Walsh, James J., Medieval Medicine, A. and C., Black Ltd., 4, 5, and 6 Sopho Square, London, 1920, p. 27.

(56) Ruhrah, John, Pediatrics of the Past, Paul B. Hoeber, Inc., New York, 1925, p. 16.

CHAPTER II

CLASSICAL ROOTS OF BRETONNEAU'S DOCTRINE OF DIPHTHERIA

Pierre Bretonneau was the first to use the term "diphtheria" to indicate the specific disease caused by the Klebs-Loeffler bacillus. In 1821, he demonstrated that croup and malignant angina were the same disease. He suggested that the term "diphtheritis" be used to refer to both affections. This term meant "disease of the membranes". Later, in 1855, he adopted from his pupil, Trousseau, the term, diphthérie which meant "the disease which forms a membrane". The term diphtheria was derived from the Greek word for a membrane, the termination signifying inflammation, and the word itself the specific disease.

In Bretonneau's Des Inflammations speciales du tissu muqueux, et en particulier de la diphthérite, ou inflammation pelliculaire, Paris, 1826, which he read before the Academy of Medicine in Paris in 1821; he stated:

> "The Memoir which I have the honour to submit to the judgment of the Academy, is extracted from a collection of observations on the special phlegmasiae of the mucous membranes. The result of my labours tends to prove, that many inflammatory lesions of the mucous tissue have been confounded together, while the gradations of the same affections have often been mistaken for so many different diseases." 1

The Greeks used the term diphtheria to indicate a piece of leather, skin, hide, velum and parchment.

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(1) Memoirs on Diphtheria, from the writings of Bretonneau, Guersant, Trousseau, Bochut, Empis, and Daviot, selected and translated by Robert Hunter SEmple, with a Bibliographical appendix by John Chatto, the New Sydenham Society, London, 1859, p. 5.

THE GREEKS AND THE TERM "DIPHTHERIA"

During the classical period, four notable writers employed the term diphthera in their works: Herodotus, Thucydides, Plato, and Diodorus.

Herodotus [2] wrote his history "in the hope of thereby preserving from decay the remembrance of what men have done, and or preventing the great and wonderful actions of the Greeks and the Barbarians from losing their due meed of glory; and withal to put on record what were their gounds of feud."

References to the term diphthera occur in the First, Fifth, and Seventh Books of The History of Herodotus. In chapter 194 of the First Book which is entitled Cleo, is found discussion of diphthera in which it is used to mean skins. He described the boats used by the Armenians which were composed of skins stretched around the hulls. He [3] wrote "The boats which come down the river to Babylon are circular, and made of skins." Further, he [4] related, "The frames, which are willow, are cut in the country of the Armenians above Assyria, and on these, which serve for hulls, a covering of skins is stretched outside, and thus boats are made, without either stem or stern, quite round like a shield."

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(2) Great Books of the Western World, Robert Maynard Hutchins, Editor in Chief, Volume 6, Encyclopedia Britannica, Inc., William Benton Publisher, Chicago, London, Toronto, 1952, p. 1.

(3) Ibid., p. 44.

(4) Ibid., p. 44.

Herodotus then discussed the means of carrying cargo, which involved filling the boats with straw, putting the cargo aboard and floating down stream. The chief freight was wine, stored in casks made of palm-tree wood. Two men stood upright in the boat, each plying an oar, one pulling and one pushing. The boats were various sizes, some large and some small. A live ass was carried on each vessel. He [5] stated: "When they reach Babylon, the cargo is landed and offered for sale; after which the men break up their boats, sell the straw and the frames, and loading their asses with skins, set off on their way back to Armenia." He [6] concluded this chapter by saying, "The current is too strong to allow a boat to return upstream, for which reason they make their boats of skins rather than wood." He said that on their return to Armenia, they build fresh boats for the next voyage.

The Fifth Book, entitled Terpischore, was a narration of the introduction into Greece of the writing art by the Phoenicians. It was Herodotus' supposition that the Greeks until then had been ignorant. The Greeks at that time were chiefly Ionians. They adopted the Phoenician letters but made some variation in them.

Herodotus [7] related, "Paper rolls were called from of old "parchments" by the Ionians, because formerly when papar was scarce they used, instead, the skins of sheep and goats -- on which material many of the barbarians are even now wont to write." He here used the reference to the employment of skins as material upon which writing was placed.

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(5) Ibid., p. 44.
(6) Ibid., p. 44.
(7) Ibid., p. 171.

The Seventh Book, entitled Polymia, contained a reference to head coverings made of leather. The statement is found: [8] "They wore about their heads skull-caps made of leather." He was speaking of Milyans who were dressed for battle.

Herodotus' dates are given as (c. 484-425 B.C.). He was born about four years after the battle of Salamis in Halicarnassus in Asia Minor. Although a Greek Colony, Halicarnassus had been a subject of Persia for some time. Herodotus came from a well respected family. After his elementary education, he appeared to spend the rest of life reading and traveling. At Athens, Herodotus seems to have been admitted into a relationship with Pericles. He presumably died at Thurii.

In the Second Book, chapter 8 of Thucydides' The History of the Peloponnesian War, is found mention of the use of skins in the construction of a wall. He [9] wrote "The timbers served to bind the building together, and to prevent its becoming weak as it advanced in height; it had also a covering of skins and hides, which protected thw woodwork against the attacks of burning missiles and allowed the men to work in safety."

Thucydides' dates are (c. 460-400 B.C.). He [10] recorded that he began writing his History of the Peloponnesian War "at the moment that it broke out" and that he was then

(8) Ibid., p. 229.
(9) Ibid., p. 407.
(10) Ibid., p. 345.

"of an age to comprehend events". His father, Clorus, was an Athenian citizen and possibly related to the Thracian prince Cimon, son of Militiades. His family was wealthy due to possession of gold mines on the coast opposite Thasos. When the Peloponnesian War broke out in 431 B.C., Thucydides was in Athens. He experienced the plague which occurred the following year. He [11] recorded, "I had the disease myself and watched its operation in the case of others". He was presumably a member of the circle of Pericles.

Plato in The Dialogues mentioned the wrapping of the body with goatskins in the form of a disguise. In the Dialogue Crito [12] is found the statements: "But if you go away from well-goverened states to Crito's friends in Thessaly, where there is great disorder and license, they will be charmed to hear the tale of your escape from prison, set off with ludicrous particulars of the manner in which you were wrapped in a goatskin or some other disguise, and metamorphosed as the manner is of runaways; but will there be no one to remind you that in your old age you were not ashamed to violate the most sacred laws from a miserable desire of a little more life?" Crito was an old and tried friend of Socrates. He had at Socrates' trial, volunteered to make up the sum of any fine that might be

(11) Ibid., p. 345.
(12) Ibid., Volume u, p. 218.

imposed against him. On that particular occasion, he made a last desperate effort to persuade Socrates to allow his friends to aid him in his escape from prison.

Plato's parents were Ariston and Perictione. His dates were (c. 428-348 B.C.). His early life occurred during the Peloponnesian War and the collapse of the Athenian Empire. After Socrates' execution, which occurred in 399 B.C., he started to travel. When he returned to Athens about 387, he founded the Academy and presided over it the rest of his life.

Diodorus Siculus in Book II, chapter 32, utilized the term diphtheria to mean records. He [13] stated, "Now Ctesias says that from the royal records, in which the Persians in accordance with a certain law of theirs kept an account of their ancient affairs, he carefully investigated the facts about each king, and when he had composed his history he published it to the Greeks." Ctesias of Cnidus lived during the time when Cyrus the Younger made an expedition against Artaxerxes, his brother. Ctesias was retained by Artaxerxes because of his medical knowledge and became a part of the king's retinue.

Diodorus Siculus, a Greek historian, was born at Agyrium in Sicily, and lived in the times of Julius Caesar and Augustus. He traveled in Egypt between 60-57 B.C. His history was called Bibliotheca historica or Historical Library. It contained forty books and was divided into three parts.

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(13) Diodorus Siculus, Diodorus of Sicily, Harvard University Press, Cambridge, Massachusetts, William Heinemann, Limited, London, 1933, Volume I, Book II, Chapter 32, p. 459.

Some other Greek writers included: Phylarchus (c. 219 B.C.) and Xenophon (c. 401 B.C.) who used the plural "skins" as used in tents. Ammonius (c. 470 A.D.) referred to "goatskin".

Three authors used the term diphtheria to mean anything made of leather, a leathern garment such as peasants wore. They were: Aristophanes (c. 160 A.D.), Arrianus (c. 124 A.D.) and Lucianis (c. 160 A.D.).

PIERRE BRETONNEAU AND THE TERM "DIPHTHERIA"

BRETONNEAU'S LIFE. Pierre Fidele Bretonneau (1778-1862) was born at St. George-sur-Cher, in the department of Indre-et-Cher, on April 3, 1778. It has been said that, "Not only were his father and uncle surgeons, but his genealogical tree, which has been worked out by Dr. Louis Dubreuil-Chambardel, for nine generations contained fifteen doctors of medicine, surgeons or apothecaries, the most celebrated of whom were Rene Bretonnayau, who flourished in the middle of the sixteenth century at Beaulieulis-Loches, and was the author of a medical poem entitled "L'Esculape François". 14

(14) Rolleston, J. D., Proceedings of the Royal Society of Medicine, 18:1-2, 1924/25.

Bretonneau did not learn to read until he was nine years of age. But, "his father seems to have inspired him in early life with a taste for natural history and medicine." [15] He chose to study meidcine, and at the age of 17, he was sent by the department of Loir-et-Cher to study medicine at the Ecole de Santé in Paris, "where his fellow students including Dupuytren, Bayle, Récamier, Esquirol and Guersant." [16] He manifested an interest in anatomical studies at this time; publishing a translation in 1798, of Mascagni's work on the lymphatics; in collaboration with Saclier. Having not quite completed three years of study, "ill health and a prolonged convalescence at home forced him to interrupt his work." [17] He was then "introduced by his father to Mme. Dupin, the Chatelaine of Chenonceaux, once one of the most beautiful and wittiest women of the time, but now an old lady of 90. In spite of her advanced age she was in full possession of her faculties and appears to have taught Bretonneau not only Italian and English, but also the art of conversation, in which he subsequently excelled. In later years he frequently used to quote her aphorism, "ce que nous savons souffre de ce que nous ne savons pas". [18]

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(15) Ibid.
(16) Ibid.
(17) Talbott, John, op. cit., p. 480.
(18) Rolleston, J. D., op. cit.

That in translation means, "That which we know suffers from that which we do not know". When she died in 1799, "he completed his medical studies in Paris, passed some of his examinations in brilliant style, but failed in botany, a favorite subject". [19] His instructor, "the truculent surgeon", Boyer, was not satisfied with his knowledge in the subject.

He then, "decided to abandon his examinations for the doctorate and to content himself with the modest title of officier de sante- a qualification now extinct - and returned to Chenonceaux, where he set up practice, his spare time being devoted to the study of chemistry, natural history, gardening, the keeping of bees, of whose epizootics he acquired a considerable knowledge; the drawing and painting, in which like Pasteur, he showed considerable skill." [21] "He forged his own cataract needles, designed capillary tubes for storing vaccine lymph, and constructed thermometers for his friends." [22]

He enjoyed a wide medical practice. "His reputation as a practitioner rapidly grew. In the salon of M. de Villéneuve, who had inherited the chateau of Chenonceaux from his great-aunt, Mme. Dupin, he made the acquaintance of M. de Keragariou, the prefect of Indre-et Loire, who invited him to come to Tours as principle physician to

(19) Talbott, John, op. cit., p. 480.
(20) Rolleston, J. D., op. cit.
(21) Ibid.
(22) Talbott, John, op. cit., p. 480.

the hospital. For this post it was necessary to qualify as a doctor of medicine. He therefore returned to Paris, passed the necessary examinations in 1814, having rapidly acquired a knowledge of Latin, in which he remained a proficient scholar throughout his life, and in 1815 read his thesis, of which the subject was the value of compression, and especially of Theden's bandage in idiopathic inflammations of the skin. The same year, namely from November 1 to April 30, but during this period he showed an unprecendented activity. He arrived at the hospital at 6 a.m., made a careful examination of each patient, and dictated the notes that formed the enormous dossiers..." [23]

In his post at Tours, he both taught medicine and cared for the sick. He, "was unhurried in his clinical examination of the patients with infectious diseases, in whom he was particularly interested. He practiced an informal Socratic method of teaching, sometimes continuing from the hospital wards into his botanical garden. Detailed clinical reports, correlating clinical observations with findings in the morgue, were prepared in longhand. The worth of his instructions may be appraised by the accomplishments of two of his pupils. Velpeau and Trousseau, who became outstanding physicians in their maturity and to whom Bretonneau owed much for their respect and loyealty." [24]

Bretonneau, also carried on experimental work at the hospital, "especially at night, the patients not infrequently

(23) Rolleston, J. D., op. cit.
(24) Talobtt, John, op. cit., p. 480. (Velpeau was a surgeon).

complaining that they were kept awake by the barking of dogs which served as the subjects of his investigations." [25] He was at Tours for twenty-three years and during that time, he was in charge of "a course of clinical medicine and materia medica." [26]

Prior to his work at Tours, Bretonneau had acquired experience with several epidemic diseases..."in the form of two epidemics of typhoid fever at Chenonceaux in 1802 and 1812, occasional outbreaks of scarlet fever, measles and malignant angina in the Valley of the Cher, and a severe epidemic of small-pox in 1814. [27] This was principally clinical experience. "After his arrival in Tours he was able to study a third epidemic of typhoid fever, which broke out in one of the barracks at Tours in 1819, and caused a large number of victims both in the civilian and military population. Almost at the same time an epidemic of peculiar form of sore throat was introduced by the soldiers at the Legion of La Vendée, and continued uninterruptedly until 1820. The epidemic was attended with a remarkably high mortality, so that in the course of a few months Bretonneau was able to carry out sixty autopsies." [28]

He was assisted in his work on the disease by Velpeau. When Bretonneau presented his ideas to the local members of the medical profession, they opposed him. He therefore, resorted

(25) Rolleston, J. D., op. cit.
(26) Ibid.
(27) Ibid.
(28) Ibid.

to exhuming the bodies of the private patients who had died of diphtheria or typhoid fever, and examining them. This so aroused the populace of Tours that they would not accept the term "diphtherite" during his lifetime. They also refused to accept his term "dothienenteritis" for typhoid fever.

Due to, "repeated entreaties from Velpeau, as well as from Duméril and Guersant, Bretonneau at last decided to communicate his researches to the Académie Royale de Médecine, before which he read two papers in 1821, the first on June 26, and the second on August 6. In the first he showed the relations existing between croup, malignant angina and scorbutic gangrene of the gums, all of which he regarded as the same affection, for which he proposed the term "diphtherite". 29

"The second memoir consisted partly of historical evidence from the earlier writers and partly a description of various therapeutical measures including alum, calomel, hydrochloric acid, blood-letting and tracheotomy, a detailed description being given of the operation on Elizabeth de Puysegur, the first successful tracheotomy to be performed in a case of laryngeal diphtheria." 30

Bretonneau's papers were well received by the members of the Académie Royale de Médecine, and they elected him a member

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(29) Ibid.
(30) Ibid.

in 1824. He made no further communication to the organization however. His reports were published in 1826. He wrote further on diphtheria in 1825, and 1855.

He was forced to resign his position as principal physician at Tours due to the opposition to his ideas from the local physicians. He dedicated himself then to his medical practice and to his garden. He died in 1862.

Bretonneau was twice married, first to a woman twenty-five years his senior, and in his old age, at 78 to a very young girl, aged 18.

BRETONNEAU'S MEDICAL CONTRIBUTIONS. "The work of Bretonneau", says Professor Gilbert, "is a trilogy composed of diphtheria, dothienenteritis, and specificity." [31] The great achievement of Bretonneau was to "have shown the identity of malignant angina and croup, and to have differentiated malignant angina from all other forms of sore throat, particularly by its progressive course and contagious character. He proved moreover that in spite of the superficial appearances and the accompanying foetor of the nature of the process in malignant angina was not really gangrene, and even went so far as to deny the existence of gangrenous angina altogether, an error in which he was subsequently corrected by Trousseau. He also showed that two distinct diseases were described by Home, one of which was merely the laryngeal localization of the diphtheritic process, while the other was a mild affection, to which he gave the name of stridulous laryngitis." [32]

(31) Ibid.
(32) Ibid.

Bretonneau established the identification of malignant angina in four ways: "(1) By extensive researches on the morbid anatomy of the disease, sixty autopsies being performed in the course of a few months; (2) by clinical observations, whereby he proved that the angina, if left to itself, almost invariably tended to attack the larynx, and thus give rise to symptoms of croup; (3) by chemical examination, by which he proved the identity in composition of the false membrane in the pharynx with that in the trachea; (4) by the study of the works of the earlier writers." 33

Some defects have been noted in Bretonneau's work on diphtheria. "Epoch-making as Bretonneau's work on diphtheria undoubtedly is, we must not let ourselves ignore its defects, like the writer in the Medical Research Monograph, who described it as "a medical classic of the first rank, to which but little has been added from a purely clinical standpoint." Apart from its complete absence of unity of composition and frequency of repititions, which made Trousseau describe it as "the most inconceivable hotch-potch ever imagined by a writer, the work contains little, if any, indication that Bretonneau regarded diphtheria as a general disease affecting the heart, kidneys, and nervous system. The only allusion, indeed, to diphtheritic paralysis in Bretonneau's writing is to be found in the letter to Blache and Guersant published in 1855, in which

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(33) Ibid.

a description is given of the attack of generalized paralysis, from which Herpin, a well-known surgeon of Tours, suffered. It is the great merit of Trousseau to have supplemented his master's teaching in this respect and to have dwelt in his clinical lectures on the constitutional effects of diphtheria, in which he showed that death was not always due to asphyxia from invasion of the larynx, as Bretonneau had taught, but was often caused by general intoxication. The symptoms of diphtheritic paralysis and the occurrence of albuminuria, which was first noted by Wade of Birmingham in 1858, are also fully described by Trousseau." [34]

It is thought further that, Bretonneau "attached too great importance to the efficacy of fuming hydrochloric acid which was applied to the inflamed mucous membrane in the hope of substituting one inflammation for another. The extraordinarily painful character of the procedure and frequent aggravation of the symptoms soon caused this method to fall into a well-deserved oblivion." [35]

Finally, "there appears to be little doubt that the so-called scorbutic gangrene of the gums, which Bretonneau regarded as diphtheritic, along with malignant angina and croup, was as Bergeron has clearly shown, the ulcero-membrane stomatitis which has so often been the scourge of armies as well as of young children and is totally distinct from diphtheria, being due to the symbiosis of the fusiform bacillus and spirillum first described by Vincent in 1896." [36]

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(34) Ibid.
(35) Ibid.
(36) Ibid.

Bretonneau's second greatest contribution was to the understanding of typhoid fever. He "succeeded in establishing the specific characters of the disease, to which he gave the name of "dothienenterite" or "dothienenterie"...not only by a clinical study for which he had ample opportunity owing to the epidemics in the garrison and civilian population of Tours in the years 1815, 1819, and 1820, but also by numerous and careful autopsies." 37

Bretonneau wrote on typhoid fever between 1821 and 1827, although this work was not published until 1922. The work, "preceded by a short introduction, is divided into four sections devoted to the anatomical lesions, the relations of the lesions to the symptoms, and the question of contagion respectively." 38

The third most important contribution of Bretonneau to medicine is the doctrine of specificity of disease. Bretonneau did not live to publish this aspect of his thought. However, the treatise which he wrote in 1828 has been published posthumously.

Bretonneau also made contributions in therapeutics, particularly in regard to the use of quinine in malaria. He worked to control the diseases; yellow fever, scarlet fever, and influenza.

In conclusion, it may be said of Bretonneau: "(1) He established the specific character of diphtheria and typhoid fever; (2) by his doctrine of specificity he made several valuable contributions to therapeutics (4) his researches, especially those connected with diphtheria show the value of the study of the history of medicine." 39

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(37) Ibid.
(38) Ibid.
(39) Ibid.

BRETONNEAU AND THE TERM "DIPHTHERIA". Bretonneau [40] in naming the disease stated: "As it is impossible to apply to a special inflammation which is so well-marked, any one of the improper names which have been given to each of its varieties, let it be permitted me to designate this phlegmasia by the name Diphtherite,..."

While in Tours during the years 1818-1820, he observed an epidemic of diphtheria. From these observations he was able to draw certain conclusions. He presented his conclusions to the Academy of Medicine of Paris in 1821. His [41] opening statement in this paper read: "The Memoir which I have the honour to submit to the judgment of the Academy, is extracted from a collection of observations on the special phlegmasia of the mucous membranes. The result of my labours tends to prove, that many inflammatory lesions of the mucous tissue have been confounded together, while the gradations of the same affection have often been mistaken for so many different diseases."

Bretonneau discussed in the introduction of the First Memoir of his Treatise on Diphthérite the differences in the formations of the exudations of false membranes in the throat. However, he did not dwell on the distinctions of the membranes but rather he [42] stated: "So far from entering into these distinctions, and insisting upon the difference of the inflammatory conditions of the mucous tissue, I undertake at

(40) Memoirs on Diphtheria, p. 20.
(41) Ibid., p. 5.
(42) Ibid., pp. 5-6.

present to prove, by the testimony of the facts, that the Scorbutic Gangrene of the Gums, Croup, and Malignant Angina, are only one and the same form of phlegmasia."

He opened sixty bodies in the course of the diphtheria epidemic. A hundred and thirty soldiers, and twenty individuals of all ages, presented the different gradations of the disease.

He also indicated, in this introduction, the intention to present in a second memoir, the historical records of the disease.

The First Memoir was divided into two sections: 1. Of Scorbutic Gangrene, and 2. Of Malignant Angina.

1. Of Scorbutic Gangrene

Bretonneau described the symptoms of the disease. There was a greyish ulceration on the border of the gums. There was an increase in the tartar deposit. An incurable looseness of the teeth occurred. There occurred also ulceration of the mucous membranes of the mouth.

This disease occurred in the soldiers of the legion of La Vendée, while they were in garrison at Bourbon. In 1818 a great number were taken with it.

He [43] thought "it is evident, that this affection had nothing in common with scurvy, however little precision was attached to this word, and however little it was taken in the acceptance laid down by Lind in his Treatise on Scurvy, a work based upon a great mass of observations, and a masterpiece of learning and criticism."

(43) Ibid., p. 8.

Therapy for the disease included: the juice of the cress, anti-scorbutics in all forms, and local application of hydrochloric acid.

He [44] believed "This disease was certainly the stomacace of the ancients, and the fégarite of the Spaniards, denominations which, with an etymology of different origin, have only a single meaning, since they both signify a foul ulcer of the mouth. It was, moreover, the affection designated by the learned commentator of Boerhaave, under the name of scorbutic gangrene of the gums, and of watery cankers, (chancres aquatiques); a disease which he subdued by means of hydrochloric acid; in fact, he believed it to be of a scorbutic nature, but still he did not fail to observe that it was exaserbated by an anti-scorbutic treatment."

He stated that Van Swieten recognized the identity of the two affections: Scorbutic Gangrene and Malignant or Gangrenous Angina.

2. Of Malignant Angina

He discussed in the first part of this section of the Memoir the multiplicity of names given to the disease. The most remarkable symptom of this malady, he noted, was that of choking and strangulation. When the disease appeared at Tours, Bretonneau and the other physicians observed and studied means of treating it. He gave six case histories to demonstrate the characteristics of the disease.

(44) Ibid., p. 9.

There was a section on the inflammatory lesions and alterations of tissue in the disease.

He noted a redness of the tissue of the mucous membranes. Diphtheritic inflammation was propagated similar to the spreading of a fluid on the surface. Pseudo-membranous matters were found in the areas of inflammation.

In relating the sameness of the three maladies, scorbutic gangrene of the gums, malignant angina, and croup, he [45] said: "Putting aside for the moment the conclusions which may be drawn from contagion (a question which belongs exclusively to the second part of this Memoir), and considering only the epidemic character in the Scorbutic Gangrene of the gums, Malignant Angina, and Croup, I think that the identity of these three affections, founded upon an identity of organic alterations, which have been demonstrated by pathological anatomy, cannot be invalidated by a few unimportant symptoms."

Bretonneau's Second Memoir, which was also read to the Academy of Medicine in 1821 was an analysis of the historical evidence of the disease, diphtheria. The first author whom he discussed was Hippocrates. He [46] related: "If some passages in the works of Hippocrates relate to Diphthérite, their brevity permits us to doubt the fact. When he said in the book on Dentition (if indeed this book is to be attributed to him) "Quibus cito in tonsillis ulcera serpentia considunt, febris ac tussi permanentibus, periculum est rursus esse generanda ulcera", it is possible that he had in view rather an apthous ulceration of the back of the mouth, than a disease all the symptoms of which would have struck so able an observer more forcibly.

(45) Ibid., p. 22.
(46) Ibid., p. 28.

Secondly, he made reference to Aretaeus, whom he gave the credit for being the first to describe the disease, diphtheria. Aretaeus described it as Egyptian and Syriac ulcers about the tonsils.

He [47] further recorded, "Aetius adds to the description of Aretaeus, a commentary and some particulars which leave no doubt that he had seen the same disease two or three centuries later."

In describing Macrobius' contribution to the delineation of diphtheria, Bretonneau [48] stated, "Macrobius, in the year 380, speaks, according to Julius Modestus, of sacrifices which were instituted in honour of a heathen goddess, "ut populus Romanus morbo qui Angina dicitur, promisso voto, sit liberatur."

He [49] thought that Guillaume de Baillou had not described diphtheria in his Epidemics. "We cannot mistake tracheal Diphtherite for the orthopnoeic affection of which Baillou speaks, in the second book of his Epidemics when giving an account of the constitution of the winter of 1576. M. Royer-Collard (Dict. des Sciences Medic. Art. Croup), observes with truth, that the quotation from Baillou, given in Lieutaud, copied in a multitude of modern works and even adopted by the authors of the collections of observations and facts relative to Croup, is very inexact. This quotation appears to him to be adapted to the idea which had been formed of this disease in

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(47) Ibid., p. 29.
(48) Ibid., p. 29.
(49) Ibid., p. 29. (orthopnoeic - inability to breathe in an upright position).

more modern times, and he thinks "that if Baillou has certainly had several kinds of Croup under his notice, it is not, therefore, proved that he knew which was Croup".

In his discussion of the epidemics of diphtheria in Spain, Bretonneau [50] related "the epidemic affection receives in Spain the name of garrotillo, because those attacked by it perished as if they had been strangled by a cord. The Neapolitans, struck by the most formidable of its symptoms, call it male in canna, disease of the air-tube or trachea. A great number of denominations proposed by the physicians of that age, such as that of passio anginosa, affectus suffocatorius, laqueus gutturis praefocans pueros, abscessus, morbus, strangulatorius, have no other meaning than popular names. But it is superfluous to discuss this matter, when the most express declarations leave no doubt upon the point."

