The Harveian Oration

ON THE DOCTRINE OF CONSUMPTION IN HARVEY'S TIME AND TO-DAY.

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(Abstract.)

RATHER more than 300 years ago, in his Lumleian lectures delivered in 1616, William Harvey first made known the results of his experiments on the circulation of the blood, though his complete work was not given to the world until 1628.

In 1656, the year before his own death, Harvey made provision for the annual delivery of an oration to commemorate the benefactors of the College, to exhort the Fellows and Members of the College to search out the secrets of Nature by way of experiment and to continue in mutual love and affection amongst themselves. In his injunction to search out the secrets of Nature by way of experiment, Harvey urges others to follow the practice which, in his hands, had led to such great results. His discovery of the circulation of the blood was founded on experiment and could not have been worked out in any other way. While learned physicians were engaged in subtle metaphysical discussions about disease, Harvey addressed himself to his own experimental work until he felt justified in publishing his revolutionary results.

In his introduction to the treatise on the generation of animals Harvey pours contempt on the exclusive reference in all discussion to the authority of the great men of the past, in these words:

The method of investigating truth commonly pursued at this time therefore is to be held as erroneous and almost foolish, in which so many inquire what others have said, and omit to ask whether the things themselves be actually so or not.

Yet Harvey was no despiser of the ancients, as his numerous references to Aristotle and Galen attest. At the present day there is no fear of undue respect being paid to the old masters; nay, the young lions of the twentieth century are too well satisfied with their own prowess to devote much thought to an ignorant age that knew nothing of vaccines, blood cultures, test meals, blood counts, and other revelations of these latter days.

We may feel sure that had Harvey lived in these days, when not only the Commonwealth of England but the whole world is full of distractions, he would still have found solace in his studies. What Harvey did we may all do according to our several capacities. Those of us who, from one cause or another, are unable to render direct service to the State can yet help to carry on the civil life of the community which is indispensable to the successful conduct of one of the most righteous wars in which our country has ever been engaged.

It is hardly necessary at the present day to insist on the value of experiment in the elucidation of disease, and Harvey's injunction to search out the secrets of Nature by way of experiments has now lost something of its original point. To-day experiment is in the air. And though much of the laboratory work published appears sterile and inconclusive, all additions to the sum of knowledge, however small and indirect, must have their value. In no disease, perhaps, has the beneficent influence of experiment been more strikingly exemplified than in consumption or tuberculosis. Experiment has been the light that lightened our darkness.

The seventeenth century, with its many wonderful achievements in literature, art, and science, marks the beginning of a new era in the study of consumption. Let us then compare the doctrine of consumption in Harvey's time with that of to-day.

In order to comprehend the state of opinion in Harvey's day we must retrace our steps to the time of Hippocrates, to whom we owe the first recorded account of consumption. Hippocrates defines phthisis as suppuration and ulceration of the lung, and includes under the same head empyema, abscess of the lung, and gangrene. He speaks also of *phūpara*, swellings or growths in the lung, as causing phthisis. In Latin editions of his works these are trans-

lated "tubercula," hence, as Waldenburg points out, it has been thought that Hippocrates was acquainted with tubercles. But Virchow, after a critical examination of the passages in which *phūpara* are mentioned, came to the conclusion that these were circumscribed abscesses, and not tubercles in the modern sense. These swellings are attributed by Hippocrates to collections of mucus or bile which suppurate, and are described as occurring also in the tonsils and in other parts. The causes of consumption are pneumonia which fails to resolve in a critical manner, spitting of blood, and suppuration in the pleura. Pituinous secretion dropping down from the head and stagnating in the lung is another cause of suppuration and phthisis.

It is an eloquent testimony to the authority of Hippocrates that these views were adopted wholly or in part by every writer of note for the next two thousand years. Celsus added nothing to the account given by Hippocrates. Aretaeus was the first to distinguish phthisis from empyema, but he makes no mention of *phūpara* or anything resembling tubercles in the lungs. Galen in the main follows Hippocrates. Phthisis is caused by ulceration of the lung. Ulcers of the lung are like ulcers of any other parts, and are due to direct injury, rupture and haemorrhage from strain, and inflammation. Galen speaks of *phūpara* as inflammatory swellings resembling furuncles and buboes.

One of the earliest references to contagion is believed to be found in these words: "It is dangerous to live with consumptives and with those whose foul breath imparts a heavy odour to the rooms in which they lie." Bulloch and Greenwood point out that Aristotle had expressed similar views concerning contagion.

The Arabian physicians closely followed Hippocrates and Galen, and made no further contribution to the subject. Phthisis remained an ulcer of the lung. The position was unchanged until the seventeenth century.

At this eventful period, when anatomical examination of the dead became more general, medical science began to burst its fetters, and a true renaissance of medicine set in. The time which produced Harvey's great work on the circulation witnessed other striking developments of medical knowledge, and this century constitutes one of the great epochs in the study of consumption. Among the writers of this time who dealt with this disease two men stand out pre-eminently—Franciscus Sylvius and Richard Morton.

A glance at the medical works of Sylvius will show how wide was the range of his studies. There were few branches of medicine that he did not touch. Apart from his anatomical work, Sylvius has been chiefly known as the author of a purely chemical theory of disease which had little permanence. Nevertheless these views possess a special interest at the present time, when the importance of physiological and pathological chemistry is fully realized. But in his work on consumption he stands out as one of the pioneers of the seventeenth century, and for this reason alone he would merit imperishable renown. The views of Sylvius on this subject do not appear to have attracted the attention which they deserve.

We see from a study of Sylvius's writings how greatly he was dominated by the influence of Hippocrates. "Phthisis sive ulcus pulmonum" is a phrase he uses more than once. Like all previous writers, he attributes phthisis in most cases to peripneumonia or pleurisy ending in suppuration. But he makes a great advance when he states that tubercles are often seen in the lung in cases of consumption. Still more important is his discovery that tubercles soften and suppurate to form vomicae. In his view, tubercles were nothing more than enlarged glands, which he supposed to exist in the lungs and other parts of the body, the enlargement being due to accumulation of viscid humours or secretions in these glands. The origin of the humours is referred to many causes, acting for the most part through the blood, especially to excess of various secretions such as bile, pancreatic juice, or saliva, also