Bretonneau asserted that Heredia, the physician to Philip IV, made no mention of the diversity of opinions among his predecessors, except in relation to treatment. Among the Italian physicians who described diphtheria epidemics, Bretonneau gave the names of Sgambati and Carnevale. He related that Carnevale, especially in his Treatise, de Epidemico strangulatorio affectu, discussed many factors of the disease.

Nola published a treatise in 1620, which Bretonneau mentioned. He stated that The Treatise of Nola did not invalidate any of the facts which Carnevale had published.

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(50) Ibid., p. 31.

He explained that in 1622, Alaymus published his Treatise on Syriac Ulcers. This treatise presented the facts which had been presented heretofore. Cortesius is then discussed by Bretonneau. About 1622, Cortesius thought that he perceived some difference between the garotillo of the Spaniards and an epidemic affection which occurred at Messina.

Bretonneau [51] noted that Marcus Aurelius Severinus... "had seen many thousand children carried off by this formidable disease, and yet he inserted in his treatise only a single post-mortem examination, and this was so vaguely described, that scarcely two lines relate to the subject." These two lines, however, are remarkable, "Larynge investigata, contecta erat pituita quadem crustacea, circa ulceris speciem."

Bretonneau [52] included information on Ghisi,; "Ghisi after having given an exact description of the epidemic angina which began to show itself at Cremona in the month of May, 1747, merely says that in some subjects, "Other mortal and treacherous cases of angina which were accompanied with scarcely any difficulty of deglutition, killed unexpectedly and exactly in the same manner as the cases of the first kind, the progress of which had been neglected."

(51) Ibid., p. 34.
(52) Ibid., p. 35.

Bretonneau [53] gave his opinion of the monograph of Michaëlis:..."Michaëlis of Gottingen, the author of a monograph on Membranous Angina. The case of his younger sister, carried off by this disease, is according to him, the type to which he refers all the examples of the malady which he was able to collect. He discovered that in the epidemic which Cullen and Crawford refer to Croup, a great number of the cases belong to Malignant Angina. He supposed that these two diseases prevailed at the same time, and that they may have been confounded together. His rule for distinguishing them, was to refer to Malignant Angina all the cases in which the fetor of the breath has been particularly observed, especially if, at the same time spots have been seen in the pharynx."

He [54] gave a discussion of Rosen in which is found the Statements: "Rosen, who recommends us not to confound Croup with Malignant Angina, falls into this error himself. The affection described by him, is said to be transmitted from one child to another, pellicles are seen in the pharynx from the beginning of the disease, and a long time before it is terminated by croupal affection."

He said that Samuel Bard...saw upon several children in the same family, thick coriaceous pellicles formed upon the tonsils, and propagated from the pharynx to the trachea; and at the period of this extension he observed all the symptoms of croup developed.

(53) Ibid., p. 36.
(54) Ibid., p. 36.

It was his belief that Fothergill's dissertation had no relation to diphtheria. But, rather that the disease which he described was Scarlatinal Angina. He thought that John Huxham had also observed Scarlatinal Angina.

He [55] further related "in 1747 and 1748, Arnault of Orleans, makes mention of terrible quinsies, which carried off the patients in twenty-four hours."

In describing Chomel's contributions, he [56] stated: "The history of the gangrenous sore-throat, edited by Chomel, presents several special observations on Diphtheritic Angina, of which all the symptoms were noted daily with great care."

In 1768, Bretonneau [57] stated that "Marteau de Grandvilliers, a physician at Aumale, published a description of gangrenous sore-throats which he had observed for several years in Picardy."

Bretonneau [58] in his additions to the second memoir made in June, 1825, wrote "it was undoubtedly Diphtheritic Angina which presented itself to the observation of M. Jurine, and of which mention is made in the following passage of the Report of the Commission. 'It is easy to distinguish Croup from Angina Tonsillaris, Angina Pharyngea, and even from Gangrenous Angina of adults. But there is another sort of Angina, generally epidemic, and perhaps contagious, which is called Gangrenous, and sometimes aphthous, which especially attacks children, and which is often complicated with Croup, that it is almost impossible to distinguish them.'"

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(55) Ibid., p. 37.
(56) Ibid., p. 38.
(57) Ibid., p. 38.
(58) Ibid., p. 58.

BRETONNEAU'S NOSOGRAPHY: ITS INFLUENCES AND DEVELOPMENT

In the nineteenth century the Paris School developed the method of anatomical diagnosis. One of the leading proponents of this method was Theophile Laënnec (1776-1821). Bretonneau was very much influenced by Laënnec and his ideas of nosography. "...it will be easily seen that the points of view and attitudes of mind revealed by Bretonneau in his writings indicate that in him a further considerable development of Laënnec's ideas concerning nosography, had taken place. The French physicians of this period were constantly engaged in isolating and describing new types of disease, and this aided greatly in maintaining and developing Laënnec's ideas." [59]

Laënnec's treatise, Traité de l'Auscultation Mediate, "belongs among the works which have marked an epoch in medicine and more particularly in internal clinical medicine." [60] Since the publication, "the physician saw the task at the bedside change. The physician began now not only to observe, but to examine the patient. Laënnec's work produced also a revolution in nosography, a revolution in the manner of describing and classifying the morbid phenomena." [61]

"In 1816, Laënnec conceived the idea of indirect auscultation, and this resulted in the invention of the stethoscope. By auscultation he was able to demonstrate the signs of morbid changes in the organs much more perfectly than he could by percussion alone.

(59) Faber, Knud, Nosography in Modern Medicine, Paul B. Hoeber, Inc., New York, 1923, p. 34.
(60) Ibid., p. 34
(61) Ibid., p. 34

and the subjective symptoms, therefore, became of secondary importance." [62]

"By comparing the conditions present in the patient with the course of the disease and the lesions found at post-mortem examinations Laënnec created a series of entirely new and classical pictures of disease. Thus he was the first to describe emphysema, acute and chronic edema of the lungs, bronchiectasis and gangrene of the lungs. He further described pneumothorax, and he distinguished pneumonia from the various kinds of bronchitis and from pleuritis. Before his time physicians had not been able to distinguish between these various affections, but merged them all under the term peri-pneumonia which had been inherited from the ancients. Having made these distinctions he was able to give a clinical and anatomical description of pneumonia which holds good to this day." [63]

It may be said that, "His greatest accomplishment...was his description of tuberculosis. It may be said that he was the first to establish the conception of tuberculosis as a morbid unity." [64]

Other than Bretonneau, several other clinicians carried on the work of Laënnec, some of them were: G. L. Bayle, Andral, Louis, A. L. Bayle, Couillaud, Cruveilhier, Chomel, Alibert, Rayer, and Piorry.

Pierre Bretonneau's doctrine of diphtheria had many influences. His study of the Greeks made him aware of their designation for the

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(62) Ibid., p. 36
(63) Ibid., p. 37.
(64) Ibid., pp. 37-8.

membrane, which was "diphtheria". He was later influenced in his ideas of nosography by René Theophile Laënnec and the Paris School's emphasis on anatomical diagnosis.

During the nineteenth century, diphtheria epidemics were prevalent in France. This was not the case in other parts of the world.

CHAPTER III

DIPHTHERIA IN FRANCE IN THE NINETEENTH CENTURY

Diphtheria epidemics have prevailed in France from early times to the nineteenth century. In the chronicles of St. Denis of 580 A.D. there is mention made of a "pest" which went by the name of "esquinancie" corresponding to "squinantia", a name subsequently applied to angina maligna. [1]

Guillaume de Baillou (1538-1616), described as the first epidemiologist of modern times; served as court physician during the reign of Henri IV of France; was the first to publish an accurate description of diphtheria in France.[2] His writings give the first deninite mention of a false membrane.

In 1576, diphtheria occurred epidemically in Paris. [3] It reappeared in Paris in 1743, where it continued until 1748. [4] Marteau de Grandvilliers described a similar outbreak in Paris in 1749. [5]

From the middle of the seventeenth century up to 1740, little mention is made of the malignant angina. [6] However,

(1) Hirsch, August, Handbook of Geographical and Historical Pathology, translated from the second German ed. by Charles Creighton, M.D., London, The New Sydenham Society, 1883-1886, p. 74.
(2) Mackenzie, Morell, Diseases of the Pharynx, Larynx, and Trachea, New York, William Wood and Company, 1880, p. 90.
(3) Trall, R. T., Diphtheria: its Nature, History, Causes, Prevention and Treatment on Hygienic Principles, New York, R. T. Trall and Company, Publishers, 1862, p. 76.
(4) Ibid., p. 76.
(5) Mackenzie, Morell, op. cit., p. 9.
(6) Slade, Daniel Denison, Diphtheria: Its Nature and Treatment; with an Account of the History of its Prevalence in Various Countries, Blanchard and Lea, Philadelphia, 1861, p. 21.

shortly after this, in 1743, the disease made its appearance in Paris; Malouin and Auguste François Chomel (1788-1858) have described it. [7]

Martino G. Ghisi gave a detailed description of the epidemic of sore throat which began to show itself at Cremona in 1747. [8] He stated that the disease proved fatal by suffocation, seen in those cases where the attention of the patient hadn't been called to the condition of the throat.[9] The absence of all difficulty in deglutition was observed constantly.

Ghisi described cases which appeared to be primary and not secondary to scarlatina. [10] He particularly noted the peculiarity of the pseudo-membranous concretion which exists in the air-passages. [11] Ghisi, in describing the epidemic angina which occurred in Cremona in May, 1747, stated:

> "Other mortal and treacherous cases of angina which were accompanied with scarcely any difficulty of deglutition killed unexpectedly and exactly in the same manner as the cases of the first kind, the progress of which had been neglected;" [12]

Ghisi gave detailed description of the sufferings attending the deaths from diphtheria. [13] When he opened the body of a child, he found a membrane in the trachea. [14]

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(7) Ibid., p. 21.
(8) Ibid., p. 21.
(9) (10) (11) Ibid., p. 22.
(12) Bretonneau Pierre, Memoirs on Diphtheria from the Writings of Bretonneau, Guersant, Trousseau, Bochut, Empis, and Daviot, London, The New Sydenham Society, 1859, p. 35.
(13) Ibid., p. 35.
(14) Ibid., p. 35.

In 1747, Louis Daniel Arnault de Nobleville (1704-1778) of Orleans, mentioned cases of malignant sore throat which carried off the patient in twenty-four hours. [15] When two children were autopsied, the mucous membrane of the trachea was found detached for the extent of several inches. [16] This membrane was described as having the consistency of parchment and a white color. [17] Marteau de Grandvilliers, a physician at Aumale, published a description of gangrenous sore-throat which he had observed for several years in Picardy. He was an attentive observer, collected a great number of facts and arranged several special narratives with great exactness. Ghisi had already discovered the inorganic nature of the false membrane at this time. De Grandvilliers preserved some of the long membraniform tubes expectorated by a patient. He confused diphtheria angina with scarlatina angina. [18]

The first trustworthy accounts of angina maligna from France date from the years 1745-1750, in which the malady was epidemic in Paris, [19] Versailles, Orleans, Lille, Rouen, Amiens, Chalons-sur-Marne, Montpellier, Nerac, and other places in Guyenne and in Bearn. It was observed at Paris in 1758, 1759, and 1762, at Forges, Lisieux, and other Norman towns in 1774 and at Poitiers in 1787. [20]

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(15) Slade, Daniel Denison, op. cit., p. 22.
(16) Ibid., p. 22.
(17) Ibid., p. 22.
(18) Bretonneau, Pierre, op. cit., p. 38.
(19) Hirsch, August, op. cit., p. 78.
(20) Ibid., p. 79.

There was somewhat of a remission, except in France, from the end of the eighteenth century until about 1860. [21] "Down to about the year 1860 there was only one part of Europe where angina maligna prevailed widely, namely France, which had been one of its principal seats in the previous century. It was not until that date that it assumed the character which it has maintained to the present day." [22]

In the first part of this period, from 1800 to 1843, there were only occasional epidemics of angina maligna observed in southern Europe, as at Padua in 1805, in the island of Crete in 1816, and in 1835 at Lisbon, where the Duke of Leuchtenbury died of it. Besides these, the epidemics which developed within the same years on French soil were both numerous and extensive. The earliest account of them dates from 1810-11, in which years the disease was prevalent in Lyons. Then comes the account which Bretonneau gave in his famous work, of the epidemic observed by himself at Tours in 1818-21, and at La Ferriere in 1824-25; following which are epidemics in Paris, in the Department of Lot, in Nantes, in Arras, and several districts of the Department of Eure-Loire. But it was in the years 1825-36 that the malady reached its wildest prevalence in France; for those years there are many accounts of epidemics - in the Orleannais (particularly Department Loire, in Touraine (mostly Loire-Cher and Indre-Loire, in Anjou (maine-Loire, Sarthe, and Mayenne, in Britanny (Nantes), (Seine-Marne and Seine), and in Isle-de-France; from which

(21) Ibid., p. 79.
(22) Ibid., p. 81.

enumeration it would appear that the disease had been confined mostly to the North-West. Outside that circle there was only one epidemic observed in those years, at Limousin in the Haute-Vienne. For the years immediately following there are accounts of angina maligna in the Vosges and at Paris (1839), and in the Nivernais (Dept. Niévre) Burgundy (Saone-Loire) and the East of France (1841). [23]

During the twenty years following the period of which we have been speaking, angina maligna presented itself in various parts of the world as before merely in sporadic cases, more or less numerous, or in small epidemics narrowly circumscribed both as regards duration and area. To that rule, however, France is again an exception; and along with it we have to include this time Denmark and Norway, where the malady had begun to be somewhat generally diffused since 1844. [24]

In France the general diffusion of the sickness appears to have been again mostly within the limits of the northern and eastern departments; at all events, nearly all the published accounts of angina maligna come from that region. Thus, we hear of it in Paris in 1846-48, at Laigle (Dep. Oine, Normandy) in 1850, in the Arrondissements of Vitry-le-Francois, Epernay, etc. (Dep. Marne, Champagne, at St. Pol (Dep. Pas-de-Calais) in 1852, in the Arrondissement of Aisne (Dep. Aisne) and in Valenciennes (Dep. Nord) in 1853, and in Paris, Boulogne, and other places in 1855. On the other hand, from the South of France we hear only of an epidemic in 1852 in the Arrondissement of Marmande (Dep. Lot-Garonne), and of another in

(23) Ibid., pp. 81-82.
(24) Ibid., p. 84.

1853 at Avignon. Connected probably with the prevalence of the disease during that period in France is the outbreak of angina maligna among the French troops in 1854 and 1855 during the war in the Crimea and in Turkey. [25]

Taking up the history of angina maligna at the point where we last left it, we shall find that France, which was obviously the greatest sufferer from the malady during the last century and first half of the present, becomes again a principal seat of it in the period fo the great pandemic. Next to France in the order of being invaded come the Iberian Peninsula, Holland and England; then Germany, Russia and North America; a little later the Scandinavian Kingdoms; and lastly Italy and the south-east of Europe. [26]

In France, angina maligna since 1859 had continued to spread over more and more of the country; it was no longer confined as before mostly to the northern and eastern provinces (Britanny, Normandy, Picardy, Ile-de-France, Champagne, Lorraine, Poitou, Sologne, and the Orleannais); but it broke out in the southern and western regions also - in Burgundy, the Auvergne, the Lynnais, Provence, Languedoc, Guyenne, and Saint Onge. In many of these places it presented itself, the authroties expressly tell us, as a malady unknown before; thus Bouillon-

(25) Ibid., p. 85
(26) Ibid., p. 87.

Lagrange says that in the southern part of the Dep. Seine-Oise, where he had practised for twenty years, there had been no diphtheria previous to 1857; Bodélio says the same for Morbihan, and particularly for L'Orient, the chief town of the department; according to Pitavy, diphtheria became prevalent for the first time in 1859 in the region of the Puy-de-Dome on the borders of the Departments of the Loire and Haute-Loire (Auvergne); from Montpellier, Courty writes under date 1862 that the disease was almost unknown there before, and had become exceedingly common of late years; in Lyons down to 1865 it had been observed only in sporadic cases, but became generally diffused from that date; in St. Die (Vosges), it became epidemic for the first time in 1880. [27]

In Tunis from 1872 to 1876 the disease was epidemic over a wide area and very malignant, and in 1882 it was seen there again among the French soldiers garrisoning the country, having been introduced from Algiers. [28]

From the Malay Archipelago there is a record of an epidemic among the French garrison at Fort Tongkeong in 1864; it is stated also by Laure that angina maligna was very common in the French fleet from 1859-62 in the China and Cochin China seas, that in one ship it was epidemic, and that the same fate overtook the crew of a United States ship-of-war cruising in Chinese waters. [29]

(27) Ibid., p. 88.
(28) Ibid., p. 98.
(29) Ibid., p. 99.

Thus Burgeois observed at St. Denis in 1827 a striking change in the cases for the worse when cold and damp weather set in. [30]

According to Mazier's observations of the epidemic of 1850-51 in the Dep. Orne, great changes of temperature always brought an accession of the disease; and there are similar statemtns as to the influence of cold and damp weather in giving the epidemic a fresh impulse, reported from Paris in 1855,...[31]

Thus, to give only a few of the facts, it is stated by Bouillon-Lagrance with reference to the epidemic of 1857-58 in the department of Seine-Oise, that the disease kept a uniform type under all kinds of weather; and Daviot says the same of the epidemic of 1841-44 in the departments of Saone-Loire and Nievre. [32]

In the Paris epidemic of 1841, the number of cases increased as the season advanced towards summer, Becquerel's conclusion from his then experiences being, "que, les jours qui ont marque le debut des trois formes de la maladie ont presque toujours presente une haute temperature, soit absolve pour les mois dans lesquels on les observait." In like manner Bodelio says of the epidemic of 1865 in Morbihan: "L'Hiver heureusment a mis a-peu-pres fin a cette affection qui semble n'avoir ete que le resultat des fortes chaleurs de l'ete." [33]

To these may be added the account of Lajarte of numerous very malignant cases of diphtheria on board a French ship-of-war during a seven months' voyage from L'Orient to China;...[34]

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(30) Ibid., p. 102.
(31) Ibid., p. 102.
(32) Ibid., p. 102.
(33) Ibid., p. 103.
(34) Ibid., p. 106.

In France five major writers on diphtheria in the nineteenth century besides Pierre Bretonneau (1771-1862) were: Paul Louis Benoit Guersant (1800-1869), Armand Trousseau (1801-1867), Bochut (1818-1891), Georges Simon Empis (1824-1913) and D. Zacharie Daviot.

BRETONNEAU ON DIPHTHERIA, 1821, 1825, 1825, 1826, 1855

The account which Bretonneau gave in his famous work of 1821 was on the epidemic observed by him in Tours in 1818-1821. Subsequent memoirs were done on the epidemics at La Ferriere in 1824-1825. [35]

Pierre Bretonneau wrote five memoirs on diphtheria. [36] These memoirs were collected and published together in 1859 by the Sydenham Society. They had been written prior to the 1859 publication, covering the Tours and La Ferriere diphtheria epidemics. In his introduction to the memoirs, he discussed the first two. He said, "On Croup and Malignant Angina", were read at the Academie Royal de Medecine, in 1821.

He credited his friend, Dr. Guersant, with enabling him to verify his observations at the Hopital des Enfans Malades. He found the characters of the Malignant Angina identical with those so judiciously noticed by a French physician, Marteau de Grandvilliers, in his treatise on Gangrenous Affections of the Throat, published in 1757.

He stated further that, in 1740, the nature of the pseudo-membranous exudation which lines the air passages was pointed out by Ghisi.

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(35) Ibid., p. 81.
(36) Bretonneau, Pierre, op. cit., pp. 1-125.

BRETONNEAU'S FIRST MEMOIR, 1821

On the Diphtheritic Phlegmasia, or Pellicular Inflammation of the Mouth, Pharynx, and Air-Passages

This memoir was extracted from a collection of observations on the special phlegmasiae of the mucous membranes. The results of his observations tended to prove that many inflammatory lesions of the mucous tissue had been confounded together, while the gradations of the same affection had been often mistaken for many different diseases.

He undertook to prove, by the testimony of facts, that the Scorbutic Gangrene of the gums, Croup, and Malignant Angina, are only one and the same form of phlegmasia. His facts, which were supported by numerous researches in pathological anatomy, were noticed and collected together, during the course of an epidemic, which prevailed at Tours from 1818 to 1820. They were obtained either in the town, the population which amounted to upwards of twenty thousand, or in the Hospital, where the number of patients varied from one hundred and twenty to four hundred. He noted the similarity in the nature of the facts he obtained with those in remotest antiquity.

Sixty bodies were opened during the course of the epidemic. He sometimes neglected the examination of certain viscera which had not presented any morbid alteration during life; but he always stueied the state of the digestive canal and of the air-passages with the most minute exactness.

He endeavoured to prosecute his researches on the bodies of those, who had more particularly presented, either the characteristic symptoms of Croup, or those of Malignant Angina, whether the progress of the disease had been left to take its course without any treatment or had been fruitlessly opposed by the most energetic and most opposite remedies.

In a great number of subjects, he was able to follow the decreasing modifications of the disease up to its perfect cure, which was obtained under the influence of special, general, or local treatment.

His examination of a hundred and thirty soldiers, and twenty individuals of all ages presented the different gradations, acute or chronic, of scorbutic gangrene, confined to the mouth, or extending to the pharynx and not differing in the latter case, from Gangrenous Angina.

In his first memoir, he examined the affections:

1. Scorbutic Gangrene

and 2. Malignant Angina

1. Of Scorbutic Gangrene

He noted the variation of the appearance of this disease as being due to its greater or less duration. He described the disease as presenting itself under the form of a greyish ulceration, occupying the undulating border of the gums. The tartar was deposited in greater quantity than in the healthy state on the

surface of the teeth, or rather the latter was coated with a grey-brown matter, of the color of rust. Their line of insertion was more particularly the seat of the disease, so that the adhesion of the gum to the neck of the tooth was gradually destroyed, an incurable looseness was the result. This was one of the ordinary and troublesome consequences of Scorbutic Gangrene.

The diseased parts allowed the blood to transude with such facility, that it was sufficient to open the lips gently, in order to let it ooze out in little drops from all the ulcerated surfaces.

When the affection was communicated from the gums to the mucous membrane lining the lips and cheeks, a white spot arose at the point of contact; it soon increased, and became grey, livid, and blackish, sometimes it sank deeply, and then the edges of this foul ulcer were swollen, and of a livid-red color; thick patches were detached from its surface, and were replaced by new layers. A sanious serosity flowed from the mouth in abundance, and this flux, which continued during sleep, soaked in and stained the linen of the patients. The surrounding cellular tissue and the circumjacent lymphatic glands became tumefied. The breath was rendered intolerably offensive, and the disease then assumed the most specious resemblance to true gangrene of the mouth, which was a more dangerous affection, and one of an entirely different nature. Bretonneau purposely omitted pecularities, the detail of which could only be observed in following the progress and the successive stages of Scorbutic Gangrene.

This disease, which he described, presented itself among the soldiers of the legion of the La Vendée, while they were still in garrison at Bourbon. When they arrived at Tours, at the beginning of 1818, a great number were attacked by it. It broke out in the western barrack, which had just before been occupied by another regiment, exhibiting no case of the disease. The disease was thought to be scorbutic in nature, and was attributed to endemic causes; the well-water was especially suspected; it was found soft and brackish; but in fact, the water of this establishment, like the filtered-water of all the district, had neither the taste which was attributed to it, nor any other bad quality.

He dismissed the relation of the disease to scurvy, although he stated that there were others who noted a relation and applied anti-scorbutics in large doses.

Hydrochloric acid, as a local treatment, was tried with a success surpassing all expectation..

He then concluded that this disease was the same as the "stomacace" of the ancients, of the "fegarite" of the Spaniards, "scorbutic gangrene of the gums" of Hermann Boerhaave (1668-1738) and watery cankers. Boerhaave had subdued this disease with hydrochloric acid.

He noted that Gerhard van Swieten (1700-1772) saw the disease in its several forms, recognized the identity of the two affections and quoted Aretaeus (81-138?) to support this opinion.

2. Of Malignant Angina

He said that many of the names given to this disease express the idea of choking and strangulation. When the disease appeared at Tours, it was new to the greater part of the practitioners, and opinions were divided as to its diagnosis and treatment. He described six cases, collected at the beginning of the epidemic, to give an idea of the true characters of the disease. He next made some general considerations about inflammatory lesions and alterations of tissue.

"Inflammatory Lesions and Alterations of Tissue: General Considerations"

He described the disease as sometimes rather difficult to discover the organic alteration of which the concrete exudation is confined to a pointed redness, arranged in irregular spots, without the least swelling; for the tumefaction of the surrounding tissue must not be attributed to the mucous covering (which has no role in it). He stated that tumefaction is nowhere more considerable than under the skin, near the lymphatic glands which correspond to the region of the mucous membrane affected. From these glands the tumescence seemed to extend and diffuse itself. Their congestion was constantly observed, and even from the beginning it was considerable and out of proportion to the slight extent and intensity of the inflammatory lesion. He had twice seen it terminate by a suppuration analogous to that of buboes. Redness of the mucous membrane without thickening of tissue, was quite superficial, and accompanied with an abundant and remarkable concrete exudation, appeared to him, a very remarkable inflammatory condition.

He saw in this membranous inflammation a specific phlegmasia, as different from a catarrhal phlogosis as the malignant pustule was from the zona, a disease more distinct from Scarlatinal Angina, than scarlatina itself is from small-pox; in fact a morbid affection sui generis, which was no more the last degree of catarrh than a squamous eruption was the last degree of erysipelas.

He made the famous statement which gave us the name "Diphthérite" for the disease he had so adequately observed:

> "As it is impossible to apply to a special inflammation which is so well-marked, any one of the improper names which have been given to each of its varieties, let it be permitted me to designat this phlegmasia by the name of Diphtherite..."37

The more attention he gave to the study of the phenomena peculiar to this inflammatory condition, the more it appeared to him to differ from every other by characters which were proper to it.

With microscopic examination of the most vivid diphtheritic spots, and those which appeared to the naked eye to be pointed with red and white, he saw that they were due to very minute vascular injection, and that the points of a brighter redness were little ecchymoses, while the white spots were prominent orifices of the mucous follicles.

Diphtheritic inflammation, he thought, was propagated in an altogether peculiar manner on the surface of the mucous membranes which it attacks; it spread on them almost like a liquid which effused or flowed over them.

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(37) Bretonneau, Pierre, op. cit., p. 20.

He stated that often seen is a long, narrow streak, of a dark red color, which extends into the pharynx, or descends into the trachea, either alone or accompanied with other distinct striae. Further, he observed a band of pseudo-membranous matter formed in the middle of each striae. At this period some rounded pores, or rather some semi-transparent bullae, were still observed in the substance of the pellicle; the sides of this growing pellicle, irregularly crenate and attenuated, were confounded with the mucus which surrounded them, and which, without being altered in its appearance, was already altered in its properties, for it had no longer any viscosity, and was coagulated, ready to be concreted. Soon the bands were enlarged, they became more dense and homogeneous, and formed, by their union, complete tubes, or a single lamina, united to the mucous membrane by little prolongations which penetrated into the orifices of the muciparous follicles. If the pellicle was detached, the redness increased in the denuded points, the false membrane was reproduced, and in proportion as the superposed laminae added to its thickness, it became more and more adherent to the organic surface. If it happened that such morbid processes took place in the respiratory canals, any chance of recovery was probably small.

This completed his description. He believed that the characters which he described distinguished also the diphtheritic phlegmasia from some other membranous inflammations with which it was necessary not to confuse it.

BRETONNEAU'S SECOND MEMOIR, 1825

On Diphtherite, or Pellicular Inflammation of the Mucous Tissue

Bretonneau discussed in the memoir some four specific points:

1. Specific Characters of Diphtheria
2. Analysis of Historical Evidence
3. Treatment of Diphtheria

and 4. A General Sketch of the Epidemic at Tours, from 1818 to 1821

1. Specific Characters of Diphtheria

He first described formation of the false membrane. Initially, a circumscribed redness occurred, covered with a coagulated semitransparent mucus. This layer was slight, supple, and porous. It could be elevated by unaltered mucus to form vesicles. In a few hours, the red spots extended perceptibly from one to another, by continuity, or by contact, like a liquid effused on a flat surface, or which flowed by streaks in a tube. The concretion then became opaque, white, and thick and assumed a membranous consistence. It could be easily detached at this period.

If the false membrane, in detaching, left the surface of the mucus membrane uncovered, the redness which was obscured by the exudation returned, and the points of a deeper red allowed blood to transude. The concrete coating was renewed and became more and more adherent upon the points which had been first attacked;

it often acquired a thickness of several lines and passed from a yellowish-white color to brown, grey, or black. At the same time the transudation of blood became still more free, and was the source of those stillicidia [37a] which had been so generally remarked by authors.

The alteration of the organic surfaces became more apparent than at the beginning; portions of concrete matter were often effused into the substance itself of the mucous tissue: a slight erosion, and a few ecchymoses are observed in the spots, which, by their situation, were exposed to some friction, or from which the avulsion of the false eschars had been attempted. It was above all towards this period that the pellicles which were being decomposed exhaled a foul odor. If they were circumscribed, the oedematous swelling of the surrounding cellular tissue made them appear depressed, and by this appearance alone, one might be tempted to believe that one was observing a foul ulcer with a considerable loss of substance. If they extended over a large surface, they were partly attached and hung in more or less purrefied shreds, and put on the appearance of the last stage of sphacelus.

2. Analysis of Historical Evidence

Persons mentioned in the history of diphtheria were: Hippocrates (460-377 B.C.) who in the book on Dentition, briefly

(37a) stillicidia -(a flowing by drops).

described an ulceration which may or may not have been diphtheria; Aretaeus (81-138 A.D.?) gave the first description of Diphtheria Phlegmasia; Aetius of Amida (502-575) who added to the description of Aretaeus, a commentary and some particulars which leave no doubt that he had seen the same disease two or three centuries later; Ambrosius Theodosius Macrobius (395-423) in the year 380 spoke according to Julius Modestus, of diphtheria; Guillaume de Baillou (1538-1616) spoke of an orthopnoeic affection in the second book of his Epidemics, which was not diphtheria.

3. Treatment of Diphtheria

Local treatment of diphtheria included: hydrochloric acid, powdered alum, caolmel, and mercury. Surgical treatment involved tracheotomy.

4. General Sketch of the Epidemic at Tours, from 1818 to 1821

Malignant Angina first occurred in the neighborhood of the principal barracks of the Legion of La Vendee. Pellicular inflammation of the gums was frequently observed among the soldiers. Several of them showed Malignant Angina. Symptoms which manifested themselves indicated without a doubt the Croup which affected the children. Some symptoms which were evident were: a change in the quality of the voice, the peculiar sound of the cough, and the paroxysms of suffocation.

In the Legion of La Vendée, Malignant Angina, when compared to Scorbutic Gangrene of the gums, was in the proportion of one in nine cases. It was believed that common use of vessels among the soldiers accounted for the spread of diphtheria. Upwards of one hundred patients died from the disease during the epidemic.

Summarizing, the first memoir showed that the membrane formed in diphtheria is a specific inflammatory process. The second memoir discussed the efficacy of local treatment in the disease. From his experience with diphtheria, Bretonneau concluded that this was no new disease but one which had occurred from the earliest times.

ADDITIONS TO THE SECOND MEMOIR, (JUNE, 1825)

Epidemic Diphthérite

He didn't know if the epidemics of diphtheria were contagious or not. He differentiated between Croup and Diphtheria.

Sporadic Tracheal Diphtheria

Tracheotomy (Communicated July, 1825)

He reported cases of diphtheria treated with tracheotomy. In the spring of 1825, a child of four years of age was operated upon by Bretonneau. By the fourteenth day after tracheotomy the child was out of danger.

Pharyngeal Diphtherite

Autopsy of Five Young Subjects, who died in the same week, at the end of November, 1819

Five autopsies were described. In each case interest was centered on the location of the exudate in the body and the extent of its development. It was found to adhere to the tonsils, trachea, mouth, nasal fossae, bronchi and other parts of the throat.

Mercurial Treatment

Cases

After the departure of the Legion of La Vendée, the Western Barrack was occupied by the soldiers of the forty-fourth regiment. A few days after their admission, three of these soldiers were affected with Malignant Angina. In the first two the disease was arrested at its commencement by local treatment. He cited five cases treated with mercury. In all cases the mercury aided in the disease; however, in one case there was the typical effects to the gums with loosening of teeth.

The Poisonous Nature of Mercury

The morbid alterations arising from prolonged courses of mercury are similar to scurvy; hemorrhage of gums; and frequent pulse.

Tracheotomy

Practical Observations

He gave the results of a case to show how to prolong the life of the diphtheria patient with tracheotomy. He stated also that there was little danger in the use of tracheotomy.

Blood-letting

Bretonneau believed that blood-letting was not of benifit in cases of diphtheria as death of the patient usually occurred.

Blisters

He believed that application of flying blisters seemed to aid if there was no vesication following the blistering.

Local Treatment

Action of Polygala (Seneca)

This agent aids in producing secretion of inflamed mucous membranes rendering expulsion of false membranes possible.

Local Treatment

Hydrochloric Acid

Hydrochloric acid, if used in the early stages of diphtheria, is beneficial but when the wxudations enter the air passages it is of no use.

Diseases Which Present the Same Appearances as Diphtheritic Angina

Some diseases which present the same appearance as diphtheritic angina are croup, scarlatinal angina, common membranous angina, stridulous angina (Pseudo-Croup of M. Guersant), tracheitis, and membranous or polypous sporadic angina.

Sporadic Diphtherite

Isolated cases of tracheal diphtheritic angina may occur. In 1823, Bretonneau observed a patient, who died of tracheal diphtheritic angina. This case occurred when there were no other cases of diphtheria present.

BRETONNEAU'S THIRD MEMOIR, (NOVEMBER, 1825) [38]

Epidemic of La Ferriére

This epidemic began at La Ferriére in November, 1824. In a population of two hundred and fifty individuals, twenty-one were attacked and eighteen died. The epidemic remained in this one locale.

Specific Characters of the Different Kinds of Angina

There were six distinct inflammatory conditions of the throat which occurred frequently. In the development and progression of each, they showed various symptoms. These six diseases were: (1) catarrhal angina (2) tonsillar angina

(amygdalitis or tonsillitis) (3) mercurial membranous angina (4) common fibrinous angina (5) scarlatinal angina and (6) diphtheritic angina.

Duration and Mode of Termination of Diphtheritic Inflammation

Bretonneau made the following statements:

> "It is extremely rare for the diphtheritic inflammation not to extend from the pharynx into the air-passages, and the disease then become so rapidly fatal, that two of the principal and truly characteristic features of this inflammatory condition have escaped the attention of the practitioners; it has not been noticed that it is the nature of diphtheritic inflammation to encroach from spot to spot, and not to be extinguished on the points which it previously occupied. I insist upon these tendencies of Diphtherite, because in them resides all the danger of Malignant Angina, and because it will almost happen, if they are mistaken, and if the most efficacious therapeutical plans are not directed against them, that the extension of the disease into the air-passages cannot be prevented." 39

BRETONNEAU'S FOURTH MEMOIR, (MARCH, 1826) 40

Epidemic at Chenusson

Since October, 1825, Diphtheritic Angina did not appear at La Ferriére. In November, a child died of Croup in Souchet, a small hamlet south of La Ferriére. Later, Malignant Angina caused the death of another child in the woods between Chenusson and Souchet. Two children died at Chenusson in November. They were followed by a young woman, eighteen years of age.

(39) Ibid., p. 138.
(40) Ibid., pp. 139-172.

At the end of December, eight children and one girl of fifteen or sixteen years of age had died with the disease.

By January, 1826, seventeen persons had died of the epidemic sore throat. Following this, patients were taken to the General Hospital. Twelve persons were admitted and three of these died.

BRETONNEAU'S FIFTH MEMOIR, 1855 [41]

On the Means of Preventing the Development and Progress of Diphtheria

(Archives Générales de Médecine, January and September, 1855)

To Drs. Blache and P. Guersant

In this memoir Bretonneau changed the word Diphtherite into Diphthérie.

He discussed four areas (1) Contagion of Diphtheria: (2) Influence of Habit; (3) Local Treatment; and (4) Case of Diphtheria.

Contagion of Diphtheria. -- the word contagion indicated that the transference of epidemic diseases is effected and accomplished directly by the contact of the patient, and indirectly by the contact of contaminated articles; then the prevailing disease is imported, exported, and transferred by a person who is attacked by it.

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(41) Ibid., pp. 173-204.

Influence of Habit. -- Physicians acquired immunity to the disease by going from patient to patient.

Local Treatment. -- The most painful treatment was alum and hydrochloric acid and solutions of nitrate of silver seemed to be the least painful and the most efficacious.

Case of Diphtheria. -- The patient, a boy of 12 years of age, was taken with Malignant Angina in May, 1854. Local treatment was given in the form of silver nitrate and calomel. The patient recovered.

GUERSANT ON DIPHTHERIA, 1835

Paul Louis Benoit Guersant (1800-1869) wrote his impressions of diphtheria in an article in 1835.

Guersant on Croup [42]

Tracheal Diphthérite of Bretonneau

(Dictionnaire de Médecine, 1835)

on Croup

Francis Home (1719-1813) was the first to use the name croup, which is a Scottish name. He used it to designate an acute inflammation of a false membrane. This term became a popular term and was generally adapted in all countries.

The disease to which he referred was the same as the garotillo of the Spaniards and the male en canna of the Italians.

(42) Guersant, Memoirs on Diphtheria..., pp. 207-232.

Other synonyms used were strangulatoris affectus, Carnevale; cynanche stridula, Wahlbom; morbus strangulatorius, Starr; suffocatio stridula, Francis Home; angina stridula, Crawford; angina suffocativa, Samuel Bard; angina polyposa sive membranacea, Michaelis; cynanche trachealis, Cullen; tracheitis infantum, Albers; angina laryngea exsudatoria, Hufeland; diphtherite tracheale, Bretonneau.

Definition of Croup. -- Malignant angina is not all of a gangrenous nature, but a true pellicular inflammation similar to that of Croup.

Diagnosis of Croup. -- He gave the nosography of the diseases commonly designated under the name of Croup. True Croup occurred when the internal surface of the pharynx, the larynx, trachea, and the bronchi were reddened and slightly swollen and there was no plastic exudation.

Stages of Croup. -- Of the membranous or pseudo-membranous pharyngo-laryngitis, or true croup, he recognized three very distinct stages of development.

> (1)slight shivering fever, sore throat, pain, swelling of sub-maxillary glands and tonsils; redness of pharynx, white patches on tonsils, the velum palati, the uvula; slight serous oozing; a fetid smell and a yellowish color from the nostrils, pseudo-membranous eschars on different parts of the body. This lasted for 4 to 5 days, sometimes 7.
>
> (2)small, dry cough, aphonia, symptoms of suffocation, somnolence, vomiting.
>
> (3)an increase of all the symptoms, aphonia complete, fits of coughing are rare and absolutely dry, the laryngo-tracheal hissing sound is very dry, metallic, and sonorous, is heard

> at a great distance; inspirations are very much accelerated and almost as noisy as in asthmatic patients, constant drowsiness.

Terminations of Croup. -- In cases of spontaneous cure, a very rare occurrence, or in cures of nature and art, the cure usually takes place in the second period of the disease.

Nature of the False Membrane. -- Characteristics of the false membrane may vary considerably. At the beginning of the disease the membrane is usually opaque, thick, and yellowish. Later it becomes thin and delicate. Little red points are found to dot the surface of the membrane.

Varieties of Croup. -- Many varieties of croup exist but it is necessary to name each variety.

Complications of Croup. -- Some diseases which complicate Croup are: membranous pharyngeal angina, membranous coryza, enteritis and entero-colitis, bronchitis, pleuro-pneumonia and pneumonia, hooping cough, and all the eruptive diseases.

Diagnosis of Croup. -- Croup has to be differentiated from laryngitis. In the case of laryngitis, the cough is more sibilant in Croup and difficulty in breathing and suffocation are constant but are renewed by paroxysms as in membranous laryngitis.

To differentiate croup from tracheitis indicates notification of the following symptoms: tracheitis starts with a fever and a dry sharp cough; there is no loss of voice as in Croup; there is

no laryngo-tracheal sibilation between the fits of coughing and articulation of words. In the second period of tracheitis, the cough becomes more moist; respiration is not comparable to the dry and metallic rhonchus of croup; in the third period of tracheitis, the wheezing and the difficulty of breathing increases, and the patients generally throw up, after violent fits of coughing, membranous ribbon-shaped shreds of greater or less extent.

Treatment of Croup. -- Treatment of Croup includes: cauterization of the affected parts with hydrochloric acid or almost pure citric acid, or better still, a solution of nitrate of silver. Insufflation into the throat of some powdered alum helps. Other treatment includes: venesection, use of mercurials, calomel, senega, syrup of ipecacuanha, irritating purgatives, and cold effusions.

Tracheotomy. -- Tracheotomy should be used in the last stage of the disease when croup has not responded to medicines. Tracheotomy has been used successfully by Bretonneau, Trousseau, Scoutteten at Metz, and Gerdy at Paris.

Prophylactic Measures Against the Diseases Designated as Croup. -- Measures indicated against these diseases are: removing children from the influence of moist and cold climates, adherence to general precautions which tend to ward off catarrhal affections, and isolation of the patients.

TROUSSEAU ON DIPHTHERIA, 1835

In 1835, Armand Trousseau (1801-1867) published a statement on diphtheria.

Troussaeu on Diphthérite [43]

(Dictionnaire de Médecine, 1835)

Trousseau described his training from Pierre Bretonneau and credited Bretonneau with pioneering research on diphtheria. He then described diphtheria of the skin and of the mucous membrane.

Cutaneous Diphthérite

It always occurred on the skin which had been previously deprived of its epidermis, or was ulcerated. When Diphtheria attacked a wound, the spot became painful, and allowed the escape of a great quantity of colorless and fetid serosity, and was soon covered with a greyish, flabby, and more or less thick membrane. A kind of erysipelas was soon developed round the excoriated part.

Buccal Diphthérite

This condition often remained limited for a long time to the commissures of the lips, to one of the gums surrounding a carious tooth, or to a portion of the tongue corresponding to a broken one; but in cases unfortunately too common, it was also propagated from the mouth to the pharynx to the larynx, finally leading to the death of the patient.

(43) Trousseau, Armand, Memoirs on Diphtheria..., pp. 235-268.

Pharyngeal and Tracheal Diphthérite

The mucous membrane of the pharynx and trachea was the most frequent seat of the Diphthérite.

Of the Causes of Diphtheria

Trousseau made the following statement:

> "It is evident to me that contagion performs the principal part in the propagation of Diphtherite, as I have said, I think amply demonstrated in the work which I have published in the Archives." 44

Of the Danger of Diphthérite

What rendered diphtheria especially dangerous was the rapidity with which it attacked large surfaces, as well as the mechanical obstacle which it offered to one of the most important functions of life, and the obstinancy with which it resisted therapeutical resources which generally modified other inflammations.

Treatment of Diphthérite

Typical remedies were: caustics, nitrate of silver, the acid nitrate of mercury, sulphate of copper, hydrochloric acid, alum, mercurial sublimate, chlorides of potassium, sodium, and calcium; oral administration of infusion of calumba, bark or quassia, iron and quinine, and succulent and fermented drinks.

On Tracheotomy in Croup

(Dictionnaire de Medecine, 1835)

Successful Performers of Tracheotomy. -- John Andre, London, 1782, Bretonneau, Paris, 1825, Trousseau, Paris, 1826, Scoutteten, Gerdy,

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(44) Ibid., p. 240.

Velpeau, Guersant, Sanson, the elder, and Blandin.

Trousseau thought that tracheotomy had been proven to be of value and discussed three questions:

(1) Is the operation necessary?

(2) The operation being deemed necessary, at what period ought it to be performed?

(3) The operation having been performed, what are the methods of ulterior treatment?

Is the operation necessary? -- Trousseau thought the operation necessary to delay death or prolong life in impending suffocation cases and that the operation was perfectly safe as sixty successful operations had been performed. He believed that the delicacy of the operation could be overcome with care and presence of mind.

The operation being deemed necessary, at what period ought it to be performed? -- The period in which, judging from known indications, there no longer remained any hope of recovery.

Of the treatment which ought to follow the operation. -- Dilate the opening made, cauterize the area by touching with caustic liquid, instillation of water to moisten mucus matter in the trachea and soften the false membrane for detachment, and use of string passed into the canula for its introduction into the opening and holding it in place.

On Cutaneous Diphthérite

(Archives Générales de Médecine, 1830)

He discussed cases which occurred in the Department of the Loire et Cher, at Nouan le Fuselier; the commune of Marcilly, Commune of

Tremblevif, the hamlet of Les Rois, and the Commune of Chaumont-sur-Tharoune.

He wrote; in his discussion of corollaries, a summary:

> "If then it is no longer possible to doubt that the affection which seizes the skin of persons attacked with Malignant Angina is of a diphtheritic nature, we are equally obliged to admit that the persons who are in relation with those who have at once the epidemic sore-throat and Diphthérite of the skin, or either of these affections, also present cutaneous inflammations of an identical nature, although in them the Angina has not developed itself. For in the first place, the slightest inflammations of the skin assume in such persons the serious character which we have remarked in others, and the consequences are no less terrible. Lastly, to complete the parallel, we find cutaneous Diphthérite commenginc in a house, propagating Malignant Angina in that house, in the same manner as the pellicular Angina, when it has taken the initiative becomes the cause of cutaneous Diphthérite." 45

BOCHUT ON DIPHTHERIA, 1852

In 1852, Bochut wrote a treatise on Croup.

Bochut on Croup [46]

(Diphthérite of Bretonneau)

(Traité Pratique des Maladies des Nouveaux nes et des Enfans a la Mallele, 1852)

He defined Croup as a disease of the larynx in which the inflamed mucous membrane is covered by a fibrinous layer of new matter, called false membrane.

Causes. -- There was, he thought, the possibility that Croup was contagious.

Pathological Anatomy. -- There was a false membrane on the surface of the mucous membrane of the larynx; this membrane might

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(45) Ibid., p. 268.
(46) Bochut, Memoirs on Diphtheria,...,pp. 271-297.

attach to tonsils, trachea, or bronchi; this membrane -- a thin elastic layer of whitish--grey color, rather tough consistence; these membranes might sometimes be thickened, and sometimes slightly softened; its epithelium usually disappears, its surface becomes unequal, eroded, and covered with a series of reddish points, which correspond to the red spots placed on the inferior surface of the false membrane.

Symptoms. -- Croup presented its progress in three periods:

First period. -- shivering, uneasy feelings, fever, sore throat hoarseness, coughing, redness of pharynx and false membranes are seen already formed on the tonsils.

Second period. -- increased fever, dry cough, paroxysms, vomiting, rejection of false membranes, hoarse and sibilous cough, feebleness and sibilous character of voice, difficulty of respiration.

Third period. -- cough and voice extinct, respiration accompanied by a well-marked sibilation, bluish facial skin, contracted pupils, hollow eyes, cyanosed lips, head thrown back, violent fits of suffocation.

Progress. -- the disease begins in the back of the throat before it extends to the larynx and the bronchi; it may commence at once in the larynx and bronchi; and there may be remissions.

Complications. -- Some diseases complicating Croup are: membranous angina, membranous coryza, lobar pneumonia, bronchitis, hooping-cough, phthisis, and eruptive fever.

Diagnosis. -- in differentiating Croup from laryngitis; noted are the following; laryngitis presented no sibilant cough or acceleration of respiration or fits of suffocation; oedematous laryngitis

presented no expectoration of false membrane: in differentiating Croup from pseudo-membranous tracheitis--none of the signs of the first period of Croup are found; the respiration is not sibilant; the larynx is uninvolved; in the second period there is no dry metallic rhonchi cough and no paroxysms of croupal suffocation; in the third period, there are similar symptoms to Croup; in stridulous laryngitis the larynx is uninvolved; there is no expectoration of the false membrane.

Prognosis. -- Cure may be effected when the false membranes are developed in the mouth-epiglottis and at the superior opening of the larynx. When the membrane is restricted to the larynx, cure is still possible. Croup is almost inevitably fatal when the membrane extends to the trachea or bronchi. Disease complications made Croup even more a serious disease.

Treatment. -- There was a two part treatment: medical and surgical. Medical treatment consisted of: blood-letting, revulsions, alteratives, emetics, and sternutatories. Surgical treatment consisted of: local medications and tracheotomy.

Aphorisms. -- Croup existed from the time when fibrinous false membranes had been effused on the mucous membrane of the larynx. A veiled, hoarse, dull cough, followed by a metallic hissing sound, and accompanied with fever and gasping, revealed the presence of Croup.

In croup, the feeble cough and voice, joined to noisy, rasping, serratic respiration, announced the fits of asphyxia and death. Croup, arrived at the period of fits of suffocation usually proved fatal. Croup should be treated by repeated emetics, alternated with doses of calomel. A case of croup which arrived at the period of fits of suffocation, when death appeared to be approaching, should be treated by tracheotomy.

EMPIS ON DIPHTHERIA, 1850

Georges Simon Empis (1824-1913) published his report on diphtheria in 1850.

Empis on Diphtheria [47]

Researches on Diphthérite, Founded upon An Epidemic of this Disease Observed at the Hopital Necker in 1848

(Archives Générales de Médecine, 1850)

The Memoir was done to study Diphtherite in general, and as it had presented itself to his notice in the epidemic which he had observed. He listed the following subjects to be covered in his memoir.

1. The pathological anatomy and physiology of Diphthérite, endeavouring to describe clearly the characters of the false membrane peculiar to the disease.
2. A few remarks on the general state of health under which the false membranes are developed.
3. The diagnosis and a parallel between the different pseudo-membranous exudations observed in different diseases distinct from Diphtherite.
4. The progress of Diphthérite and its presumed causes.
5. Observations upon the prognosis and treatment of the disease.

He defined Diphthérite as a specific disease, characterized anatomically by the development of a perfectly specific pseudo-membranous exudation on the mucous or cutaneous surfaces.

He stated that Bretonneau's denomination given to this disease presented the serious inconvenience of being capable of

(47) Empis, Georges Simon, Memoirs on Diphtheria...,pp. 301-342.

application to affections of a totally different nature from that of the disease which it ought to designate, it has, at least, in the present day, this advantage, namely, that it has been current in science for the last twenty-five years, and by that very circumstance, requires no longer to be created.

Pathological Anatomy and Physiology of Diphthérite

False membranes of mucous and cutaneous tissue were not so different, hence a general description of the exudate was given. The development of the diphtheritic pseudo-membrane was divided into three periods; first, the period of development, second, the period of complete formation, and third, the period of decline and cicatrization.

Period of development. -- exudation of a sero-mucous, transparent, slightly viscous, and ropy liquid, preceded the appearance of the pellicle on the affected part, which thickened.

Period of maturity. -- the pellicle was transformed into a true membrane.

Period of decline and cicatrization. -- the membrane shrank in circumference and a process of reparation and cicatrization had been established from the healthy towards the diseased parts, and by degrees brought back the latter to the healthy condition.

Of the Seat of Diphthérite

In the epidemic at the Hôpital Necker, the disease presented itself sometimes on the cutaneous tegument, sometimes upon the mucous membranes, and often it simultaneously affected both these tissues.

Cutaneous Diphthérite. -- the epidermis must be absent for cutaneous diphtheria to develop.

Diphtherite of the Mucous Membranes. -- Empis had never found any remarkable difference between Diphthérite developed on the musous tissue and cutaneous Diphthérite. In both cases the membrane passed through the same phases and presented the same characters. He observed that only those parts exposed to air had the membrane and focused on the theory of contagion when he asked:

> "may the presence of the air, then exert, in these circumstances, some influence which escapes our notice." 48

General Pathology of Diphtheria

He stated that Diphtheria is a phlegmasia, which passed through three stages; the subjects attacked by Diphtheritic Angina had always, before the appearance of the pseudo-membrane, felt a certain degree of uneasiness, loss of appetite, a slightly febrile condition, difficulty in swallowing, tumefaction of the lymphatic glands, etc.

Progress of Diphthérite

The exudation extended in surface and spread gradually to the parts which surrounded the spots first affected. The exudate might be localized or spread over various parts of the body. The duration of the existence of the membrane varied from a few to many days.

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(48) Ibid., p. 311.

Diagnosis of Diphthérite

Diagnosis was conducted by microscopic observation of the characters. Some of the special characters were: buffy coat of blood, pleuritic false membrane, membrane of a blistered surface, false membrane of Diphtherite, and false membrane of Scarlatinal Angina.

Etiology of Diphthérite

He accepted the contagious nature of the disease as did Bretonneau and Trousseau.

Prognosis of Diphthérite

Diphtheria is a disease which is always serious, according to Empis.

On the Treatment of Diphthérite

Local applications consisted of hydrochloric acid, the nitrate of silver, the acid nitrate of mercury, calomel, and alum. Internal administration of calomel.

DAVIOT ON DIPHTHERIA, 1845

D. Zacharie Daviot published a report in 1845 on the subject of diphtheria.

Daviot on Diphthérite [49]

(Relation Historique d'une Épidémie de Diphtheropathic observée dans le Department de Saone-et-Loire et da la Nievre, pendant les annees 1841, 1842, 1843, et 1844, par D. Z. Daviot, Autun, 1845)

Epidemic Pharyngeal Diphthérite

Daviot described three stages to this disease:

1. slight uneasiness in the throat, accompanied by scarcely any difficulty in deglutition, a more acute pain in the pharynx, while the movements of the neck were constrained and there was some degree of torticollis; cervical and sub-maxillary glands soon became engorged; the face was congested and puffy, with injection and lachrymation of the eyes, the lower part of the buccal cavity, the guttural fossae presenting a deep-rose color in children and a more deep-brown in adults, swelling of one of the tonsils, more rarely of both, more marked in the inverse proportion to the age; the uvula was almost always tumefied and relaxed; there was almost habitually coryza; fever.

2. membranes appeared on the tonsils, uvula, velum palati, posterior surface of the pharynx, increased glandular engorgement, swollen tonsils, difficult deglutition, altered voice, infrequent or absent cough, nasal secretion, mouth odor, cephalagie, swollen tongue, frequent nausea and vomiting; abscesses at the base of the lower jaw.

3. enlarged tonsils, thickening of membranous patches, laborious respiration, feeble voice, nasal discharge; mouth odor, cephalagia, weakness and langour, constipation or diarrhea, thready pulse; cold extremeties, drowsiness in children; death or recovery.

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(49) Daviot, D. Z., Memoirs on Diphtheria..., pp. 345-382.

Common membranous angina was propagated from the guttural cavity where it was developed, towards the more deeply-seated organs. This disease was usually of short duration.

Scarlatinal membranous angina was so similar to Diphtheria, it might as well be called epidemic pharyngeal diphtheria.

Diphtheritic angina usually attacked the air passages.

Presumed Causes of the Epidemic

Daviot stated:

> "In my opinion, Pharyngeal Diphtheria must derive its origin from some agent, which is occult in its nature, but which always determines pellicular inflammation, and is similar in its effects to certain chemical substances, as mercurials, chlorine, ammonia, the caustic alkalies, the ethereal tincture of cantharides, etc., which induced the same pathological state. Might not the re-agents which demonstrate the presence of these different bodies assist in discovering in the atmosphere the nature of the epidemic agent?" 50

Treatment

Antiphlogistic treatment consisted in general bleeding, local bleeding, emetics, purgatives, and cutaneous revulsives. Local medication was alum, nitrate of silver, protochloride of mercury, hydrochloric acid, chloride of soda, nitrate of mercury, scarification of the tonsils, ablation of the tonsils, tearing away of the false membrane, and tracheotomy.

Some Observations on Croupal Diphthérite

1. a peculiar snoring sound in sleep, dry metallic cough which meant that the inflammation was to continue.

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(50) Daviot, D. Z., op. cit., p. 353.

2. moist and crepitant cough meant the false membranes were detached and floating.

3. these observations served to determine if tracheotomy was required.

On the Use of Emetics

He thought that continued use of emetics caused development of tolerance and required larger and larger doses for effect.

Cutaneous Diphthérite

This disease manifestation occurred on the skin lesions which were present.

General Treatment

Antiphlogistics and blood-depletion were used. Local treatment involved use of emollients, caustics, and catheretics (mild caustics).

In the nineteenth century, France was one of the focal points of diphtheria in compariosn to the rest of the world. Major writers on diphtheria in France were: Pierre Bretonneau, Paul Guersant, Armand Trousseau, Bochut, Georges Empis, and D. Zacharie Daviot.

Tracheotomy was one of the therapeutic procedures used by French physicians in cases of diphtheria. Armand Trousseau, one of Bretonneau's most brilliant students, popularized the use of tracheotomy in diphtheria cases.

CHAPTER IV

TROUSSEAU AND NINETEENTH CENTURY TRACHEOTOMY

Armand Trousseau (1801-1867) has been described as a "master expositor of clinical medicine in composition, in the clinics, and at the bedside." 1

He "entered clinical medicine after a short professorship in rhetoric." He "was born in Tours, the capital of Old Gaul, where his father a provincial boarding school keeper, had been impoverished by the Napoleonic Wars." 2

After studying as a youth at lyceums in Orleans and Lyons, at 20 years of age, Trousseau "served on the faculty at the college of Chateroux." 3

Bretonneau (1788-1862) exerted a profound influence on Trousseau, causing him to focus on medicine as a career. Bretonneau, at that time, was the "leading physician at Tours." Trousseau spent three years of study under Bretonneau's tutelage. In 1825, Trousseau received the M.D. degree at the veterinary school at Alfort, received professional status in 1827, and prepared a text on veterinary surgery the following year." After this, he conducted investigations of diphtheria epidemics in the Sologne and accompanied Louis and Chervin on a yellow fever survey at Gibralter, where he contacted yellow fever in a mild form." 4

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(1) Talbott, John H., A Biographical History of Medicine, Excerpts and Essays on the Men and Their Work, Grune and Stratton, 1970, p. 595.
(2) Ibid., p. 595.
(3) Ibid., p. 595.
(4) Ibid., p. 595.

It was Trousseau's desire to return to Tours to practice, after completing his medical training, but Pierre Bretonneau insisted and urged him to remain in Paris. He "entered competition in Paris and won." However, he spurned Parisian social life and declined to have his name proposed for the Acadmey of Medicine until he was certain in 1856 of his acceptance. In 1831, he received a hospital appointment with the Central Bureau, and served successively at Hotel Dieu, at St. Marguerite (renamed Hôpital Trousseau), at Necker, and at St. Antoine. From the years 1833 to 1848, Trousseau coedited with Le Baudy and Gourauc the Journal of Medical and Surgical Information. He was advanced, in 1839, to the "chair of therapeutics" in the University. [5] There the wide recognition of the exceptional quality of his lectures led to the highest academic appointment as professor of clinical medicine and physician to Hotel Dieu in 1852. He abandoned this post shortly before his death from carcinoma of the stomach, and returned to the department of therapeutics. [6]

Trousseau "neither discovered nor described in detail a new disease in the usual sense of the expression and was no peer of the German clinicians of his time in the advancement of scientific medicine." He was unparalled in "the enticing spirit of his personality, the brilliance of his lectures at

(5) Ibid., p. 596.
(6) Ibid., p. 596.

Hotel Dieu, and the clarity of his descriptions of clinical-pathological findings." 7

Trousseau and Alfred Velpeau (1795-1867) were the most talented pupils of Bretonneau. 8

Trousseau published two monumental treatises during his career in medicine, one on therapeutics [9] which was the result of the first half of his career and a second on clinical medicine, [10] which resulted from the second half of his career.

During the period which he served as professor of therapeutics, "he took his cue from Bretonneau and succeeded in expanding the limited means of management, largely bloodletting and purging, to include the rational use of herbs and chemicals, conservative abstinence from the use of potent substances in some diseases, local surgical intervention in others." It is thought that, "Trousseau led the therapeutic renaissance in French medicine." In therapeutics, "several of his best agents were received from Bretonneau." "The use of iron in the anemia of goiter and chlorosis was recommended; he revived the use of quinine in malarial fever and cod-liver oil in rickets." In the area of local surgical intervention, he "was one of the first in Paris to perform a tracheotomy in diphtheritic croup and popularized thoracentesis for pleural emphysema and exudative pleurisy." [11]

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(7) Ibid., p. 596.
(8) Ibid., p. 596.
(9) Ibid., p. 596. (see Trousseau, A. and Pidoux, H.: Traité de Therapeutics (Fr), 2 vol., Paris: Bechet Jeune, 1836-39).
(10) Ibid., p. 596. (see Trousseau, A: Clinique Médicale de l'Hotel-Dieu de Paris (Fr), 2 vol., J.-B. Bailliere, 1861.
(11) Ibid., p. 596.

"The first edition of his Therapeutics was published with Pidoux as co-author in two volumes between 1875-1877." "It was translated into English, Spanish, and Italian; the translation by Lincoln of the ninth edition was published in New York in 1880." "A comprehensive history of each agent or procedure introduced each section." 12

Trousseau's clinical lectures, "were rivaled only by those of Charcot at Salpêtrière, first appeared in print in 1861." 13 These works "went through several editions in translations and were published in English by the New Sydenham Society. Especially notable contributions include the concept of aphasia and a deficiency of speech and thought, a description of cutaneous diphtheria, chromochromatosis, and infantile tetany. His presentations of unusual nervous diseases were guided by the elocution and clinical acumen of Duchenne. The eponymic term, Addison's disease, was assigned by him to chronic adrenal insufficiency." 14

Trousseau wrote a report on cutaneous diphtheria [15] which was translated into English by Crissey and Shelly. It has been stated that "Trousseau, up to 1842, had operated 119 times with but 25 recoveries; but at a later date (1854) he reported 222 operations with 127 recoveries." [16] These were tracheotomies.

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(12) Ibid., p. 596. (see Trousseau, A; and Pidoux, op. cit.)
(13) Ibid., p. 596. (see Trousseau, A: Clinique Médicale...,)
(14) Ibid., p. 596.
(15) Ibid., p. 596. (see Trousseau, A., "Cutaneous Diphtheria," (Fr) Arch. Gen. Med., 23: 383-402, 1830, in Shelley, W. and Crissey, J. Classics in Clinical Dermatology, Springfield, Ill., C. C. Thomas, 1948.
(16) Cohen, J. Solis, Croup in Relation to Tracheotomy, Lindsay and Blakiston, Philadelphia, 1874, p. 6.

Trousseau used the term "tracheotomy" to refer to incision of the trachea. Prior to that time other designations had been given to this operation.

ORIGIN OF THE TERM "TRACHEOTOMY"

The operation of tracheotomy has been discussed by various authors from antiquity till contemporary times. Various terms have been employed to designate it. It is indeed interesting to take a look at the evolution of the terminology for this operation.

"...One of the surgeons of whose work Galen made use was Antyllus who stands out as one of the greatest surgeons of antiquity. Antyllus probably lived in the first half of the second century B. C. but unfortunately, little is known about his life. Certain fragments of his writings, which fortunately exist, indicate the surprising perfection to which he carried the surgery of his time. He not only gave careful and minute directions for surgical operations, but discussed technical details with care and precision which indicated a master of the art. He performed tracheotomy by a transverse incision between the rings of the trachea, but rightly considered it contraindicated when the bronchi and lungs were involved in the obstructing process." [17]

Two of the early writers on tracheotomy are Aretaeus of Cappadocia (81-138 A.D.?) [18] and Galen of Pergamon (130-200 A.D.) [19] Aretaeus condemned the operation of tracheotomy first proposed by Asclepiades and held:

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(17) Lund, Fred B., Greek Medicine, Paul B. Hoeber, Inc., New York, 1936, pp. 90-91.

(18) Aretaeus, The Extant Works of Aretaeus, the Cappadocian, (tr. and ed. Francis Adams) London: Syd. Soc., 1856, p. 406.

(19) Galen, Introductio seu Medicus, (tr. Carolus G. Kühn), Lipsiae: C. Cnobloch, 1821-33, xiv, p. 734.

> "the heat of the inflammation become greater from the wound and contributes to the suffocation, and the patient coughs; and even if he escapes this danger, the lips of the wound do not unite, for both are cartilaginous and unable to grow together." 20

Galen and Aristotle (384-322 B.C.) used the word "larynx" to indicate the highest point of "artery". [21 & 22] Galen referred to "the rough artery which we also call the larynx".[23]

Fabricius of Aquapendente (1537-1619) was one of the persons to substitute "trachea" for "artery". [24] Guillaume de Baillou (1538-1616) published Epidemiorum et ephemeridum libri duo [25] in which he described a diphtheria epidemic in Paris in 1576. Some time later, he suggested the use of tracheotomy, though there is no evidence that he ever used it. Lorenz Heister (1683-1785) used the word "trachea". [26]

Use of "artery" and "rough artery" as designations for the windpipe continued till the nineteenth century. Caelius Aurelianus

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(20) Elliott, James Sands, Outlines of Greek and Roman Medicine, London, Danielson, 1914, p. 87.

(21) Aristotle, History of Animals, (tr. D. A. W. Thompson, Book I, chs. 12 and 16; vol. iv. of The Works of Aristotle, Oxford, Clarendon Press, 1949.

(22) Galen, De Compositione Medicamentorum secundum Locos, (tr. Carolus G. Kühn), xiii, p. 3 and De Motu Musculorum, (tr. Carolus G. Kühn), iv. p. 379, Lipsiae, C. Cnobloch, 1821-33.

(23) Galen, De Placitis Hippocrates et Platonis, (tr. Kühn), Lipsiae, C. Cnobloch, 1821-33, v, p. 237.

(24) Fabricius Hieronymus ab Aquapendente, Opera Chirurgica, Francofurti, 1620, cap. xliv.

(25) Heister, Lorenz, A General System of Surgery, London, Whiston, 1763, p. 51.

(26) Caelius Aurelianus, On Acute Diseases and On Chronic Diseases, (tr. I. E. Drabkin), The University of Chicago Press, 1950, p. 321.

(c. 5th C. A.D.) in describing the division of the artery called it "laryngotomy". [27] Paul of Aegina (620-690) discussed laryngotomy in a chapter in his book. Quoting from Antyllus (2nd C. A.D.) that in the operation, the arteria aspera should be divided at about the third or fourth ring; which indicated a tracheotomy. [28]

Rhazes (860-932) described the operation as incising the canalis pulmonis between two rings. [29] Similar descriptions were put forth by Haly Abbas (930-994). [30] Albucasis (936-1013) in his great work, Al Tesrif, described performance of a tracheotomy, and stated "I feel therefore, authorized to say that incision of the trachea is without danger." [31] Nicolas Fontyn or Fontanus (1622-) referred to laryngotomy and stated that Arabian writers were the originators of the term subscannatio or sectio cannae pulmonis. [33]

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(27) Paulus Aegineta, The Seven Books of Paulus Aegineta, (tr. Francis Adams) London, Syd. Soc., 1846, volume 2, p. 301.

(28) Ibid., p. 301.

(29) Rhazes, Habes, candide lector continentem Rasis, etc., (tr. of the Liber Continens by H. Surianus), 1509, Lib. vii, f., lxxvii, verso.

(30) Haly Filius Abbas, Liber totus Medicinae necessaria continens, etc., (tr. Stephanus), 1523, Lib. IX, Practicae, cap. xxxviii, p. 280.

(31) Billings, John S., The History and Literature of Surgery, from System of Surgery, edited by Frederic S. Dennis, Phila., Lea Bros. and Co. 1895, Vol. I, pp. 17-144) p. 37.

(32) Avicenna, Liber Continens, (tr. Georg Olms Hildesheim), Darmstadt, Germany, 1964, p. 234 recto.

(33) Nicolaus Fontanus, Observationium rariorum analecta, 1641, cap. iii, Quaestio tertia, p. 9.

In 1546, Antonius Musa Brasavola (1500-1570) said that he found the operation (tracheotomy) necessary in a case in which the trachea was obstructed. He referred to the trachea as canna pulmonis or guttur. [34]

Fabricius of Aquapendente explained the operation as perforation of the aspera arteria. [35] Julius Casserius termed the operation laryngotomy. [36]

The word bronchus originally meant windpipe, as used by Galen who stated that it was so designated due to the little cartilaginous bodies forming the greater part of it known as bronchia. [37]

Fredericus Monavius (1592-1659) used the term bronchotomy though he said laryngotomy was frequently given to mean cutting of the bronchus or larynx. [38]

In 1646, Marcus Aurelius Severinus (1560-1656) considered the operation a divine contrivance. [39] Tracheotomy as a term was first taken up in Thomas Feyens' or Fienus' (1567-1631) work published in

(34) Brasavola, A. M. , ...in libris de ratione victus in morbis acutis, etc., 1546, p. 114. Comment on Sect. xxv of Lib iv. of Hippoc. De ratione victus in morbis acutis.

(35) Fabricius Hieronymus ab Aquapendente, op. cit., p. 155.

(36) Casserio, Julius Placentinus, De Vocis Auditusque Organis Historia Anatomica, 2 pts., Ferrariae, Exc. V. Baldinus, Typ., p. 119.

(37) Galen, De Compositione Medicamentorum etc., (tr. Kühn), Lipsiae, C. Cnobloch, 1821-33, xiii, p. 2.

(38) Fredericus Monavius, Bronchotome, Gnichwichii D., In Montis Regii Academia types Johannes Reusneri, anno 1644, pp. 1-2.

(39) Marcus Aurelius Severinus, De Efficaci Medicine, Francofurti, J. Beyer, 1646, cap. XL, p. 101.

1649. He entitled Tracatus IV of his book "De Trachetomia". [40] Pierre Dionis (1643-1718) French surgeon, anatomist and writer, in 1717, thought it wrong to call the operation laryngotomy, but that it should be called bronchotomy. [41] Tracheotomy as a term was again found in use by Lorenz Heister (1683-1758) in 1718, in his Chirurgie. [42] Hiester, in a later edition of this work, related that all terms should be discarded in favor of "tracheotomy" to indicate the operation. Garengeot (1688-1759) described in detail the procedure for performing a bronchotomy. [43] A dictionary of John Qunicy's (died 1722) published in 1726, listed tracheotomy as a synonym for bronchotomy. [44]

Tracheotomy as a term was used by De Bourg (c. 1755) in 1748, [45] and Baron François Percy (1754-1825) in 1792. [46]

J. A. Ehrlich (1760-) in 1795, called the operation luftröhrenöffnung or tracheotomy. [47]

(40) Thomas Fienus, Libri Chirurgici XII, Francofurti, T. M. Goezium, 1649, p. 35.

(41) Pierre Dionis, Cours d'Operations de Chirurgie, Brussels, 1738, p. 329.

(42) Lorenz Heister, op. cit., p. 51.

(43) Renarus James Croissant Garengeot, A Treatise of Chirurgical Operations, etc., translated from the French by Mr. St. Andre, London,

(44) Quincy, John, Lexicon physico-medicum, or a New Medical Dictionary, London, J. Osborn and T. Longman, 1726, p. 450.

(45) B. de Bourg, Quaestio Medico-Chirurgica An Trachatomiae, etc., 1748, in Albert Haller's Disp. Chirurg. Selectae, tome ii, 1755, p. 443.

(46) Baron Percy, Manuel du Chirurgien d'Armee, 1794, p. 67 and p. 119.

(47) Ehrlich, J. A., Beobachtungen chirurgische auf Riesen, etc., Leipzig, Barth, 1795, ch. 7, pp. 77-85.

P. J. Desault (1744-1795) made the precise distinction between laryngotomy and tracheotomy. [48] Laryngotomy, he defined as the operation of cutting transversely through the crico-thyroid membrane or ventrically through the cricoid cartilage. Tracheotomy, he defined as cutting transversely between the rings of the trachea or vertically through the rings. Both terms, laryngotomy and tracheotomy are included by him under the heading bronchotomy.

The words laryngotomy and bronchotomy as well as tracheotomy were in use until the early nineteenth century. In 1815, the French translation of Kurt Sprengel's book used the term bronchotomy. [49] In 1839, the term, bronchotomy was seen in Gendron of Chateau-Renaud's (1762-) paper on tracheotomy. [50] In 1839, Louis Florentin Deshayes Gendron (1762-) used the term "trachéé-artère" as well as "trachea". [51]

Bretonneau (1788-1862) and Trousseau (1801-1867) who popularized the use of tracheotomy in laryngeal diphtheria, both give the one term tracheotomy, which has been in use since their time.

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(48) Desault, Pierre J., The Surgical Works, or Statement of the Doctrine and Practice of P. J. Desault, by Xavier Bichat, (tr. Edward Darrell Smith) M.D., London, Thomas Dolison, 1814, p. 234.

(49) Sprengel, Kurt, Histoire de Médecine, (tr. A. J. L. Jourdan), Paris, Deterville, T. Desoer, 1815-1832, tome vii, ch. vi, pp. 131-151.

(50) Gendron, Louis F. D., Bull. de L'Acad. Roy. de Med., tome iii, 1838-39, p. 914.

(51) Ibid., p. 909 and p. 916.

TROUSSEAU'S CONTRIBUTIONS TO THE DEVELOPMENT OF TRACHEOTOMY

TROUSSEAU'S FIRST TRACHEOTOMY, 1831. In 1831, Trousseau performed the first tracheotomy in Paris. By December 18, 1839, he had 100 cases, with 24 recoveries, after which his luck was variable. In 1850, he operated six times with seven recoveries; in 1855, four times with three recoveries. Through his whole experience, as he told us, Trousseau averaged about 25 per cent recoveries in all his 200 cases. [52]

The patient in his first case was Gustava Marcillet, six years of age. The case history was the first paper published in Trousseau's Journal des Connaissances Medico-chirurgicales, Paris, 1833-34. The case was described in the following manner:

> "Case 1. Gustava Marcillet, six years of age, was seized on the 21st of November with fever and some pain in the throat; the cough was spasmodic and the voice hoarse; during the nights of the 22nd and 23rd, the cough became more frequent, hoarse, and suffocating. These symptoms, with oppressed respiration, became aggravated on the 23rd, when leeches and blisters were applied to the neck. At this period, the infant was visited by Drs. Trousseau and Rue. It presented all the characters of Croup in its third stage; the respiration was extremely anxious and oppressed; the dry gifflement of cramp was distinct; pulse rapid and nearly insensible; cough horase and frequent in the morning; in the day absent, through the weakness of the child; the skin was warm and covered with sweat, and the anxiety of countenance excessive. Towards evening, the fits of suffocation became more violent and frequent; the child seemed on the point of death; and as all the usual remedies had failed to arrest the disease, it was determined to have recourse to tracheotomy as a last hope.

(52) Garrison, Fielding H., "Armand Trousseau: A Master Clinician," Internat. Clinics, 1916, vol. 3, p. 292.

Mr. Trousseau was fortunately furnished with instruments on the spot, while the parents removed themselves from the house to avoid seeing as they imagined, the last gasp of their child.

The operation was simple, and conducted after the manner recommended by M. Bretonneau. An incision was first made from the angle of the thyroid cartilage to the sternum, a little inclining to the left side, in order to avoid the innominata. This incision gave an open wound of about two inches, and in the moment of inspiration, the space between the sterno-thyroid muscles was very strongly marked. The vessels and nerves on the right side of this space were pushed aside with the index and middle finger of the left-hand, and the deep incision continued close by the side of the nails. At this time numerous thyroid veins were unavoidably divided, and gave a good deal of blood; this caused some embarrassment, when the point of the blade was close to the trachea, for on the one hand it was impossible to press the fingers more strongly on the trachea as a guide, for fear of compressing the air tube, while on the other the blood completely obscured the trachea itself; this it became necessary merely to touch with the knife gently the rings of the trachea each time it rose during inspiration; in this way one or two rings were exposed and opened near the lower edge of the wound. The division of the rings was then continued upwards as far as the cricoid cartilage; this part of the operation was completed in 5 or 6 seconds; the blood immediately penetrated into the trachea, and was rejected with great force; but the moment respiration was established through the wound, it ceased altogether.

The respiration now became less difficult, but extremely rapid; the child recovered the full use of the senses and expressed himself as being better; however, the fits of coughing came on nearly every moment, when he spat up bloody mucus and bits of false membrane. As the cough became more calm, an attempt was made to introduce a canula into the trachea, but this was impossible, through the pain it caused, and the irritability of the child. An assistant was now left with the child to keep the wound if possible open, while M. Trousseau sought a canula of a different construction. On returning with an instrument which had already been used in two similar operations,

M. Trousseau found the lips of the opening almost closed by mucosity and remnants of false membrane; however, the canula was introduced without difficulty, and immediately provoked a convulsive cough, followed by the expectoration of thick mucus and portions of membrane. When this coughing had somewhat ceased, 15 to 20 drops of a saturated solution of alum were introduced into the trachea; the cough was thus re-excited with great violence, and a quantity of false membrane spit up; after a short period, a solution of nitrate of silver (10 grains to ℈j of distilled water) was injected into the trachea, and provoked the cough in a much less degree than could have been imagined; the expution of false membrane followed this injection also. Shortly after, the cough became calm, and the infant slept, with the respiration considerably improved. During the night, the patient's aunt was constantly employed in keeping the passage of the canula free, either by a little sponge, or by dropping an emollient fluid into the trachea.

Eight hours after the operation, the countenance was good, the pulse developed, respiration 32, rale ronflant in the bronchi, and perfect resonance of the chest. The nitrate of silver was again dropped in, and the canula occasionally cleared.

Solution of nitrate of silver (10 gr. in ℈ of water) was dropped into the trachea six times, each application being followed by violent coughing and expution of false membrane. Whenever, in spite of the injections, the respirations became embarrassed, the canula was withdrawn, and the wound left open, while the instrument was cleaned, a process which was frequently necessary in the course of the day and night. However, the edges of the wound became a little sore and irritable on the 26th, and the secretion from the trachea was transparent and spotted with blood, but these were the signs of pneumonia.

Sixty hours after the operation the child slept peaceably during the night; the instillation of the emollient fluid was continued, which always excited cough, but an expectoration of simple mucus instead of false membrane; the pulse is regular, and the respiration not embarrassed; thirty-six in the minute.

Four days after the operation, the injection of nitrate of silver discontinued; respiration easy; the respiratory sound is heard nearly in the whole of the chest. During the day, the child spoke a little in a low voice; the canula has been removed and cleaned; whenever the respiration becomes oppressed, the marshmallow water is injected into the trachea.

On the sixth day after the operation, the child coughed only four or five times; no expectoration; respiration not embarrassed; the child commences to speak a little. When the canula is closed purposely, the air passes readily through the glottis and nares. On the ninth day the canula was completely closed, and on the twelfth the child was able to respire entirely by the larynx; in consequence of which the wound was dressed with lint and plaster, and in the space of three days was completely healed. The child now enjoys the most perfect health. Jour. des Connaissan. Med.-Chir., No. 1." 53

(53) The Lancet, 1832-33, Vol. 2, London, p. 811.

TROUSSEAU'S ADVICE ON THE PROCEDURE FOR TRACHEOTOMY. In Trousseau's Clinical Medical Lectures, he described what he considered to be the appropriate method for conducting a tracheotomy. The subtopics in this section of the book were: (1) Mode of Operating, (2) The Dilator, (3) Operation ought to be very slowly performed, (4) Dangers of Rapid Performance, (5) Dressing, (6) Cauterization of the Wound, (7) The Neckcloth, (8) General Treatment, (9) The Chances of Success are the Greater, the Less Energetic the Anterior Treatment has been, (10) Alimentation of the Patients, (11) Removal of the Cannula, (12) Infected Cannulae, (13) A Condition favorable to success is to Operate as Soon as Possible, (14) Unfavourable Conditions, (15) Death is Certain in Malignant Diphtheria, and (16) Death is Almost Certain in Children under Two Years.

He gave a detailed description of the operation:

> "The instruments required are a sharp-pointed somewhat convex bistoury, and a probe-pointed bistoury; two blunt hooks with good handles, or failing them two hair-crimping pins; a dilator, like a sort of dressing-forceps, curved at the extremity, with the two limbs forming at the end of the instrument a sort of spur projecting outwards, so as to enable it to fasten the lips of the tracheal wound, and prevent their displacement by the respiratory movements. The use of this instrument is to dilate the opening made in the trachea, so as to allow the tube to be introduced. The tube ought to be double-an external and an internal canula. In the expanded extremity of the external tube are two apertures to receive tapes, which are tied at the back of the neck, so as to keep the apparatus in its place. Besides these two apertures, there is in the upper part of the expanded extremity of the external cannula a sort of key which fits into a slit in the corresponding part of the internal canula. The internal which necessarily has a less diameter than the external canula, has two ears projecting from its expanded extremity, by which it can be held when it is wished to take it out or replace it; it is fixed to the external canula by the little key which I have mentioned, and which can be easily

opened and shut. The diameter of the tube ought to be considerable; it can never be too large, provided the instrument can easily enter the trachea. Its curve ought to form a quarter circle; this is the principle upon which all these instruments are now made by M. Mathieu, who adopted the fixed standard to avoid in conveniences which I pointed out to him, the courve of the different tubes previously shown to me being either too great or too small, in consequence of the workmen having always departed from the exact form of the model placed in their hands. That the tube be double, is an absolute necessity; and when we see the manner in which Van Swieten insists on the necessity of using a double tube, and that he does so on the authority of the English author, George Martin, it is remarkable that the precept was forgotten; it is strange, too, that although the double cannula was recommended by Bretonneau, who from his earlier operations employed an uncurved double tube, I myself for years employed the single tube.

The dilator is indispensable. I have only once lost a child during the operation; the patient was under the care of my honorable colleague, Dr. Barth. I went to the consultation ignorant of the state of matters, and found the child dying. Dr. Barth was prepared with tube and bistoury. From not having a dilator, I was unable to keep aside the vessels as I should have wished: I felt about with my finger for a long time before I was able to make an entrance into the trachea, and during that time a great quantity of blood entered the bronchi and suffocated the patient: this could certainly not have happened, if I had had a dilator which I could at once, on making the incision, have introduced into the windpipe. When a dilator cannot be obtained, recourse may be had to a plan devised by Dr. Paul Guersant: it consists in arming the tube with an ordinary gum-elastic catheter, projecting some centimetres from the inferior opening of the tube. You can understand how much the manual proceedings will be simplified by this contrivance. The gum elastic catheter is easily introduced into the tracheal wound, the finger being used as a conductor; and then all that is required is to get the canula into position is to cause it to slide upon the catheter.

I shall now describe the operation. The patient is laid on a table, on which there are a mattress and several folds of a blanket: a doubled up pillow, or better still a rouleau made with sheets, is placed under the shoulders and back of the neck, so as to put on the stretch the anterior region and bring the trachea as much as possible into relief. This is undoubtedly a very distressing position for an individual in a state of asphyxia, but it has not to be long endured. An assistant placed behind the patient is appointed to hold the head firmly; another assistant, placed opposite the operator, is charged with keeping aside the different layers of tissue and the blood vessels, by means of a blunt hook held in the left hand, while he is on the alert to use, when required, the right hand in sponging the wound with small sponges placed beside him ready for use. The assistance of other persons is also needed to prevent the patient moving. Finally, that I may omit nothing, let me add, that if you operate at night, there must be some one to hold for you a candle giving a strong light. If the operation is performed in full daylight, the patient ought to be placed directly in front of a window of the room, the feet being next the window, so that the light may fall on the neck.

These precautions taken, the operator standing on the patient's right-observe, I say the right and not the left, because otherwise, unless he be ambidexter, he will be embarrassed by the projection of the chin: the operator, then, standing on the right of the patient, grasps the tracheal region with the left hand, when with the right hand he makes an incision in the median line, from the cricoid cartilage to within a little of the sternum. The importance of making an incision in the median line is so great, that if this rule be neglected, the operator is liable to be very much embarrassed during the whole of his proceedings. I recommend those who have no pretensions to surgery to draw on the skin the proper course of the bistoury with ink or a cord blackened in the flame of a candle. Having incised in succession the skin and the cervical aponeurosis, there is reached a small white mark indicating an interstice between the muscular masses. The

blood now flowing is soaked up by the sponges; the operator then cuts in the line of the small white mark, separating the sterno-hyoid and sterno-thyroid muscles, which by means of the blunt hook in his left hand, are held aside, while, at the same time, the assistant who is in front of the operator separates them from each other. This is the point at which difficulties begin.

The isthmus of the thyroid gland has now been reached; its size and position vary so much, that is is sometimes found covering the first rings of the trachea, and at other times is much higher up. Lower down we find the thyroid plexus of veins, and Neubauer's artery when it exists. Now is the time when the operator must bear in mind the cardinal precept, to avoid wounding the blood vessels. If he see a large vein he must dissect it out, and draw it to one side with the blunt hook. If the left subclavian vein, gorged with blood, shows itself in the jugular fossae, it may be depressed and protected by a finger, and the terrible accident be thereby avoided wich would result from its being wounded. For still stronger reasons attention ought to be paid to the trunk of the brachio-cephalic vein. which in children often projects considerably beyond the substernal fourchette.

As soon as the trachea is brought into view it ought to be denuded, and a small incision made in it, as near as possible to the cricoid cartilage, the bistoury being directed upon the nail of the index finger which is placed at the bottom of the wound. A hissing noise indicates that the trachea has been opened: the sponge is now used, and then, by means of the probe-pointed bistoury, the incision is forthwith enlarged. If the original opening has been made far from the cricoid cartilage, it must be enlarged by cutting from below upwards, so as to avoid the trunk of the brachio-cephalic vein. Many practitioners prefer opening the crico-thyroid space, cutting the cricoid cartilage or the two first tracheal rings, in accordance with Heister's plan. It is evident that, by proceeding in this way, we penetrate the larynx itself; and that - as often happens - if the tube remain some weeks in the wound,

the result will be partial necrosis of the cricoid cartilage, and even of the thyroid cartilage, the probable source of serious ulterior consequences, among which may be mentioned an irremediable alteration of the voice. Let it be understood that I am now speaking of what ought to be done in cases of croup occurring both in adults and in children; for afterwards, when I shall have to speak to you of tracheotomy in other laryngeal affections, I shall have to point out that in the more aged a different method of proceeding is sometimes required. In cases of croup it is only necessary to open the trachea.

I cannot gentlemen, too strongly insist upon the necessity of dividing the tissues layer by layer, holding aside the vessels and muscles by the blunt hooks, and entirely denuding, before opening, the trachea. I lay great stress upon the absolute necessity of proceeding very slowly. If, even during the operation, the child has a suffocative attack, stop to allow him to struggle, and permit him to sit up that he may get his breath: you may thus perhaps lose a minute, but of that you need not be afraid. I have never seen an accident arise from too much slowness; but I have often witnessed the difficulties and dangers of a too nimble tracheotomy, even when performed by an able operator." [54]

(54) Trousseau, A., Clinical Medical Lectures, tr. by Sir John Rose Cormack, 2 vols., Phila., P. Blakiston Son & Co., 1882, pp. 419-423.

TROUSSEAU'S HISTORICAL REVIEW OF TRACHEOTOMY. In his Clinical Medical Lectures, Trousseau gave a brief summary of the history of tracheotomy.

He stated that the operation of tracheotomy was recommended by Stoll, [55] who, however, seems never to have performed it. John Andree [56] a London surgeon performed it for the first time, and, with success, in 1782. The subject operated on was a child, an account of whose case Jacob Locatelli sent to Borsieri, by whom it was published in his Institutes. [57]

He further stated that at the beginning of the present century, Caron, a French physician, renewed the praises of tracheotomy, although he had only performed it once, and that unsuccessfully. [58]

In another section of his lectures, Trousseau mentioned other aspects of the history of tracheotomy.

He related that in 1856, Sanctorius, who seems to have been the first to practice bronchotomy, proposed puncture of the trachea with the trocar which he had invented for performing abdominal paracentesis. In 1748, Garengeot recommended laryngocentesis as being very superior to the operation by which we reach the trachea

(55) Ibid., p. 419. (see Stoll: Aphorismes sur l'angine Inflammatoire).
(56) Ibid., p. 419.
(57) Ibid., p. 419. (see Borsieri: Tome IV Angina Trachealis, ch. ccccxxxvi).
(58) Ibid., p. 419.

step by step: he, however, advises that the skin, without disturbing the muscles, should be incised in the first instance, at least in thin subjects. [59] Further, he stated; direct puncture, without previous incision is also recommended by Heister, [60] because it is more expeditious, and because it saves suffering to the patient, as one stroke makes the puncture with the trocar and introduces the canula into the windpipe. He mentioned that Decker, Bauchot, Barbeau-Dubourd, and Richter had thought of bronchotomy, with a view of rendering the operation safer and quicker. [61] Also, Trousseau said, Van Swieten, in the 813th Commentary,...speaks at some length of bronchotomy, which he denounces as dangerous, after having performed it experimentally on the dead body, and on living animals. [62]

This summary presents comments on just a few of the physicians who either wrote on or conducted tracheotomies prior to the nineteenth century.

In the nineteenth century, various French physicians performed tracheotomies.

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(59) Ibid., p. 423. (see Garengeot: Operations de Chirurgie, t. iii, p. 153, annee 1770).
(60) Ibid., p. 423.
(61) Ibid., p. 423.
(62) Ibid., p. 423. (see Van Swieten, Commentaria in Boerhaavi Aphorism de coognosc. et curand. morbis: Aph. 813, t. ii, p. 627.

OTHER FRENCH PHYSICIANS PERFORMING TRACHEOTOMIES IN THE NINETEENTH CENTURY

TRACHEOTOMIES IN THE 1830'S IN FRANCE. Pierre Bretonneau reported a case of his to the Academy of Medicine in France in July, 1825:

> "A case description, communicated to the Academy in July, 1825, presents a child, aged four, critically ill from diphtheritic croup who was subjected to tracheotomy, a procedure previously performed successfully by Bretonneau on animals. A curved silver cannula was inserted on the seventh day of the disease when the patient was in critical respiratory difficulty. By the fourth day after insertion, improvement was sufficient to permit temporary withdrawal of the cannula for cleaning. On the 11th day after the operation, the cannula was removed and not replaced.
>
> Seventh day; at 4 A.M. after two hours of sleep, dry cough, wheezing inspirations; the lips and the body became purple; crying and alternating spells of convulsive cough were followed by expectoration of membrane-like tenacious masses. Imminent danger forced me to prepare for tracheotomy...the bluish pallor of the face, which indicates progressing asphyxia, did not permit delay.
>
> On the basis of experience from animal experiments, with successful tracheotomy, I modified the operation in this instance.
>
> I proportioned the size of the canula to the size of the trachea; and in order to make it easier to insert and to maintain I designed it cylindrical, slightly flattened and curved along its length, and beveled at an angle at each end.
>
> The head was held back by an aid in a fashion to force the deep portion of the neck...the incision, made along a previously marked line, extending from the interior border of the thyroid to the suprasternal fossa. Five rings of the trachea were divided and a curved silver canula was placed in the airway. Respiration became calm, easier, and the oozing of blood gradually ceased.

> The canula was held in place by a twisted string, tied around the neck and passing between the rings protruding at the orifice.
>
> Immediately after the dressing was applied, the child asked for a drink and lifted the glass to the lips with own hands.
>
> A second tube, closely adapted to the canula, which can be removed and cleaned with ease, helps to avoid the inconvenience of displacement of the canula which, although not painful, caused considerable discomfort. I had this second tube prepared by a skillful craftsman, but it was too late to be of any use in this patient." 63

Statistics concerning Bretonneau, in 1849, given 20 tracheotomies performed and 6 recoveries. [64]

(63) Talbott, John, op. cit., p. 481.

(64) The American Journal of the Medical Sciences, ed. Issac Hays, M.D., New Series, Vol. XVII, Phila., Lea & Blanchard, London, Wiley & Putnam, and John Miller, 1849, p. 335.

Guersant lost his first 23 cases between 1834-1841; but after that saved 17 out of 82. [65]

In a discussion which took place in the Parisian Academy of Medicine in 1839, [66] the following results were presented:

Operators	No. of Tracheotomies	Recoveries
Amussat	6	0
Baudelocque	15	0
Blandin	5	0
Bretonneau	18	4
Gerdy	6	4
Roux	4	0
Trousseau	80	20
Velpeau	6	0
	140	28

(65) Cohen, J. Solis, Croup in its Relations to Tracheotomy, Lindsay & Blakiston, Phila., 1874, p. 5.

(66) Ibid., p. 9.

TRACHEOTOMIES IN THE 1840'S IN FRANCE. Guersant reported in 1847, a case of recovery at fourteen years of age. [67] He also reported that up to 1845, he had used a single tube without a cravat, and had saved but 2 cases out of 32 operations. His results would be as follows: [68]

	No. of Operations	No. of Recoveries
Between 1834 and 1845	32	2
After 1845	124	26
	156	28

TRACHEOTOMIES IN THE 1850's IN FRANCE. The success immediately after 1849 was in remarkable contrast to previous years, as will be seen by the following exhibit: 69

Years	No. of Tracheotomies	No. of Recoveries
1850	20	6
1851	31	12
1852	59	11
1853	61	7
1854	44	11
1855	48	10
1856	55	14
1857	71	15
1858	90	30
1859	164	40
1860	130	23
1861	82	25
1862	136	29
	991	233

(67) Ibid., p. 23. (see Gaz. des hop., Feb. 23, 1847; Am J. Med., Sc., Oct., 1847, p. 491.).

(68) Ibid., p. 15. (see Med. and Surg. Rep., Phila.; 1864, p. 9, from British Med. Journ.)

(69) Ibid., p. 11. (The statistics for 1850-1857 are from H. Chaillou, Am. Journ. Med. Sci., July, 1885, p. 251; for 1858 from Bouvier, Bull. Acad. Med., XXIV, 1858-9, p. 191; for 1859-1861 from Haughton, Indiana State Med. Soc., 1867, p. 125; and for 1862 from Barthez, Gaz. Med. Paris, Aug. 1, 1868, p. 449.).

MM. Fischer and Brichetau [70] gave the following table as the results in their hospital for the 12 years, 1851-1863:

	No. of Operations	No. of Recoveries
On Boys	539	131
On Girls	474	133
	1013	264

The following statistics are from Bouchut: [71]

Years	No. of Tracheotomies	No. of Recoveries
1854	6	0
1855	9	3
1856	13	5
1857	25	6
1858	119	21
1859	123	20
1860	55	7
1861	24	2

Sanne gives a different list for some of these years:[72]

Year	No. of Operations	No. of Recoveries
1855	9	2
1856	14	3
1858	73	11
1859	76	20
1860	34	7
1861	37	7
1862	62	19
1863	54	18
1865	290	27
1866	64	29
1867	39	10
1868	82	17

(70) Ibid., p. 12.
(71) Ibid.
(72) Ibid., p. 14.

Barthez, in a letter to Rilliet [73] on the comparative results of the treatment of croup by tracheotomy and by medication during the years 1854-1858, stated that the first year the Hopital Sainte-Eugenie was opened, 13 croup patients were submitted to tracheotomy, of whom the first died during the operation, and 11 others in succession after the operation; the first recovery taking place in the thirteenth case. Yet Barthez had many successes afterward.

Millard, in a thesis, "De la tracheotomie dans le cas de croup". Paris, 1858, [74] based on observations in the female wards during his service, made between January, 1857, and July, 1858, gives a result during that period of 21 recoveries among girls out of 62 operations, and 8 recoveries among boys out of the same number; the sum total being 124 operations and 29 recoveries. Of 20 operated upon under 2 years of age, none recovered; of 36 between 2 and 3 years, only 5 recovered; the remaining 24 recoveries being in children between 3 and 9 years of age.

Trousseau presented the following statistics: [75]

Operator	No. of Tracheotomies	Recoveries
Bardinet (& confreres at Limoges)	57	17
Saussier (Froyes)	6	3
Beylard (Paris)	13	4
Moynier (Paris)	17	8
Archambault (Paris)	21	8
Perrochaud (Boulogne)	3	2
Delarue (Paris)	3	1
Lalois (Belleville)	6	3
Viard (Monthard)	2	1
Petel (Cateau)	9	5
Bauchin (Nantua)	4	3

(73) Ibid., p. 5. (see Gaz. Med. de Paris, 1868, p. 449).

(74) Ibid., p. 12 (see Bull. de l'Acad. Med., 1858-9, and Gaz. Hebd., Noc. 26, 1858, p. 826).

(75) Ibid., p. 10. (see Bull. de l'Acad. Med., XXIV, p. 231 and Gaz. Hebd., Dec. 3, 1858, p. 884).

Malgaigne and Thierry [76] in a discussion before the Academy, presented these figures:

Operators	No. of Tracheotomies	Recoveries
Malgaigne	8 (of 10)	1
Thierry (in children)	37	3

TRACHEOTOMIES IN THE 1860'S IN FRANCE. We have the following figures from Bourdillat: [77]

Years	No. of Tracheotomies	No. of Recoveries
1860	55	8
1861	76	13
1862	111	22
1863	112	34
1864	121	15
1865	147	46
1866	129	45
1867 (first six months)	62	25
1867 (second six months)	40	8
	853	216

Barthez gave the following figures: [78]

	Operators	Recoveries
For 1861-1867	785	222
And for 1866-1867	223	79

(76) Ibid., pp. 9-10.
(77) Ibid., p. 14.
(78) Ibid., p. 13 (see Gaz. Med. Paris, 1868, p. 449).

Tracheotomy as a therapeutic procedure in diphtheria attained great popularity in the hands of French physicians in the early part of the nineteenth century.

The latter half of the nineteenth century witnessed the valuable work of Émile Roux and the development of the diphtheria antitoxin.

CHAPTER V

ROUX AND DIPHTHERIA THERAPEUTICS IN THE NINETEENTH CENTURY: EVIDENCES OF THE HUMORAL THEORY

A study of diphtheria therapeutics revealed three distinct periods: (1) the pre-Roux period when treatment was essentially palliative; (2) the Roux-period, when diphtheria antitoxin was introduced and utilized effectively in the control of disease; and (3) the post-Roux period, which brought virtual control of diphtheria and development of large-scale inoculation techniques, investiagion of hypersensitivity and purification of the serum.

As recently as the end of the nineteenth century, diphtheria therapeutics reflected the remedies used in many of the prior centuries. During the first half of the nineteenth century, blood-letting was often used for throat infections which might have been diphtheria. (1) Blisters of cantharides or other counter-irritants were sometimes placed on the neck, and, after acute symptoms had passed, purgation might be drastic. (2) After 1850, more attention was paid to supporting the patient's strength, possibly with tincture of iron perchloride given internally, and the throat was swabbed with some styptic mixture. (3) Iron perchloride was beneficial in cases of anemia and it also possesses

astringent properties. This was the only treatment for diphtheria before the days of antitoxin. (4) Tracheotomy subsequently attained a vogue, more in France than in England, as a life-saving measure. [1]

Evidences of the humoral theory, in concepts of disease pathology and therapeutics, are found. The humoral theory developed from the concept of the four elements of the earth. This idea is found in the medical literature of the Chinese as early as the eighth century B.C. The Buddhists and Hindus had similar ideas. The Greeks developed this concept and elaborated it from the four elements of air, water, earth, and fire to the four humors of blood, phlegm, yellow bile and black bile. [2]

"Health", for the Greeks, "consisted in a proper balance between the four humors, while disease was caused by an undue preponderance of one or more of them." [3]

Variations of this concept was held by the Romans, of whom Galen (c. 130-200) was the greatest exponent; the Arabians, the Renaissance physicians, and physicians of the eighteenth century. "During the Renaissance," stated Temkin, "and long afterwards, pathology rested on the theory of the humors which

(1) Parish, H. J., A History of Immunization, E. and S. Livingstone, Ltd., Edinburgh and London, 1965, pp. 118-119.
(2) Mettler, C. C., History of Medicine, Philadelphia, The Blakiston Company, 1947, p. 9.
(3) Winslow, Charles-Edward Amory, The Conquest of Epidemic Disease, Princeton, New Jersey, Princeton University Press, 1943, p. 56.

had become deranged in sickness and had to be purged by bleeding, cathartics, and emetics. Nature in her attempts to free the body from the morbific matter tried to eliminate it through pustules, abscesses, ulcers, and other discharged and cutaneous eruptions." [4]

PRE-ROUX DIPHTHERIA THERAPEUTICS AND HUMORALISM

During the pre-Roux period, diphtheria was responsible for many deaths. The first writer on diphtheria was Aretaeus of Cappadocia (81-138 A.D.), a Greek physician, who lived in Rome during Nero's reign. He gave a first hand account of a throat affection which could have been diphtheria. In his work "On Ulcerations about the Tonsils" [5] he described ulcerations which he referred to as Egyptian and Syrian ulcers. His therapeutic recommendation was, "minister to the chest as to the purposes of voice and respiration; and to the belly for the conveyance of food; and to the stomach for deglutition." [6]

He recommended abstainence from swallowing "cold, rough, hot, acid, and astringent substances," [7] if the tonsils were inflamed.

Paul of Aegina (625-690) wrote in his third book, "Inflammation of the trachea is very rare in children and always traumatic

(4) Temkin, Owsei, "Therapeutic Trends and the Treatment of Syphilis before 1900," Bull. Hist. Med., 1955, 29; 312.
(5) Aretaeus, the Cappadocian, "On Ulcerations About the Tonsils," in his Extant Works, ed. F. Adams, London, 1856, 253-5.
(6) Ibid., p. 254.
(7) Ibid., p. 254.

in origin." [8] Mettler commented that this would indicate a knowledge of diphtheria. Paul of Aegina was the last of the Greek eclectics and compilers. His seven books were entitled the Epitome.

Guillaume de Baillou (1538-1616) published "Epidemiorum et ephemeridum libri duo" [9] in which he described a diphtheria epidemic in Paris in 1576. Some time later, he suggested the use of tracheotomy, though there is no evidence that he ever used it. His two books on epidemic and ephemeral diseases were published posthumously.

Evidence of the humoral theory in his work is found in his revival of the doctrine of "epidemic constitutions". This same work may have influenced the work of Sydenham (1624-1689).

There were five major medical writers on the disease, diphtheria, in the eighteenth century: (1) George Martine (1702-1741); (2) John Fothergill (1712-1780)' (3) John Huxham (1692-1768); (4) Francis Home (1719-1813); and (5) Samuel Bard (1742-1821).

George Martine discussed, in his treatise, "Account of the operation bronchotome, as it was performed at St. Andrews," [10]

(8) Pauli Aeginetae de re Medicae libri septem graecie, translated by F. Adams. (iii 27)

(9) Guillaume de Baillou, "Epidemiorum et ephemeridum libri duo." Paris, J. Quesnal, 1640 (see John Ruhräh, Pediatrics of the Past, New York, Paul B. Hoeber, Inc., 1925, pp. 242-246.

(10) Martine, George, "Account of the operation of bronchotome as it was performed at St. Andrews," Phil. Trans., 1730, 36, 448-55.

the first British tracheotomy for diphtheria. His patient was a young lad.

Immediate therapy by Martine consisted of (1) repeated bleedings; (2) blistering betwixt his shoulder, and (3) cupping, etc.

Martine's therapy is indicative of the prevalence of the humoral theory of diseases. In the case of a disturbance of the humors of the body, various means were utilized to remove some part of these humors. The tracheotomy which he performed was a last resort to save his patient.

Martine was a Scottish physician who had studied medicine at the University of Edinburgh and the University of Leyden, where he received his M.D. degree in 1725.

The first authoritative account of diphtheria was published by John Fothergill (1712-1780). He failed to differentiate diphtheria from scarlatinal angina, however. The tract was entitled An account of the sore throat attended with ulcers. [11] This tract was translated into several languages.

Fothergill was graduated M.D. from Edinburgh in the year of 1736. After this he studied at St. Thomas's Hospital and later practiced in London. He was a friend to William Hunter (1718-1783) and a follower of Thomas Sydenham (1624-1689). He befriended Benjamin Franklin (1706-1790).

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(11) Fothergill, John, An account of the sore throat attended with ulcers, C. Davis, London, 1748, reprinted in Medical Classics, 1940, 5, 58-99. (see George Fredric Still, The History of Paediatrics, London, Humphry Milford, Oxford University Press, 1931, pp. 384-385.

John Huxham (1692-1768) in his essay, A dissertation on the malignant, ulcerous sore-throat, [12] made the following observation of the paralysis of the soft palate associated with diphtheria. He thought that diphtheria and scarlatina was one and the same.

He was from Totnes, Devon, and a pupil of Hermann Boerhaave (1668-1738) at the University of Leyden. He studied Hippocrates in the original and won the Copley Medal for his essay on antimony. His study of Hippocrates no doubt gave him an appreciation of the significance of the humoral theory of disease and therapy.

Francis Home (1719-1813) gave the first, clear complete clinical description of diphtheria in his essay, An Enquiry into the nature, cause, and cure of the croup. [13] He stated that evacuants were very beneficial in these cases. His recommended therapy consisted of bleeding, applying blisters to the throat, applying leeches to the throat, applying warm wet cloths to the throat, purging, stimulating the patient's breath and steams of warm water and vinegar, giving vomits, and giving sudorifics. Indicative of the humoral pathology was this statement which he made, "These evacuations operate in several different ways, viz. by thinning the dense mucus, while yet circulating

(12) Huxham, John, A dissertation on the malignant, ulcerous sore-throat, J. Hinton, London, 1757.

(13) Home, Francis, An enquiry into the nature, cause, and cure of the croup, Edinburgh, MDCC, LXV, 1765.

in the blood; by diverting its flux from the parts affected, as there is great communication and consent betwixt the different mucus glands thro' the body; but, particularly, by increasing the absorbent power of the vessels on emptying them; by which means the purulent matter will be sucked in from the lungs." [14]

Home also recommended bronchotomy if the patient was in danger of suffocating.

Samuel Bard (1742-1821) published An enquiry into the nature, cause, and cure, of the angina suffocativa, or sore throat distemper, as it is commonly called by the inhabitants of this city and colony [15] in 1771. This has been characterized by Osler as "an American classic of the first rank". [16] It described, accurately, the disease -- diphtheria.

Pierre Fidele Bretonneau (1778-1862) became famous because he performed a tracheotomy for croup in 1825. In his Des inflammation speciales du tissu muqueux et in particulier de diphthrite (1826) [17] he showed diphtheria to be a specific clinical entity. He also recognized the difference between typhus and typhoid fever. He initiated, in 1855, the germ theory of disease.

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(14) Home, op. cit., p. 56.

(15) Bard, Samuel, An enquiry into the nature, cause, and cure, of the angina suffocative or sore throat distemper, as it is commonly called by the inhabitants of this city and colony, S. Inslee and Car., New York, 1771. (see John Rurah, Pediatrics of the Past, New York, Paul B. Hoeber, Inc., 1925, pp. 460-464.

(16) Garrison, Fielding H., An Introduction to the History of Medicine, W. B. Saunders Company, Phila. and London, 1929, p. 111.

(17) Bretonneau, Pierre Fidele, Des inflammations speciales du tissu muqueux et en particulier de la diphtherite, or inflammation pelliculaire, Crevat, Paris, Paris, 1826.

Bretonneau's pupil, Armand Trousseau (1801-1867) wrote Du tubage de la glotte de la tracheotomie in 1859. [18] He was a pioneer in utilization of intubation of the larynx. A French clinician, Trousseau served as professor in the Paris Faculty in 1850; at the Hopital St. Antoine in 1839; and at the famed Hotel Dieu in 1850.

Theodor Albrecht Edwin Klebs (1834-1913) published an article entitled, "Ueber Diphtherie" in 1883. [19] This was the first account of Corynebacterium of diphtheriae or Klebs-Loeffler bacillus. He identified it due to the tendency of the bacillus to form an involutional form which was club-shaped (coryne).

This pioneer in bacteriology at Konigsberg, East Prussia, made outstanding contributions in diphtheria therapeutics. Some of the positions which he hald in his lifetime were: Assistant to Virchow at the Pathological Institute, Berlin (1861-1866); Professor Pathological Anatomy at Berne (1866), Wurzburg (1871), Prague (1873), Zurich (1862), and Chicago (Rush Medical College, 1896).

In his experiments, he was the first to filter bacteria and to experiment with filtrates. [20] He invented the fractional method of obtaining pure cultures of bacteria known as "Darwining",

(18) Trousseau, Armand, Du tubage de la glotte, et de la tracheotomie, J. B. Baillou, Paris, 1859.
(19) Klebs, Theodor A. E.,"Ueber Diphtherie", Verh. Congr. inn. Med., 1883, 2, 139-54.
(20) Garrison, op. cit., p. 581.

that is killing off the competing germs in the impure culture by successive transfer through a series of fresh media, which was followed by Lister's method of dilution (1877) and prepared the ground for Koch's work. [21]

Friedrich August Loeffler (1825-1915) German bacteriologist, "confirmed and extended Kleb's discovery and published a full account of this work which is still considered a classic." [22] In his article "Untersuchungen Uber die Bedeutung der Midroorganismen fur die Entstehung der Diphtherie beim Menschen bei der Taube und beim Kalbe", [23] he reported his success in cultivating C. diphtheriae.

He suggested, but did not prove, that the bacillus caused death by elaborating a powerful poison or toxin.

Joseph P. O'Dwyer (1841-1898) of Cleveland, Ohio perfected the operation for laryngela intubation in croup. He discussed this operative technique in his article "Intubation of the larynx," 1885. [24]

Eugene Bouchet (1818-1891) introduced intubation of the larynx in Croup in 1856-8. It was first done in Paris in connection with tracheotomy by Trousseau (1851-59). O'Dwyer's work followed and now he is equal to Ignaz Semmelweis (1818-1865) and

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(21) Ibid., p. 581.

(22) Parish. op. cit., p. 119.

(23) Loeffler, F. A. J., "untersuchungen die Bedeutung der Mikroorganismen fur die Entstehung der Diphtherie Beim Nenschen bei der Taube und beim Kalbe," Mitt. K. Gesund. Amte., 1884 2, 421-449.

(24) O'Dwyer, J. P., "Intubation of the Larynx," N. Y. Med. J., 1885, 42, 145-7.

Carl Sigmund Franz Crede (1819-1892) "as one of the great benefactors of infant life". [25]

O'Dwyer published (1888) "Analysis of Fifty Cases of Croup treated by Intubation of the Larynx". [26]

Émile Roux and his contemporaries carried on fundamental research in the development of the antitoxin for diphtheria in the latter part of the nineteenth century.

(25) Garrison, op. cit., p. 613.
(26) O'Dwyer, J. P., "Analysis of Fifty Cases of Croup treated by Intubation of the Larynx," N. Y. Med. J., 1888, 47, 33-7.

ROUX'S DIPHTHERIA THERAPEUTICS AND HUMORALISM

The discovery of the diphtheria and tetanus antitoxins in the latter part of the nineteenth century provided support for the humoral theory of immunity. During this time there arose a controversy regarding the mechanism of immunity. One group supported the concept that immunity was due to some quality in the body fluids. Another group supported the concept that immunity was due to the body cells.

Nine major works were published on diphtheria in the period encompassing 1888-1894; which is the period in which Émile Roux (1853-1933) made his great contributions to diphtheria therapeutics. Four of the works were Roux's; three were by Emil Adolf von Behring (1854-1917). The remaining two were publications of William Henry Welch (1850-1934).

The three articles of Émile Roux initiated a new period of research in diphtheria which was concluded by his classic report of 1894.

During the years of 1888, 1890, Émile Roux and Alexandre Emil Jean Yersin (1863-1943) collaborated in experimental researches which confirmed Loeffler's work and which initiated the development of immunizing serum. The work described in the 1894 report was done in collaboration with André Louis François Justin Martin (1853-1921).

The 1888 paper [27] was a presentation of Roux's attempt to prove the existence of the toxins of diphtheria bacilli and to experimentally produce paralytic diphtheria. This paper was divided into four sections: (1) bacilli of the diphtheria, (2) action on the animals, (3) experimental diphtheria paralysis and (4) the diphtheria poison.

Roux began his discussion by giving due credit to Loeffler. He stated, "You must recognize that if the work of Mr. Loeffler did not resolve the question of the etiology of diphtheria, he very well prepared the way for the study of this malady." Further, he said, "He (Loeffler) helped us to the point of departure in the researches that we publish today in which we confirm that the bacilli of Mr. Klebs and Mr. Loeffler is the specific bacilli of diphtheria." [29]

Roux expressed, in the introduction of this paper, his confidence in their work and prepared a summary of their major findings. He stated that they accomplished four things: (1) isolated the diphtheria bacilli from patients and prepared pure cultures; (2) reproduced the false membranes in animals (3) gave the paralysis analogous to that which they observed in man as a result of diphtheria; and (4) demonstrated that the cultures of the bacilli contained poison, which according to

(27) Roux, Émile and Yersin, "Contribution à l'étude de la diphthérie," Ann. Inst. Pasteur, 1888, 2, 629-61.
(28) Ibid., p. 631.
(29) Ibid., p. 631.

the doses which they injected, rapidly killed the animals or gave them paralysis without the intervention of the living microbes.

There were three divisions of the first part of the discussion on the diphtheria bacilli: its separation; its characters; its culture. The separation procedure, according to Roux was "very little different from that of Mr. Loeffler". [30] He explained, "With the platinum inoculating loop we spread on the surface of the tube of coagulated serum, a small part of the false membrane. With the same loop, without reloading of inoculum, we made several streaks on the different tubes of serum. In the inoculated tubes there developed at the temperature of 33 degrees a great number of colonies in the long streaks." [31]

Roux, in studying the effect of the bacilli on the animals, administered the bacilli by sub-cutaneous, intravenous, and peritoneal injections. There is mention also of the virulence of the cultures and research of the effect on the diphtheria bacilli on the organs.

Experimental paralysis was produced by inoculating the pharynx and trachea and injecting bacilli intranveously. Experiments with the diphtheria poison were conducted on various species of animals; pigeons, rabbits, and rats. The filtering of cultures through pprcelain and the attenaution of the poison wiht heat were also discussed.

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(30) Roux and Yersin, "Contribution à l'étude de la diphthérie," Ann. Inst. Pasteur, 1888, p. 632.

(31) Ibid., p. 632.

The 1889 paper [32] dealt with some of the properties of the diphtheria poison. Six sections of the paper were devoted to: (1) attenuated poison effect: (2) effect of poison on mortality; (3) effect of sunshine and air on the poison: (4) effect of an acid or alkaline medium on the poison; (5) precipitation of the poison; and (6) determining the potency of the poison.

Roux described the effect of the attenuated and the unattenuated poison; "A liquid filtrate, which injected under the skin at the dose of 1/8 cc, kills the guinea pig, but not when the same dose has been heated two hours at 58 degrees." [33] Another example which he gave was of a rabbit, "The same liquid heated for 20 minutes at 100 degrees when introduced into the veins of a rabbit at the dose of 35 cc. caused no immediate discomfort, while before the heating 1/2 cc. injected subcutaneously or intravenously would have brought sure death." [34]

Comparing the deaths of animals receiving the bacilli and those receiving toxin, Roux declared, "If we compare the history of these animals to that of the guinea pigs and rabbits which received the diphtheria culture (filtered and heated), we will find convincing proof

(32) Roux and Yersin, "Contribution à l'étude de la diphthérie," Ann. Inst. Pasteur, 1889, 3, 273-88.
(33) Ibid., pp. 278-279.
(34) Ibid., p. 279.

that the cause of death is the same in the two cases". [35] "This", he stated, "gives a new proof that the bacilli of Mr. Klebs and Mr. Loeffler is the cause of diphtheria". [36]

Roux conducted experiments with the filtrate in sealed and unsealed tubes to ascertain the effect of sunshine and air on the toxicity. The toxicity diminshed when air was excluded from the filtrate. However, when the tubes without air were exposed to sunshine, there was no real decrease in toxicity. The effect of the sunshine on the tubes which were exposed to air was nil.

Roux stated that, on a whole, acid media attenuated the poison, whereas alkaline media did not. To produce a precipitate of the poison, Roux evaporated it in vacuo over sulphuric acid. This residue, he said, "in solution, in a little water, is very toxic, since it contains, in a small volume, the active matter of a great quantity of the culture." [37] Roux recommended fractionating the precipitate three times to get a pure precipitate. "The precipitate", he stated, "which carries away the most easily the active substance of the diphtheria is the phosphate of lime. A filtered culture, added drop by drop, and in agitating, a solution of chloride of calcium there is formed a precipitate in the bottom of the vessel." [38]

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(35) Ibid., p. 281.
(36) Ibid., p. 281.
(37) Roux and Yersin, "Contribution à l'étude de la diphthérie," Ann. Inst. Pasteur, 1889, p. 282.
(38) Ibid., p. 284.

It is very difficult to ascertain the potency of the poison because it is very difficult to get it in the pure form, according to Roux. Also, he said, it is difficult to "accustom the animals to the diphtheria poison, precisely because of its activity." [39]

The 1890 paper [40] was divided into eight parts; (1) diagnosis of diphtheria; (2) duration of bacilli on the mucous membranes; (3) duration of the diphtheria virus on the exterior of the organism; (4) virulence of the diphtheria bacilli in the false membranes; (5) pseudodiphtheria (6) attenuation of diphtheria virus; (7) attenuated diphtheria poison and virus; and (8) return of the virulence to attenuated diphtheria bacilli.

In the Introduction, Roux said, "Since two years, a great number of works have been published on diphtheria; they confirm, for the most part, the results obtained by Mr. Klebs and Mr. Loeffler, and also those which we have set forth in the collection." [41] He drew some conclusions: "Diphtheria is characterized by the bacilli described by Mr. Klebs and Mr. Loeffler; for to make the precise diagnosis of this malady, it suffices to put the bacilli in evidence. It is easy to arrive at this result by microscopic examination and the inoculation on the serum, according to the procedure indicated by Mr. Loeffler. This means of diagnosis, which puts under your eyes and between

(39) Ibid., p. 288.
(40) Roux and Yersin, "Contribution à l'étude de la diphthérie," Ann. Inst. Pasteur, 1890, 4, 385-426.
(41) Ibid., p. 385.

your hands the same cause of the malady, are particularly vital in the case where the diagnosis is difficult, the same for the medical practice. We have employed it in more than 100 cases of diphtheria, and we think that it permits a scientific diagnosis. Also, we begin the work by exposing the technique that is convenient to follow your research of the specific bacilli in the false membrane."[42] For diagnosis of diphtheria, Roux outlined this procedure: remove a particle of false membrane; place on blotting paper; place on cover glass, making sure that the false membrane is not contaminated with mucus; pass the cover glass through the flame, color in the blue of Loeffler or the genitan violet after the method of Gram; wash the preparation in water; examine while wet or moist with the objective at immersion; look for heaps of diphtheria bacilli which usually appear in the form of rods or club-shaped. This is the procedure for the diagnostic smear.

He ended the section on the duration of the diphtheria bacilli in the mouth with "The conclusion of this chapter will be that, in diphtheria, the specific bacilli can disappear from the mouth in the same time that the false membranes, but may persist some days after it, where they dwell in a state of virulence during a sufficiently long time, but of which it is impossible to be precise." [43]

(42) Ibid., pp. 385-386.
(43) Ibid., p. 400.

On the outside of the organism, the diphtheria virus does not last long, said Roux; "The diphtheria virus remains on the false membrane a long time if not exposed to sun and water, if this is done, it is weakened and the virus is destroyed." [44]

In summary, Roux stated, regarding the virulence of the bacilli; the more virulent, the more serious the disease. He named the nonvirulent bacilli-pseudodiphtheria and said some authors have noted differences in the appearance of the colonies in comparison to the true bacilli.

"Some think," said Roux, "the pseudobacteria is the attenuated form of the true bacteria." [45] The true bacteria and pseudo-bacteria have some properties in common:

(1) the colonies of pseudo-diphtheria, cultivated on serum are identical to those of the true diphtheria bacilli.

(2) at a temperature of 33-35 degrees, their growth is rapid, and it is continued at the ordinary temperature, but slowly.

(3) in the microscope, the aspect of the bacilli forms the colonies in the same way as that of the diphtheria bacilli.

(4) it takes well by teh blue of Loeffler and the staining in an intense way by the method of Gram.

(5) sometimes, it is the color of one uniform manner, where well it appears granular.

(6) if grown in the bouillon alkaline in giving a deposit on the wall of the vases of culture, and presents frequently in the medium the forms swollen in bulbs or in clubs.

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(44) Ibid., p. 401.
(45) Ibid., p. 401.

(7) a temperature of 58 degrees, in humid medium, the bacilli dies in less than ten minutes.

"As differences between them." Roux said, "one can note that the pseudodiphtheria is most often short in the colonies on serum; that these cultures in the bouillon are very abundant; that they continue at a temperature of 20-22 degrees; to which the true bacilli grow very slowly. When one makes by comparison the cultures of the two bacilli in the bouillon, they become acid, then alkaline; the changes or reactions are produced much more quickly in cells or pseudodiphtheria bacilli. As the true bacilli, the pseudodiphtheria grow quickly, but less abundantly, that which is the inverse of that which occurs in the cultures of air." [46]

It may be possible, concluded Roux, to show that the two bacilli are one and the same.

The attenuated bacilli, when artificially prepared, is confused often with the pseudodiphtheria; said Roux, "as it grows most abundantly and at one temperature most low, it renders the bouillon very rapidly alkaline, it grows very little in the vacuum." [47]

Roux attempted to answer the question, "Do the attenuated bacilli and pseudobacilli produce diphtheria poison?" [48] His answer to this seemed to be yes. On the return of virulence to attenuated bacilli, he stated, "The attenuated virus is very

(46) Ibid., p. 411.
(47) Ibid., p. 419.
(48) Ibid., p. 420.

diffused, it is able to revive its virulence; by consequence, it is necessary, at the beginning of the simple anginas and the anginas of the measles and of the scarlatina, to practice the antiseptic leavge of the throat." [49]

Emil Adolf von Behring (1854-1917) collaborated with Shibasburo Kitasato (1852-1931) researching the immunizing property of antitoxins. They published, in 1890, the results of their work on immunity in diphtheria and tetanus. [50]

Parish, in 1965, recounted Behring's work. He said, "Behring and Kitasato were the first to observe the formation of an antidote or 'antibody' to toxin, which they termed an 'antitoxin'." [51] In preliminary experiments, their colleague, Carl Fraenkel (1861-1915) had injected a toxic substance, extracted from diphtheria culture, into animals, and had found that if they recovered from its effects, they would withstand an injection of living diphtheria bacilli. The degree of immunity obtained by Fraenkel was only slight. Behring and Kitasato's joint paper which dealt with such an artificially produced immunity in animals against tetanus, was published in the first week of December, 1890, one day after Fraenkel's paper; and one week later, Behring, alone, published a further article enumerating five different methods by which

(49) Ibid., p. 426.

(50) Behring and Kitasato, "Ueber das Zustandekommen der Diphtherie-Immunitat und der Tetanus-Immunität bei Thieren," Dtsch. med. Wschr., 1890, 16, 1113-4; 1145-8.

(51) Parish, op. cit., p. 120.

a similar immunity against diphtheria could be obtained. After 1892, there ensued a series of priority disputes between Fraenkel who was no longer at Koch's laboratory, and Behring. Ogata, at the University of Tokyo and Emmerich at the University of Munich were also involved in priority disputes with Behring who enjoyed such disputes and found them stimulating. Behring and Kitasato observed that the serum of an animal, which received injections of sublethal doses of living or killed broth cultures of diphtheria or tetanus bacilli; each containing the corresponding toxin, had acquired a new property, it now contained something which enabled it to prevent the harmful effect of many lethal doses of the bacilli of the toxin. They found later, that even when minute amounts of broth culture filtrates of diphtheria bacilli were used for immunizing laboratory animals, a specific immunity was produced against the organisms or their toxic products. The antibody was protective not only to the directly immunized animal; an injection of its blood serum could transfer the protection to another animal, and could even cure one in which symptoms due to the toxin had already developed. Although guinea pigs had been used for the earlier experiments, Behring soon realized that large animals such as sheep, goats, and eventually horses, would be required, if the antitoxin was to be obtained for the treatment of diphtheria in man." [52]

(52) Parish, op. cit., pp. 120-121.

Parish continued, "The German work created a sensation at first, and progress was continuous and sufficiently rapid for clinical trials to be begun at the end of 1891. The first patient treated by diphtheria antitoxin (prepared in a sheep) was a little girl in von Bergmann's clinic in Berlin, who was injected by Geissler on the night of Christmas, 1891. She recovered." [53]

"After some further clinical successes," Parish stated, "the firm of Meister, Lucius and Bruning began to make antotixic serum on a commercial basis in their Höchst factory in 1892. In this year, also, Behring and E. Wernicke showed that animals could be immunized more rapidly by using increasing doses of living cultures after a protective dose of antitoxic serum, which reduced the severity of the toxin reaction. It was later found that a preferable method of immunization was to give increasing doses of toxin partially neutralized by antitoxin. Behring and Wernicke also demonstrated that passive immunity to diphtheria in man was produced by a protective dose of antitoxin. Later, other workers showed that this type of immunity is short-lived--lasting only for about two weeks." [54]

William Henry Welch (1850-1934) and Simon Flexner (1863-1946) collaborated on two articles; one in 1891 and one in 1892. [55]

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(53) Ibid., p. 121.
(54) Parish, op. cit., p. 121.
(55) Welch. William H. and Simon Flexner, "The histological changes in experimental diphtheria," Johns Hopk. Hosp. Bull., 1891, 2, 107-10.

This was an account of the pathological changes brought about by the experimental inoculation of diphtheria toxins.

A summary of the 1891 paper is: the experimental animals were guinea pigs, rabbits, and kittens. They studied the gross anatomical lesions. Microscopical study of the organs was made in the fresh state by means of frozen sections, and again, after hardening in different ways; alcohol, Fleming's solution and Mueller's fluid having been used. These hardened tissues which were stained with various aniline dyes, hematoxylin and stained with fuchsin or methylene blue, gave, as a rule, the most satisfactory results. Some of the areas studied were: seat of inoculation, lymphatic apparatus, liver, kidneys, adrenals, and lungs. Cultures were made from the blood, liver, kidney, and spleen of the animals. Results were negative in all cases.

The 1892 paper [56] dealt with the lesions produced by the inoculation of the toxic products of the diphtheria bacillus. They obtained the toxic products by filtering through a new and sterilized Chamberland filter a culture of the organisms in glycerine-bouillon several weeks old. They tested the fluid which they obtained by means of cover-slips and inoculations on glycerine-agar, and proved to be sterile. Guinea pigs were used for the experimental inoculations.

(56) Welch and Flexner, "The histological changes in experimental diphtheria," Johns Hopk. Hosp. Bull., 1892, 3, 17-8.

Welch drew certain conclusions; "It may be considered as established now that the toxic products and not the bacilli invade the tissues in diphtheria. This fact would at once suggest that the general lesions (those produced at a distance from the seat of inoculation in animals, and the situation of the local process in human beings) were the effects of the soluble poison diffused through the body. Hence, it was desirable to demonstrate the assumption experimentally; and it is not unimportant to know that the lesions in the tissues produced by the bacilli and the toxic principle on the one hand, and the toxic principle alone on the other, are in perfect correspondence with each other. And, moreover, it would seem not to be superfluous to emphasize the occurrence of definite focal lesions in the tissues of the body, produced by a soluble poison circulating in the blood." [57]

In the years 1893 and 1894, Behring published two papers dealing more fully with the use of diphtheria antitoxin. [58]

Roux and Martin published a classic paper in 1894 [59] which dealt with the value of Behring's specific antitoxin in the treatment of human diphtheria, in which he showed that it could be mass produced. Actually, there were two papers published

(57) Welch, op. cit., p. 18.

(58) Behring, "Die Behandlung der Diphtherie mit Diphtherie-heilserum," Dtsch. med. Wschr., 1893, 19, 543-7; 20, 645-6.

(59) Roux and Martin, "Contribution à l'étude de la diphthérie (serum therapie)," Ann. Inst. Pasteur, 1894, 8, 609-39; 640-661.

simultaneously; the first was divided into four sections: (1) preparation of diphtheria toxin; (2) immunization of animals; (3) antidiphtheric serum; and (4) action of the serum in diphtheria of the mucous membranes. The second paper presented the results of three hundred cases of diphtheria treated with antidiphtheric serum and was divided into only two sections: (1) anginas and (2) croups.

Roux introduced the first paper with a comment on the reason for the great interest in diphtheria therapeutics. He said, "Since Behring and Kitasato have taught the properties of the serum of animals rendered immune against tetanus and diphtheria" and "'antitoxines appear to be scientific remedies for two of the most serious diseases so feebly combated by empirical means until now"; serum therapeutics has become the question of the day. [60]

Roux compared the tetanus and diphtheria antitoxin; "The antitoxin of tetanus has been first studied because it is easier to obtain and exhibits its preventive action with marvellous force." [61] "In practice", he said, "It has not justified our expectations and everyone now agrees, we believe, that, if always useful in tetanus, it is not a reliable remedy.

(60) Ibid., p. 609.
(61) Ibid., p. 609.

This is due, no doubt, to the fact that we only recognize tetanus upon the appearance of the muscular contractions -- that is to say, after the poisoning has taken place. When the treatment is begun the disease has already entered its last phase, therefore it is not astonishing that the antitoxin is so frequently inefficacious." [62]

"This," declared Roux, "is not so with diphtheria; the disease is also toxic, but the poisoning follows angina or laryngitis, and we are warned by the presence of false membranes in the throat and larynx before the poison does its work." "If," he stated, "instead of attacking parts readily accessible to examination, and giving rise from the commencement to symptoms difficult to misconstrue, the false membranes develop, for instance in the stomach or in the intestines the disease declares itself by the following signs of diphtheritic poisoning: (1) paleness of the face; (2) albuminuria; and (3) respiratory and cardiac troubles." "It would be too late then," he concluded, "to intervene, and the antitoxine of diphtheria would be found to be a remedy no more certain than that of tetanus." "The fact that diphtheria is firstly a localized affection," he believed, "developing under our observation, should enable us to arm ourselves more effectively against the disease." [63]

(62) Ibid., p. 609.
(63) Ibid., pp. 609-10.

Roux then proceeded to give Behring credit for his work in the field of serum therepeutics. Following this, he stated that he and his colleagues had followed up the work of Behring since 1891 and "Today we can announce that our results confirm essentially those of Behring and his collaborators in the treatment by antitoxin both of animals and of children affected by diphtheria." [64]

In the first section of the paper, Roux outlined the procedure for preparing the toxin. The toxin is utilized to accustom the animals which furnish the antitoxin. Roux stated, "The most rapid process for obtaining the toxin consists in making the culture in a current of moist air. Vessels with flat bottoms and with lateral tubes are used; into these is poured an alkaline bouillon peptonized to 2 per cent, the liquid being spread in a thin layer. After sterilization recent and very virulent diphtheria bacilli are added, and the temperature of the chamber is raised to 37 degrees Centigrade. When the development has fully commenced, in a manner easily imagined, the current of air that passes into the neck of each of the phials is regulated, after bubbling through a wash bottle. After three weeks, or the most a month, the culture is sufficiently strong to use. The completed cultures are filtered

(64) Ibid., p. 610.

through a Chamberland filter, and the clear liquid is kept in well-filled vessels, corked and sheltered from light, at the ordinary temperature. Prepared in that manner, a dose of one-tenth of a cubic centimeter of the toxin generally kills a guinea pig of 500 grams in from forty-eight to sicty hours. It finally loses its activity, but only slowly if properly kept under the conditions mentioned." [65]

The second section of the paper discussed immunization of animals. The horse was the animal used. These immunized horses produced excellent serum. The third section was concerned with the antidiphtheritic serum. This was tested on species of small animals.

The fourth section dealt with the action of the serum on the mucous membranes. Rabbits were used. They were inoculated in the trachea and treated with the serum. They all recovered. In conclusion, Roux asked, "Is the anti-diphtheritic serum capable of staying those forms of diphtheria with complications?" [66] His answer was that it is possible if treatment is begun during the first twelve hours.

The second paper was entitled "Three hundred cases of diphtheria treated with antidiphtheric serum". [67] It had two sections (1) anginas and (2) croups.

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(65) Ibid., pp. 611-612.
(66) Ibid., p. 629.
(67) Ibid., pp. 640-661.

In the discussion of anginas, Roux divided this category into pure anginas and diphtheritic anginas with associations. His discussion of croups was divided into croups--not operated on and croups--operated on.

Roux discussed in the introduction the importance of the work done with the clinical cases of diphtheria. The work was conducted at L'Hôpital des Enfants Malades. The period of experimentation extended from February 1, 1894 to July 24, 1894.

As a control for the experiment, data was obtained form L'Hôpital Trousseau, where there was no serum administered. The total mortality of children administered during the four years before the experiment was a mean of 51.71%. [68]

Results at L'Hôpital des Enfants Malades:

No. of patients	No. of deaths	Mortality rate
448	109	27.2%

Results at L'Hopital Trousseau

520	316	60.0%

"It cannot be said," declared Roux, "that the epidemic during which we experimented was a genign epidemic; but it is desirable to distinguish between angina and croup requiring tracheotomu." [69]

(68) Ibid.
(69) Ibid.

With the serum, the mortality rate for angina decreased from 33.94% to 12.00%. With the serum, the mortality rate for croup--operated on decreased from 73.10% to 49.00%.

Roux deducted the cases of false diphtheria from the number of children treated and arrived at the figures:

No. of patients	No. of deaths	Mortality rate
300	78	26.00%

Roux and his team injected serum daily until the pulse and the temperature returned to normal. During convalescence, some times a urticaria occurred, which was due to the serum. Injections were given subcutaneously. Usually, the disease was curtailed, the appetite quickly returned and there was little loss in body weight when the serum was administered.

The first section of this paper on angina is a discussion of the effect of the serum on (1) general state (2) false membrane (3) glands (4) temperature (5) pulse (6) respiration (7) albuminarai (8) complications and (9) mortality.

The quantity of serum injected varied from 20 to 85 cc. The general state of the children was quickly imporved; symptoms were promptly relieved and the time of the hospital stay was markedly decreased. The false membranes ceased growing in 24 hours after the first injection and detached, generally, after 36 to 48 hours.

The cervical glands are usually engorged but not the cellular tissue. They remain this way for some time. The serum causes a decrease in the temperature after the second or third dose.

After repeated injections of serum, the pulse returns to normal. In most cases use of the serum prevented the necessity of a tracheotomy. The serum definitely diminishes the action of the toxin on the kidneys and therefore diminishes the albuminaria. Diphtheria cases with complications such as measles, broncho-pneumonia, scarlatina, urticaria, or suppuration of the cervical glands were benefited. There was a decrease in mortality in the years 1891 and 1892 from 41.0% to 7.5%.

Roux concluded this discussion with the statement, "Of all that which precedes, we believe that one can conclude that all pure angina diphtheria is curable if it is treated in time by the serum." [70]

Some of the bacteria which associate with the angina diphtheria: (1) the associations with a small cocci, fairly frequent in anginas, that we designate by the name Brisou, because it was provided at first by Mr. Roux and Mr. Yersin, used by Mr. Martin on a child with the name Brisou.

(70) Ibid., p. 650.

(2) the associations with the staphylococci pyogenes;

(3) the associations with the streptococci.

In the discussion on croups, there were two categories; (1) croups--not operated on and (2) croups operated on. About the croups--not operated on, Roux said, "It is not a trifle to speak in particular on the croups not operated on, if they are not those which cure easily with the serum, then, given a sufficient dose, arrest the laryngeal troubles, ordinarily in less than three days. Several of these children have rejected the false memebrane. The average dose of serum used is 35 cc." [71]

Of the croups operated on, there were 121 cases, 56 deceased, with a mortality of 46.00%.

Pierre Paul Émile Roux was born December 17, 1853 at Confolens, Charente, where he spent his boyhood. His father was the principal of his childhood school. He began medical study at Clermont-Ferrand, where he became acquainted with Emile Duclaux. Duclaux, a distinguished chemist, accepted a chair at the Agricultural Institute in Paris. When he went to Paris, Roux went with him.

One afternoon, in 1878, Duclaux introduced Roux to Pasteur. This meeting was the beginning of a lifelong friendship between Roux and Pasteur. In the years following this, Roux

(71) Ibid., p. 653.

and Pasteur communicated a series of papers to the Academy of Sciences. When Pasteur died in 1895, Roux was appointed the assistant director of the Pasteur Institute. In 1904, he took the position which Duclaux had held as director and carried on the tradition of Pasteur.

Roux made contributions to science both directly, and through those whom he inspired. He had the ability to surround himself with brilliant men and he stimulated them to their best efforts. He assisted in the investigations of (1) rabies (2) chicken cholera (3) anthrax (4) Asiatic cholera (5) tuberculosis (6) tetanus and (7) diphtheria.

Roux taught a series of courses in bacteriology in 1889 which, continued, except during the war years; and for which students came to attend from all over the world. It is said that more than 3,000 students came to his classes.[72]

Roux's work on diphtheria, though maybe not his best work, is that which is most widely known. His investigations with Yersin into the nature of diphtheria toxin indicated Behring's work which led to the discovery of antitoxin.[73]

Émile Roux realized the significance of the new discovery and with the assistance of Nocard, Louis Martin and Chaillou, he set out to explore the therapeutic possibilities of the antitoxin. They found that the horse would provide an adequate

(72) "Émile Roux," The Lancet, 1933, Volume II, p. 1125.
(73) Ibid., p. 1125.

supply of antitoxin. From this, they worked out the method of preparation and dosage of the antitoxin.

He acquired fame when he made his communication to the International Congress of Medicine at Budapest, Hungary, in 1894, in which he claimed that the antitoxin had value both as a prophylactic and a remedy. He based his conclusions on the 300 cases which he had observed.

One of the Paris periodicals, Figaro, opened a public subscription, and in a few weeks more than a million francs had been acquired. The funds were utilized fro the preparation and distribution of antitoxin by the Pasteur Institute. The antitoxin, which had previously been limited, due to Roux's efforts now became available to all.

Roux's outstanding work in diphtheria therapeutics led to his triumph in 1894. There were others who made notable contributions in the development of diphtheria therapeutics.

POST-ROUX DIPHTHERIA THERAPEUTICS AND HUMORALISM

The humoral versus cellular doctrine of immunity controversy was settled with the work of Sir Almroth Wright (1861-1947) which he published in 1903. The major proponent for the humoral theory was George Henry Nuttall (1862-1937) who had published his findings in 1888. Nuttall was a graduate in medicine from the University of California at San Francisco. Elie Ilya Metchnikoff (1845-1916) provided the impetus for the cellular doctrine of immunity with a publication in 1884.

The post-Roux period of diphtheria therapeutics covered the period of 1897 to 1931. There were eight major writers on diphtheria in this time period. They were: (1) Paul Ehrlich (1854-1915); (2) Bela Schick (1877-1967); (3) Behring (1854-1917); (4) William Hallock Park (1863-1939); (5) Karl Erhard Kassowitz (1886); (6) Gaston Ramon (1886-1963); (7) Alexander Thomas Glenny (1882-); and (8) James Stirling Anderson (1891-).

Paul Ehrlich improved Behring's diphtheria antitoxin and established an international standard for this and other antitoxins. He published, in 1897, the results of his work.[74] He was a German bacteriologist, born in Silesia, of Jewish parentage. He began early in his career to study aniline dyes. He dis-

(74) Ehrlich, Paul, "Die Wertbestimmung des Diphtherieheilserum," Klin. Jb., 1897, 6, 299-326.

covered in 1907, the dye, known as "trypan red" which, when injected into the blood of animals infected with trypanosomes effectively destroyed the organism. This led to the treatment of veneral disease with chemicals. He created "salvarsan" which cured syphilis.

Bela Schick published an important paper in 1908; [75] another in 1913. [76] He was the inventor of the Schick test for diphtheria, described in 1913. He was born in Boglar, Hungary, in 1877. He was connected with the Children's Department of the University of Vienna from 1902 to 1923. In 1923, he came to New York City to function as Director of the Children's Deaprtment of Mount Sinai Hospital.

He served as army surgeon and as professor at Halle (1894) and Marburg (1895). He and Kitasato showed that immunity against diphtheria and tetanus could be obtained by injecting the serum from an animal which had been injected with the living culture into another animal. Diphtheria antitoxin was marketed in 1892.

William Hallock Park published a paper in 1914. [77] This paper dealt with the production of immunity by treatment with antitoxin. Park's results in the 1914 paper were:

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(75) Schick, Bela, "Kutanreaktion bei Impfung mit Diphtherietoxin," Munch, med. Wschr., 1908, 55, 504-6.

(76) Schick, Bela, "Die Diphtheritoxin - Hautreaktion des Menschen als Vorprobe der prpphylaktischen Diphtherieheilseruminjektion," Munch. med. Wschr., 1913, 60, 2608-10.

(77) Park, Wm. H., "Active immunization in diphtheria and treatment by toxin-antitoxin," J. Amer. Med. Ass., 1914, 63.

"Active immunization produced a very decided increase of antitoxin in a relatively short time in all persons who had natural antitoxin. These, however, were immune to diphtheria before the injections were made. In a series of 700 scarlet fever patients of varying ages tested by us for natural immunity by the Schick reaction, 400 gave a negative reaction. Fifty-seven per cent were, therefore, naturally protected and needed enither active or passive immunization. Less than one quarter of the remaining 43 per cent, which were probably susceptible to diphtheria, reacted to active immunization with mixtures of diphtheria toxin and antitoxin to a degree sufficient to immunize them surely. A large percentage developed a trace of antitoxin which was possibly enough to give a slight protection. [78]

Karl Kassowitz published, in 1924, an article which discussed the "scratch test" -- a cutaneous reaction for determining susceptibility to diphtheria. [79]

Gaston Ramon, in 1928, published results which revealed the efficacy of a modified diphtheria toxin produced by the use of formaldehyde. [80] This modified toxin lost its toxic

(78) Ibid., p. 860.

(79) Kassowitz, Karl E., "Ueber cutane Hautreaktionen mittels Diphtherie-Toxin zum Nachweis der Diphtherie-Immunität, Klin. Wschr., 1924, 1317-8.

(80) Ramon, G., "L'anatoxine diphthérique," Ann. Inst. Pasteur, 1928, 42, 959-1009.

properties while keeping its antigenic virtues. This "anatoxin" superseded the antitoxin as an immunizing agent against diphtheria.

Alexander Glenny, in 1930, published his results which presented an alum-precipitated toxoid for active immunization against diphtheria. [81] In his summary, he said, "The immunity produced by the precipitate, formed by the addition of alum to tetanus and diphtheria toxoids, is greater than that produced by toxoid alone. This increase in certain experimental conditions has reached evan a thousandfold." [82]

James Anderson was the first to distinguish intermediate types C. diphtheriae. [83] He published results on this in 1931. In his summary he stated that there are two kinds of diphtheria bacilli; the B. diphtheriae gravis associated with the severe forms of the disease and the B. diphtheriae mitis associated with milder cases of the disease. [84]

Diphtheria therapeutics reached an advanced stage of development in the nineteenth century. There was a change in the focus from curative to prophylactic measures due to the great efforst of the physicians in France.

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(81) Glenny, Alexander T., "Insoluble precipitates in diphtheria and tetanus immunization," Brit. Med. J., 1930, 2, 244-5.

(82) Ibid., p. 245.

(83) Anderson, J. S., "On the existence of two forms of diphtheria bacillis -- B. diphtheriae gravis and B. diphtheriae mitis," J. Path. Bact., 1931, 34, 667-81.

In America, physicians were also taking an interest in diphtheria therapeutics. Victor Fourgeaud, a former student of Pierre Bretonneau's, was of great assistance to his colleagues in the control of diphtheria in California.

CHAPTER VI

FOURGEAUD AND DIPHTHERIA THERAPEUTICS IN AMERICA IN THE NINETEENTH CENTURY: BRETONNEAU'S INFLUENCE

FOURGEAUD AND DIPHTHERIA THERAPEUTICS IN AMERICA IN THE NINETEENTH CENTURY: BRETONNEAU'S INFLUENCE

Diphtheria therapeutics in America in the nineteenth century was much affected by French physicians and their ideas.

Victor Fourgeaud (1815-1875) is a prime example of this; as he, though attending medical school in America, took three years medical training in France under Pierre Bretonneau. He absorbed much of the teaching of French medicine and therapeutics. When he returned to America to practice -- he transplanted this knowledge.

His most valuable contribution in this regard was to assist fellow practitioners of medicine in attempts at controlling epidemic diphtheria in California, using Bretonneau's practices.

FOURGEAUD'S LIFE AND MEDICAL TRAINING

Victor Fourgeaud was born in Charleston, S.C., obviously of French lineage. The events of his early life are known to us chiefly by inference. [1]

(1) Read, J. Marion, "The Lure of Medical History -- California's First Medical Historian, Victor Jean Fourgeaud, A.B., M.D.," Calif. and West. Med., Vol. 34, Jan. - June, 1931, p. 107. (see Eldredge, Z., The Beginnings of San Francisco, Vol. ii, p. 588, 1912 and Davis, William Heath, Victor Fourgeaud, unpublished biographical sketch in possession of the late Dr. George D. Lyman).

When about ten years old he was taken to France, where he received much of his preliminary education. He returned to South Carolina to study medicine and received the M.D. degree from The Medical College at South Carolina in 1937, when he was twenty-one. He left immediately for France, where he studied for three more years. [2]

When he returned from Paris, in 1841, he practiced successfully in St. Louis, Missouri. While pursuing this endeavor he co-edited the St. Louis Medical and Surgical Journal.[3] St. Louis, then with about fifteen thousand inhabitants, wea the frontier city of the country. Its location on the western edge of civilization and a large French-speaking population were probably the influences which led Fourgeaud to locate there for the practice of his profession. [4]

We know that Fourgeaud achieved a considerable degree of success in the practice of medicine during his seven years' residence in St. Louis, and that his fellow practitioners there came to respect him, as others did later in California. During this period he took unto himself a wife and to the couple, while still living in St. Louis, was born a son. [5]

When Doctor Fourgeaud had been practicing about three years the first issue of the St. Louis Medical and Surgical Journal made

(2) Ibid., pp. 107-108.
(3) Harris, Henry, California's Medical Story, Charles C. Thomas, Pub., Springfield, Illinois, Baltimore, Maryland, 1932, p. 339.
(4) Read, op. cit., p. 108.
(5) Ibid., p. 108.

its appearance bearing the date of April 15, 1843, and under the editorship of M. L. Linton, professor of Medicine in the St. Louis University. The second article in this initial issue was a translation by Fourgeaud from the French of an essay upon "Auscultation During Pregnancy". In a footnote the translator gives a critical review of the opinions then held concerning physiology contined to excite Fourgeaud's curiosity for some years...[6] Dr. Fourgeaud was a coeditor with Dr. Linton and McPheeters for twenty months prior to his departure from St. Louis.[7]

In the August, 1845 issue of the St. Louis Medical and Surgical Journal, Fourgeaud id described as one of the physicians of the St. Louis Hospital. Two of his undertakings are particularly worthy of mention. In March, 1844, he published the first article of a series based upon annual analysis of the mortality statistics in St. Louis. The title was "Mortality Among Children in St. Louis", and his chief concern was the heavy death rate among small children from cholera infantum. Reviewers for the American Journal of the Medical Sciences took cognizance of these articles and published complete abstracts of them upon two occasions.[8] On December 23,

(6) Ibid., p. 108. (see V. J. Fourgeaud, St. Louis Med. and Surg. Journ., Vol. i, p. 10, April, 1843).
(7) Ibid., p. 108.
(8) Ibid., pp. 108-109. (see Fourgeaud, V. J., "Mortality Among Children in St. Louis, St. Louis Med. and Surg. Journ., Vol. i, p. 181, March, 1844).

1845, this rising French physician, then twenty-nine years old, delivered, "An Introductory Lecture on the History of Medicine" before the Medico-Chirurgical Society of St. Louis. [9]

When a malpractice suit was brought against him, Fourgeaud made a written reply in which he described the rigorous tests which had to be passed by a physician. The article was entitled "Medical Responsibility - The Public and the Physician". Disillousioned, disappointed, and deeply perturbed by the malpractice suit, our enthusiastic young physician decided to leave St. Louis. [11]

Upon learning of Fourgeaud'd decision to leave St. Louis, Dr. Linton, his colleague and co-editor, wrote an article which declared that they regretted very much that he was leaving. [12]

And so in April, 1847, he, his wife, his little son, and his brother left St. Louis to head for the frontier of the west. It is recorded that at the first sunset they camped under some oaks twenty miles out from the city. But for the remainder of the six months' trek to California we can follow them only in fancy. [13]

It was General's Sutter's habit to keep a record of events of the fort and one item reads, "October 3-9 arrival of immigrants, Gerke, Fairchild, Fourgeaud, and Beston." [14] On October 20,

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(9) Ibid., p. 109. (see Fourgeaud, V. J., "An Introductory Lecture on the History of Medicine," St. Louis Med. and Surg. Jour., Vol. iv., p. 481, April, 1847).

(10) Ibid., p. 109. (see Fourgeaud, V. J., "Medical Responsibility-The Public and the Physician," St. Louis Med. and Surg. Jour., Vol. iv, p. 289, December, 1846.

(11) Ibid., p. 110.

(12) Ibid., p. 110. (see Editorial, St. Louis Med. and Surg. Jour., Vol. iv, April, 1847.)

(13) Ibid., p. 110.

(14) Ibid., p. 185.

Fourgeaud and his family arrived at Yerba Buena. He lost little time in starting to practice, for in the Californian of November 17, 1847, appears this:

"Medical Notice"

> Dcotor Fourgeaud has the honor to offer his professional services to the citizens of San Francisco and its vicinity. Office at Jones' Hotel. 15

Within a few months he had made a place for himself in the San Francisco area. [16]

He was utilized as a resource person by the community to counteract publications which presented a negative view of California. Some ideas promulgated were: (1) migration to the new territory was a mistake and (2) that California had not sufficient resources to grow enough food for its own necessities. In a reply to these detracting opinions of California, he published in the California Star of April 1, 1848, a six-column article on "The Prospects of California". It was considered of such merit that a courier was at once dispatched to Missouri with 2,000 copies. [17]

It is believed that in 1848, he made the first gold assay which Marshall had acquired while building Sutter's Mill-race on the American River. Naturally, he was seized with the contagious and exciting gold fever that quickly swept the entire country. During that year, he mined in Yuba County. [18]

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(15) Ibid., p. 185.
(16) Harris, Henry, op. cit., p. 340.
(17) Ibid., p. 340.
(18) Ibid., p. 340. (see H. H. Bancroft, History of California, (Pioneer Register) and Dr. G. D. Lyman, Annals of Medical History, 1928, p. 460.

Follwoing this experience, he practiced medicine and conducted business in Sacramento until 1863 - when he returned to San Francisco. He remained in San Francisco, practicing medicine until his death, January 2, 1875. Both in San Francisco and Sacramento, he was recognized as a leader prominent in the then formed medical organizations. [19]

His most important medical work consisted in the recognition of diphtheria which appeared as an epidemic about the San Francisco Bay Region in 1856. [20]

A controversy between Fourgeaud and James Blake and Hubbard arose due to Bourgeaud's ideas on diphtheria and diphtheria therapeutics. Fourgeaud had acquired the ideas he had from Pierre Bretonneau's teaching while in France. He regarded the disease as a specific, local one of the pharynx. The treatment consisted of early diagnosis and cauterization with muriatic acid. Muriatic acid is another name for hydrochloric acid. [21]

In 1856, Fourgeaud published a treatise on diphtheria which was a good resource for physicians attempting to treat diphtheria in California.

Following publication of his treatise on diphtheria, Fourgeaud made extensive publications to periodicals. "In

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(19) Ibid., p. 340.
(20) Ibid., p. 340.
(21) Ibid., p. 340.

the Pacific Medical and Surgical Journal of 1863 and part of 1864, during which period Fourgeaud was editor, he published thirteen papers on the history of medicine. He had begun these while a student in Paris. In a smoothly running, scholarly diction, with something of the stilted classical tendency of its time, the author paraded the philosophic and medical thought of the ancients extended on to the medicine of Christian Europe during the Middle Ages. He discontinued publications in this upon resigning as editor of the journal." [22]

A few quotations from his major work are indicative of his medical writing:

> "Let us lift the veil of long past centuries, and through the obscurity which surrounds the earliest periods of the history of our race endeavor to ascertain the birth of our science. Its origin, says an elegant French writer, may be traced to the cradle of mankind. Medicine was born with pain, therefore with man himself. The feebleness, the nakedness of this pretended king of nature, the instinct of self-preservation, the natural impulse to succor our fellow-creatures,- such were its primary causes. A suffering being--a heart won by piety--behold the first patient and the first physician." 23

A quotation from his work on Galen reads as follows:

> "In the condition of medicine at the period in which Galen appeared, a man endowed with so many advantages, possessing such profound and extensive erudition, would have been of incalculable benefit to the science, if instead of unwisely framing a system based on the erroneous vitalism, solidism, and humoralism of his age, he had declared himself the determined adversary of hypotheses. Nature and study had given Galen all the requisite qualifica-

(22) Harris, op. cit., p. 341.
(23) Ibid., p. 341.

> tions for performance of this service. But with all his great qualities, the physician of Pergamus was deeply imbued with the speculative spirit of his age. Yielding himself to the guidance of imagination, he promulgated as doctrines those wild dreams and vagaries which were destined for so long a period to govern the medical world." 24

Three of his quotations about the Arabians and their contributions to medicine were given:

> "The celebrity of the Arabian School of medicine was greatly enhanced by the contrast it presented with the state of barbarism and superstition which prevailed among contemporaneous nations." 25

The second was written thusly:

> The practice of medicine made but little progress under them, and if we except the descriptions of a few diseases--such as smallpox, rubeola, elephantiasis of the Arabs, etc.--their works composed of compilation from the Greeks, and principally from Aristotle, and Galen, are far inferior to their models." 26

> "The Arabs, he said, "distinguished themselves in two departments of our science--chemistry and pharmacy.' 27

A third quotation is concerned with the Greek or Hippocratic Schools of Medicine and the Medical Schools of Rome, Cordova, Montpelier and Paris:

"The Hippocratic humors, blood, phlegm, yellow and black bile; the different bodies of thought, Dogmatics, Empirics, Methodics, Pneumatics, Eclectics; the changing high-pressure centers of medical activity and instruction, Greece, Alexandria,

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(24) Ibid., p. 341.
(25) Ibid., p. 341.
(26) Ibid., p. 341.
(27) Ibid., p. 341.

Rome, Cordova, Montpelier and Paris -- all in splendid chronological sequence -- are adequately described, and here and there illuminated by well-selected excerpts. Later excavation in Egypt and Mesopotamia, wiht more recent studies of manuscripts and incunabla of monastic Europe, would change, the emphasis rather than alter the thought of this 'zealous pioneer's splendid History of Medicine". 28

Fourgeaud carried this medical history with him from St. Louis to California in 1847. He finally published it sixteen years later in an obscure medical journal.

FOURGEAUD'S TREATISE ON DIPHTHERIA

In the December 6, 1856 publication of Alta California, he expressed his views. In a later brochure entitled "Diphtheria", published in Sacramento in 1858, he reiterated these views. [29]

The complete title of Fourgeaud's work was: [30]

> Diphtheritis: A concise Historical and Critical Essay-on the Late Epidemic Pseudo-Membranous Sore Throat of California, (1856-7), with a few remarks illustrating the diagnosis, pathology and treatment of the Disease; Sacramento: James Anthony and Co., Printers, Union Job Office, 1858.

(28) Ibid., p. 342.
(29) Ibid., p. 340.
(30) Ibid., p. 340.

The essay was divided into three sections: [31]

General Remarks

Symptoms

Treatment

Under General Remarks, he discussed the epidemic which he had observed around the Bay of San Francisco; and the relation of this malady to the diphtheria of Pierre Bretonneau. He gave a brief history of the disease, mentioning Aretaeus.

In the section called Symptoms, he presented a detailed description of the progressive symptoms of diphtheria.

Finally, his recommendations for diphtheria therapy were given in the part of his treatise devoted to Treatment.

GENERAL REMARKS. On page four of the treatise, he started the description of an epidemic which he witnessed with the subtitle; "The Prevailing Epidemic -- Diphtheritis, or Membranous Sore Throat. There seemed to be a great difference of opinion regarding diphtheria; as Fourgeaud wrote: "As much diversity of opinion seems to be entertained in regard to the true character of the malignant sore throat, which has been, and still is, prevailing throughout the country around the Bay of San Francisco, and as I have had a good opportunity for observing it, in its various stages, in the valley of Sonoma, where it has been exceedingly fatal, I deem it a duty

(31) Ibid., p. 340.

to give publicity to my views in relation to it, through the daily press." [32]

He continued "I can do so, I think wihtout impropriety, and without violating the principles of medical ethics, inasmuch as I am not, at present, a practising physician." [33]

He referred to the disease of diphtheritis, stating, "The epidemic which has fallen under my observation is Diphtheritis (from a Greek word signifying membrane) or the Membranous Sore Throat of Bretonneau, a disease which, though not of recent origin, has not been well and distinctly described until a late date." [34]

"Diphtheritis", he related, "is a disease of comparatively rare occurrence, appearing either in the sporadic or the endemic form. It has made its invasion several times, and at long intervals, in different parts of the world." [35]

He gave a brief history of the disease:

> "Aretaeus was the earliest writer on the subject. The disease appeared as an epidemic in Holland, in the year 1337. Three centuries after it reappeared in Spain, and in the year 1618 in Italy. The city of Naples suffered severely from it. Seventeen years after this period the same epidemic raged in Kingston, Canada and was extremely fatal among children. Some years afterwards it made its appearance in England, and in France, and great mortality was produced by it in the school of the Legion d'Honneur, at St. Dennis, near Paris. Dr. Bell (Stokes and Bell's

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(32) Fourgeaud, V. J., Diphtheritis: A Concise Historical and Critical Essay -- on the Late Epidemic Pseudo-Membranous Sore Throat of California, (1856-7) with a few remarks illustrating the diagnosis, pathology, and treatment of the disease; Scaramento, James Anthony and Co., Printers, Union Job Office, 1858, p. 4.

(33) Ibid., p. 4.

(34) Ibid., p. 5.

(35) Ibid., p. 5.

> Practice) mentions having witnessed an epidemic somewhat similar in the United States, from the year 1813 to 1816." 36

He then proceeded to discuss aspects of the disease as he had observed them: "This disease," he said, "which has great analogy with the Putrid Sore Throat that often accompanies Malignant Scarlet Fever, is not however, the same malady; and it is important to make the distinction. It has been observed in countries where not a single case of Scarlatina occurred during the epidemic. I have heard of no cases of Scarlatina in Sonoma during my stay there. Diphtheritis, or Membranous Sore Throat, differs essentially from the Gangrenous Sore Throat attending Scarlatina, of which Fothergill has given a good description. In the pseudo-membranous Sore Throat true gangrene is of uncommon occurrence, attending only the fatal cases, and is seldom present in these. Ulceration of the throat is very rarely observed in this disease. Membranous Sore Throat seldom terminates fatally without the previous attendance of all the symptoms of croup; in Pultaceous Sore Throat, following Scarltatina, Croup is not often an attending symptom. Diphtheritis has also been mistaken for severe cases of croup, which as will be seen, is only a symptom attending the disease when it reaches the larynx. In the formation of the false membrane, however, it

(36) Ibid., p. 5.

has great analogy with the latter; and in its general character, it partakes of many of the most striking symptoms of both croup and Pultaceous Sore Throat of Scarlatina." [37]

In his discussion of the effects of the disease on the brain, he related, "In membranous Sore Throat the brain is remarkably free from all unfavorable symptoms, the patients being generally perfectly conscious until a few hours or even minutes before death. A case has come under my observation where the patient preserved the full and perfect faculties of the brain until within a few minutes before death, notwithstanding the disease had reached its greatest extension in the cavities of the throat, and the whole right side of the face, from the lower part of the neck to the forehead, was affected with an erysipelatous swelling." [38]

His discussion on the effect of diphtheria on boys versus its effect on girls, ended with the conclusion, that girls were most frequently taken with the disease: "The disease may attack persons of all ages, but children of feeble constitution and of lymphatic temperament, are most predisposed to it. Girls are more frequently affected with it than boys. In a family consisting of five girls and two boys, in Sonoma, all living in the same house, and under the same influences, all the girls were taken with it (resulting fatally with four) the boys escaping without the slightest symptoms of the malady.

(37) Ibid., pp. 5-6.
(38) Ibid., p. 6.

When Scarlatina and Diphtheritis appear at the same time in a locality, the patients affected with the first are predisposed to the latter." [39]

He concluded that: "Epidemic Membranous Sore Throat is in some degree contagious. Many well attested cases are cited which seem to leave but little doubt on this score." [40]

There seemed to him to be a predisposition for other maladies of the throat to occur concurrently with diphtheria. He stated, "When the epidemic is at its height I have observed a great tendency to other affections of the throat, which must not be confounded with the disease I am describing. In Sonoma, these affections were exceedingly common, consisting of slight inflammation of the throat, and swelling of the glands, coated tongue, and excited pulse. Attended to early, by the administration of an emetic, followed with small doses of ipecac and calomel, keeping the throat covered with flannel, and the extremities warm, I found them easily subdued." [41]

SYMPTOMS. He described in great detail, the symptoms of diphtheria. "The disease", as he expressed it, "begins in a very insidious manner, by a little engorgement or inflammation of the soft palate, pharynx, and one of the tonsils. (The attack seldom commences on both at the same time, but soon extends to both, if not

(39) Ibid., p. 6.
(40) Ibid., p. 6.
(41) Ibid., p. 6.

arrested.) At this period of the malady the patient complains but little; there is oftne no fever, or it is very moderate. The pain in the throat is much slighter than in the usual forms of common sore throat, so indeed, that the little patients go about playing, as if nothing was the matter. In some exceptional cases, however, the fever and inflammation about the pharynx are considerable from the beginning. The characteristic signs of the affection soon follow this invasion. They consist in small patches of white or yellowish lymph, deposited on the soft palate, the tonsils, and the posterior part of the pharynx. The cervical and submaxillary glands become inflamed and swollen, and the pain in swallowing and in opening the mouth is occasioned more by the engorged state of the glands than by the internal secretion of the lymph." [42]

He continued, "These deposits go on increasing in size, more or less rapidly, and in violent cases, in a few hours the whole cavity of the throat is covered by them. Generally one side is more affected than the other, and upon examination, the glands corresponding with the parts affected will be found more swollen than those of the opposite side." [43]

Further, he observed, "The disease, therefore begins with the inflammation of the mucous membrane of the soft palate, tonsils and pharynx, terminating in the secretion of a false membrane, without ulceration or destruction of true skin." [44]

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(42) Ibid., p. 7.
(43) Ibid., p. 7.
(44) Ibid., pp. 7-8.

"As the local affection goes on progressing." he further stated, "a discharge of matter and blood exudes from the borders of the false membrane, and, mixed with an offensive saliva, flows from the corners of the mouth. A similar discharge is often observed coming from the nostrils, being a sure indication that the disease has made its invasion in the nasal cavities. Bleeding from the nose is then an attending symptom. As the extension of the false membrane progresses, the larynx becomes affected, and all the symptoms and fatal results of croup are observed. At this period of the disease the swelling of the glands is considerable.' [45]

In describing the ejection of the false membrane, he said, "At length, after a period varying from eight to ten days, the false membrane either falls in mass, and is ejected through the mouth, or is separated in fragments, and is discharged by degrees. But it is often reproduced." [46]

Noting the effect of diphtheria on the digestive system, he said: "The appetite is but little affected until the disease has reached its second state. There is no vimiting, nor diarrhea, unless the mucous coat of the stomach and intestines becomes the seat of the disease. The tongue is generally heavily coated." [47]

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(45) Ibid., p. 8.
(46) Ibid., p. 8.
(47) Ibid., p. 8.

Further, he related, "After the period of invasion more or less fever is observed, which, however, when the progress of the affection is arrested, is sometimes totally absent, the pulse becoming regular, and the surface of the skin moist and comfortable long before the false membrane become entirely detached from the surface of the mucous membrane of the throat." [48]

He gave a detailed description of the recovery process; "In favorable cases recovery generally commences before the disease reaches the larynx, trachea, and bronchies; when the false membranes are produced on these parts the patients seldom recover. The portions of the mucous coat, by which the false membranes have been secreted, present a red surface sometimes appearing excoriated, but without any degree of actual excoriation. The swelling of the cervical glands subsides, and at the end of a week or ten days recovery follows. In these favorable cases the duration of the disease, from the date of the invasion to that of the total expulsion of the false membrane, is generally from two to three weeks." [49]

"But," Fourgeaud continued, "when the disease assumes a more serious form, the inflammation and false membranes extend into the air passages, producing hoarseness, aphonia more or less complete, then the harsh, suffocating cough peculiar to croup. The expression

(48) Ibid., p. 8.
(49) Ibid., pp. 8-9.

of the face is extremely anxious, the countenance cadaverous, the skin cold, the pulse feeble and hurried; the face, lips, and extremities become purple, and death closes the scene after a very short period of stupor." [50]

He concluded his discussion of symptoms by describing the pathological findings of Guersant and other physicians in cases of diphtheria:

> "According to Guersant, and other pathologists who have made post mortem examinations in this disease, the morbid appearances observed after death are not always confined to the pharynx, larynx, and trachea, but false membranes are sometimes discovered in the oesophagus, stomach, and intestines. In the latter case vomiting and diarrhea are attending symptoms." 51

TREATMENT. In the section of this essay entitled "Treatment" Fourgeaud advocated local application of caustics to the areas affected. He recommended as did the French the use of acids and caustics:

> "This disease being as we have seen, originally local, confined to the mucous membrane of the soft palate, tonsils, and pharynx, the treatment must be principally local. Some French practitioners must have been so much impressed with this that the treatment they recommend is merely topical. For this, acids and caustics are used. Although sufficient in many cases, I am convinced that by a wise administration of a general treatment the disease is more manageable, and with it many cases which would otherwise prove fatal may be saved. I shall, therefore, say a few words on the general treatment which I have adopted with success, before entering into the details of the more important local applications." 52

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(50) Ibid., p. 9.

(51) Ibid., p. 9. (These gastro-intestinal complications are or rare occurrence. V.J.F.).

(52) Ibid., p. 9.

He believed that emetics were useful in cleansing the stomach during the course of the disease:

> "Whenever there is no contraindication, I have found that early administration of an emetic of great value in cleansing the stomach, throat and tongue, and in creating action on the surface of the skin; and I have repeated it in the course of the malady, when judged necessary. The treatment should be continued by small doses of calomel and ipecac, the latter in barely sufficient doses to create slight moisture on the skin." 53

In his discussion of the use of quinine, he related:

> "At a later period, when the progress of the inflammation has been mastered, I have found quinine, given alone or in combination with the above, of great service. Flannel should be placed around the throat, and the extremities kept warm by hot applications, foot baths, and sinapisms." 54

On various drinks to be administered to the patient he advocated: "During the period of irritation, mucilaginous drinks will be found most serviceable; after the inflammation has been subdued, lemonade and other acid drinks." Blisters, he thought, "should be discarded, as they do more harm than good in this disease." 55

He then discussed the use of hydrochloric acid at length:

> "As I have observed before, the most important and effectual treatment is the local application of acids. Of these, experience shows that hydrochloric acid is attended by the best results. I have used it in the cases that have come under my care, with the most satisfactory result. The acid may be conveyed to the diseased parts by means of a camel's hair pencil, or by a piece of sponge, or linen rag, fastened to a small wooden stick or a piece

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(53) Ibid., pp. 8-9.
(54) Ibid., p. 10.
(55) Ibid., p. 10.

> of whalebone. The strength of the acid must depend upon the age of the child, on the extent of the false membrane, and the rapidity with which the secretion of lymph is developed. I have used, successfully, pure hydrochloric acid twice a day, in the case of a child twelve years old, in which the tonsils, the soft palate, and a considerable portion of the pharynx were covered with the false membrane. It acted at once in arresting the further progress of the affection, by circumscribing it, as it were, in the limits it occupied. From that moment the general symptoms gradually improved. I continued the application of acid, together with the general treatment, which when occupying a considerable portion of the throat, require several days treatment before disappearing entirely. The acid should be pressed or rubbed firmly on the parts affected, so as to insure its contact with the vital parts." 56

He stated that the acid acted principally as a powerful stimulant on the surface of inflammation restoring it to its natural state. He further recommended gargles, emollients and astringents as useful in treating diphtheria.

He concluded this treatise with the recommendation that the patient's room be well ventilated.

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(56) Ibid., p. 10.

OTHER CONTRIBUTORS TO DIPHTHERIA THERAPEUTICS IN AMERICA IN THE NINETEENTH CENTURY

William H. Welch published two articles which dealt principally with the causation of diphtheria. The first was "The Etiology of Diphtheria," published in 1891. [57] Welch's studies of the morphological and biological properties of the Klebs-Loeffler bacillus were in the main, simply confirmatory of the results of other investigators. He, therefore, gave only a brief description of this part of their work, emphasizing only certain points which were not clearly brought out in the publications of previous observers. He did not think that the mere production of pseudomembranous inflammation could be claimed as establishing by itself alone the etiological role of the diphtheria bacillus. Such an inflammation could be produced experimentally in a variety of ways. He attached greater significance to the demonstration of certain peculiar alterations no less characteristic of the specific action of the diphtheritic virus. He was aware of the way in which the diphtheria was produced in the body. He observed that as in human diphtheria so it was in all susceptible animals inoculated with the Loeffler bacillus, there was only a local development of the bacilli at the point of infeciton, and that this had been demonstrated especially by Roux and Yersin and by Brieger and Fraenkel. They had shown that extraordinarily poisonous products formed by

(57) Welch, W., "The Etiology of Diphtheria," Johns Hopk. Hosp. Bull., Balt., 1891, 2, 25-31.

the bacilli were absorbed from the site of local development of the bacilli and gave rise to the constitutional symptoms and the lesions of internal organs.

Welch thought that the knowledge of diphtheria had been greatly increased due to the separation in a state of purity of the toxins of the bacillus and the inoculation of this into animals. The subsequent production of paralysis and other symptoms of diphtheria added to the chain of proof that the causative agent was the Loeffler bacillus.

To Welch, it seemed that every postulate necessary to prove that the specific cause of primary diphtheria was the Klebs-Loeffler bacillus had been fulfilled, and that the bacillus might well be designated Bacillus diphtheriae.

He detailed three points which might have cast doubt on this conclusion; (1) the uncertainty as to what should be called diphtheria, and the possibility that included under this name were various affections which might be due to different causes; (2) the abundance of bacteria present in the diphtheritic membrane; and (3) the problem of bringing positive evidence that the experimental disease was in reality identical with human diphtheria.

He discussed each of these points in turn. He thought the first point had been settled by the labors of many investigators since Loeffler's first publication in 1884. Loeffler's work and that of the following investigators provided the most rigid

proof of the dependence of an infectious disease upon a given microorganism, that is, the constant presence of this organism in the lesions of the disease, the isolation of pure cultures, the reproduction of the disease by inoculation of pure cultures, and similar distribution of the organism in the experimental and in the natural disease.

Welch [58] published a second paper, "The Causation of Diphtheria," in 1891. He thought that it was now established that the Klebs-Loeffler bacillus was constantly present in large numbers in the pseudomembranes of all cases of primary diphtheria, and that no other species of bacteria was constantly to be found in that situation. Further, he explained that the occurrence of a bacillus, with all the properties of the virulent diphtheric bacillus, in persons not affected with diphtheria, was so extremely exceptional that Loeffler, not withstanding years of searching, had been able to find it only once under such circumstances.

He found also, that the Loeffler bacillus could be readily obtained in pure cultivation on artificial media and its properties studied outside of the body. He believed that the sum of these properties sufficed for its positive and ready identification.

Welch attempted to make a distinction between the terms diphtheritis and diphtheria. He defined the term diphtheritis as a word used in an anatomical sense to designate a certain kind

(58) Welch, W., "The Causation of Diphtheria," T. M. and Chir. Fac. Maryland, Balt., 1891, 242-250.

of pseudomembranous inflammation of a mucous membrane which might be produced by a variety of causes. It was not generally recognized, thought Welch, that it was best to limit the use of the word diphtheria to a definite disease and not to an anatomical process, thus making a distinction in the employment of the terms diphtheria and diphtheritis.

It was his contention that there was perhaps, no other disease, with the exception of tuberculosis, upon which greater light had been shed by the discovery of its specific cause than upon diphtheria.

The first of the two articles which Welch [59] published on diphtheria pathology was "The Histological Changes in Experimental Diphtheria," in 1891. The two studies mark the most original and important work of Welch on diphtheria. They extended the knowledge of the pathology of the liver and kidney, principally in rabbits.

The second article by Welch [60] on diphtheria pathology was "The Histological Lesions Produced by the Toxalbumen of Diphtheria," published in 1892. This was a supplement to the 1891 article. He presented his experimental results of injection of the diphtheria toxin into guinea pigs.

Welch [61] made a report for the American Committee on Diphtheria of America to the Eighth International Congress of

(59) Welch. W., "The Histological Changes in Experimental Diphtheria," Johns Hopk. Hosp. Bull., Balt., 1891, 2, 107-110.

(60) Welch. W., "The Histological Lesions Produced by the Toxalbumen of Diphtheria," Johns Hopk. Hosp. Bull., Balt., 1892, 3,17-18.

(61) Welch. W., "Bacteriological Investigations of Diphtheria in the United States," Am. J. M. Sc., Phila., 1894, n.s. 108, 427-461.

Hygiene and Demography which was held in Budapest, Hungary, September 1 to 9, 1894. In this address, he summarized the results obtained by investigators of diphtheria in the United States. He entitled this report, "Bacteriolgoical Investigations of Diphtheria in the United States". The investigatiohs which he reported were made by various persons in New York, Baltimore, Boston, and Philadelphia.

Prudden [62] was the first to study pseudomembranous inflammations in the United States in the modern manner. His first paper was published in 1889. Prudden [63] in April, 1891, published results of twelve cases of diphtheria unassociated with complicating lesions, and found the bacillus of Loeffler in all but one.

Abbott [64] reproted in August, 1891, that under varying conditions the virulence of the true diphtheria bacillus might be observed to fluctuate in the degree of its intensity. At one time possessing the property in a high degree, at another presenting a decided attenuation and not infrequently a complete absence of pathogenic power.

Abbott [65] in October and November of 1891, published results of studies of 53 patients, 9 of whom were suffering from

(62) Prudden, T. M., "On the Etiology of Diphtheria. An Experimental Study," Amer. Jour. of the Medical Sciences, April and May, 1889, 97, 329-350, 450-478.

(63) Prudden, T. M., "Studies on the Etiology of Diphtheria, Second Series," The Medical Record, April 18, 1891, 39, 445-450.

(64) Abbott, A. C., "The Relation of the Pseudo-diphtheritic Bacillus to the Diphtheritic Bacillus," Johns Hopk. Hosp. Bull., Balt., August, 1891, 2, 110-111.

(65) Abbott, A. C., "Further Studies upon the Relation of the Pseudo-diphtheritic Bacillus to the Diphtheritic Bacillus," Johns Hopk. Hosp. Bull., Balt., October, November, 1891, 2, 143-147.

acute pharyngitis, 14 from acute follicular tonsillitis, 8 from ordinary post-nasal catarrh, 2 from simple enlarged tonsils, 15 from chronic laryngitis, 1 from rhinitis, and 2 from an affection of the tonsils and pharynx which rendered a diagnosis without bacteriological aid more or less difficult. He conducted experiments with inoculation of the pseudo-diphtheric bacillus and the new diphtheritic bacillus by culturing them on potato. He drew no real conclusions from this investigation.

Park [66] published investigative results on diphtheria and allied pseudomembranous inflammations in July and August of 1892. He had examined 140 pseudomembranous cases uncomplicated with scarlet fever, in which the clinical diagnosis had been made. He found the Loeffler bacillus in 54 cases (39 per cent). Of the remaining cases, the membrane was confined to the tonsils in 58, and these latter were all mild.

A report on diphtheritic conjunctivitis was published by Woods [67] August 20, 1892. He described four cases of diphtheritic conjunctivitis. He concluded that adequate proof of the diphtheritic conjunctivitis was the presence of the Loeffler bacillus.

The relation of true diphtheria to simple catarrhal anginas was discussed by Koplik [68] in his August 27, 1892 article.

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(66) Park, W. H., "Diphtheria and Allied Pseudomembranous Inflammations. A Clinical and Bacteriological Study," The Medical Record, July 30 and August 6, 1892, 42, 113-122; 42, 141-146.

(67) Woods, H., "Diphtheritic Conjunctivitis: Report of Two Cases, with the Bacteriologic Study of the False Membrane," The Medical News, August 30, 1892, 61, 197-201.

(68) Koplik, H., "Forms of True Diphtheria which Simulate Simple Catarrhal Angina," The New York Medical Journal, August 27, 1892, 56, 225-234.

He had for the past three years directed his attention chiefly to the study of those forms of diphtheria which clinically did not present any of the classical symptoms of the disease. The direct outcome of these studies had been to demonstrate how multiform diphtheria might be, from a clinical standpoint, in its various local manifestations.

Booker [69] in publications in October and November in 1892, reported on pseudo-diphtheritic angian. He had observed, during an epidemic the prior winter, cases of scarlatina complicated with pseudomembranous angina. He observed 23 cases in the scarlatina epidemic. Of these, 16 had scarlatina, 3 had measles, 3 had follicular tonsillitis, and 1 had pseudomembranous angina. He made cultures of the patients' infections.

A new method for culturing diphtheria bacilli was outlined by Johnston [70] in a December 10, 1892 publication. He used Sakaharof's plan with slight modifications. This involved use of hard-boiled eggs as the culture media. One end of the egg was peeled free of shell and the diphtheria exudate was placed on the egg with a plain needle or silver suture wire held in an artery forceps. The egg was then inserted into an ordinary egg-cup, upside down. Eggs and egg-cups were sterilized by boiling.

(69) Booker, W. D., "The Relation of Pseudodiphtheritis Angina to Diphtheria with special reference to Scarlatinal Pseudomembranous Angina," Johns Hopk. Hosp. Bull., October-November, 1892, 3, 109-116.

(70) Johnston, W., "A New Method for the Culture of Diphtheria Bacilli in Hard-Boiled Eggs," The Medical News, December 10, 1892, 61, 659-660.

Park [71] studied diphtheria cultures and cultures of other pseudomembranous inflammations between August 25 and December 25, 1892. He reported his findings February 11, 1893.

In 73 of these cultures the Loeffler bacilli were present, usually associated with streptococci and often with other bacteria. In 31 of these cultures, the Loeffler bacilli were absent; in 26 of these, the streptococci were the most numerous bacteria present. The staphylococcus pyogenes aureus was only irregularly present, and usually in small numbers.

Abbott and Ghirskey [72] observed frequently after inoculation of diphtheria bacilli into the testicles, less frequently after subcutaneous injection, of guinea pigs, small nodules in the omentum composed mostly of polynuclear leucocytes and containing the bacilli in large numbers.

Another April, 1893 paper was presented by Flexner. [73] He had examined two cases of diphtheria in humans in which the smaller bronchi had been invaded by the diphtheria bacillus. Howard [74] had reported a case of acute ulcerative endocarditis without diphtheria. He observed infarctions in the spleen and kidneys, in which, both by cultures and microscopical examination, bacilli indinstinguishable from diphtheria bacilli, but without virulence, were found.

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(71) Park, W. H., "Diphtheria and Other Pseudomembranous Inflammations, A Clinical and Bacteriological Study. Second Paper," The Medical Record, February 11, 1893, 43, 161-168.

(72) Abbott, A. C. and Ghirskey, A. A., "A Contribution to the Pathology of Experimental Diphtheria," Johns Hopk. Hosp. Bull., Balt. April, 1893, 4, 29-31.

(73) Flexner, S., "Diphtheria with Bronchopneumonia," Johns Hopk. Hosp. Bull., Balt., April, 1893, 4, 32.

(74) Howard, W. T., "Acute Ulcerative Endocarditis due to Bacillus diphtheriae," Johns Hopk. Hosp. Bull., Balt., April, 1893, 4, 32-34.

Abbott [75] published a paper May 13, 1893 on membranous rhinitis. He had studied two cases of membranous rhinitis. From these cases he had inoculated guinea pigs with cultures. The guinea pigs did not succumb to the bacilli which he had inoculated and he concluded that the bacilli which failed to kill the guinea pig but had all the other characteristics of diphtheria should be called attenuated or non-virulent bacilli.

Pathology of diphtheria was discussed by Councilman [76] in a November, 1893 publication. He described the lesions in diphtheria and other pseudomembranous inflammations of the throat and the methods used at the Boston City Hospital in distinguishing between the various diseases in which pseudomembranous inflammations of the throat appeared.

One case history was presented in Booker's [77] paper on pseudomembranous inflammation of the larynx and trachea. He published this paper in 1893, which dealt with differentiating between the pseudomembranous larynx affection called inflammatory croup and diphtheria. He concluded that this croup was always due to the diphtheria bacilli or some other infectious disease. He thought also that the diphtheria bacilli could migrate to other parts of the body such as the spleen, liver, lymphatic glands, and the heart.

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(75) Abbott, A. C., "The Etiology of Membranous Rhinitis (Rhinitis Fibrinosa)," The Medical News, May 13, 1893, 62, 505-509.

(76) Councilman, W. T., "The Pathology and Diagnosis of Diphtheria," The Amer. Jour. of the Med. Sciences, November, 1893, 106, 504-552.

(77) Booker, W. D., "As to Etiology of Primary Pseudomembranous Inflammation of the Larynx and Trachea, with Remarks on the Distribution of the Diphtheria Bacilli in Organs of the Body Distant from the Seat of Local Infection," Transactions of the American Pediatric Society, 1893, 5, 24-34.

Results of clinical cases of diphtheria were given in Morse's [78] reports of February 15 and February 22, 1894. He found in 301 cases without scarlet fever admitted to the diphtheria ward of the Boston City Hospital, the Loeffler Bacillus in 217 (72 per cent). The outcome of his study was that 28 per cent of the cases admitted to the diphtheria ward of the Boston City Hospital did not manifest diphtheria bacilli.

Koplik, [79] in a publication dated March 10, 1894, reported that in a series of 39 cases of acute lacnar or follicular inflammation of the tonsils, 12 were proven to contain the Loeffler bacilli in the depths of the tonsillar lacunae. Thus, fully one-third of the cases were diphtheria. This demonstrated how insidious an affection lacunar amygdalitis might be.

Townsend [80] observed in 14 cases of diphtheria, mostly of mild character, occuring in 14 cases of diphtheria, mostly of mild character, occurring in the Children's Hospital in Boston, 7 cases in which the nose was affected. Of the latter, in 5 cases the disease was primarily nasal, the membrane being confined to the nose in 4. These cases of primary and exclusively nasal diphtheria were mild and the Loeffler bacilli was found in all the cases.

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(78) Morse, J. H., "A Bacteriological Study of Four Hundred Cases of Inflammation of the Throat, Occurring Diphtheria and Scarlet Fever. with Especial Reference to Pathogenesis," The Boston Medical and Surgical Journal, February 15 and 22, 1894, 130, 162-165; 130, 182-186.

(79) Koplik, H., "Acute Lacunar Diphtheria of the Tonsils with Studies on the Relation of the Real to Pseudobacillus diphtheriae," The New York Medical Journal, March 10, 1894, 59, 300-305.

(80) Townsend, C. W., "Primary Nasal Diphtheria," The Boston Medical and Surgical Journal, May 24, 1894, 130, 513-516; 130, 520-522.

In 1895, Welch [81] published a paper based on an address which he had given before the Association of American Physicians, in Washington, May 30, 1895. Entitled "The Treatment of Diphtheria by Antitoxin," it presented some of the more important general considerations bearing upon the treatment of diphtheria by antitoxic serum, together with statistics of results already reported.

Incorporated in this paper were four tables which summarized statistics which he gathered related to the use of antitoxin. The first table, "Fatality of Cases of Diphtheria Treated with Antitoxin," contained the results of 82 European workers. It detailed the number of cases treated with antitoxin, the number and percentage of deaths, and the previous fatality in these reports. The total cases was 7166, and deaths amounted to 1239 or 17.3 per cent. These were reports from the years 1894 and 1895.

The second table was headed with the title "Fatality in Operated and Not-operated Cases of Diphtheria Treated with Antitoxin". He had three columns of data: tracheotomy, intubation, and intubation followed by tracheotomy, taken from European papers.

There were 38 reports with 4294 cases. The number of deaths was 784 or 18.3 per cent. The not-operated cases totaled 3127 and

(81) Welch, W., "The Treatment of Diphtheria by Antitoxin," Tr. Ass. A. Physicians, Phila., 1895, 10, 312-384.

the number of deaths in this group was 350 or 11.2 per cent. The operated cases involved 1167 with a fatality of 434 or 37.3 per cent.

The third table was denoted "Ages of Patients Treated with Antitoxin," and presented cases treated and ages of the patients treated for the ages of one year to over fifteen years. There was a total of 1234 cases with 215 deaths and a percentage of 17.4 per cent fatality. The age bracket of two to four years contained the largest number of cases (327) and the age bracket of over-fifteen years contained the least number of cases (24).

Table four was concerned with "Fatality According to the Day of Disease upon which Antitoxin is Injected". It gave the number of cases and the number of fatalities per day. The greatest fatalities seemed to occur on the second day.

Welch said that the natural interpretation of their statistics was that the antitoxin exerted a specific curative power over diphtheria. He based this on over 7000 cases, with at least five-sixths from hospital practice treated with antitoxin. There was an extraordinarily low percentage of deaths for this class of cases with an apparent reduction in fatality of from 50 to 60 per cent by the use of antitoxin.

In another statement, he declared it apparent that antitoxin is most strikingly beneficial in progressive fibrinous diphtheria,

and especially in the prevention and cure of laryngeal diphtheria. In septic diphtheria, he thought the serum treatment of little avail.

The principal conclusion which he drew from this paper was that their investigation of the results of the treatment of seven thousand cases of diphtheria by antitoxin demonstrated beyond all reasonable doubt that anti-diphtheritic serum was a specific curative agent for diphtheria, surpassing in its efficacy all other known methods of treatment for the disease.

A seventh and final publication of Welch's [82] on diphtheria was an address which he had made at the Conference of Health Officers, Baltimore, February 17, 1897. It was called, Clinical and Bacteriological Diagnosis of Diphtheria. Welch took the position that bacteriological diagnosis of diphtheria should not take the place of clinical diagnosis but must be a supplement to it.

He believed that the diphtheria bacillus afforded a positive and practically unfailing means of diagnosis in diphtheria. It was also his contention that it would be of great value to the medical profession to establish bacteriological laboratories in connection with the municipal and state boards of health.

The nineteenth century witnessed the clarification of the etiology, pathology, treatment, and diagnosis of diphtheria.

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(82) Welch. W., "Clinical and Bacteriological Diagnosis of Diphtheria," Maryland M. J., Balt., 1896-7, 36, 392-395.

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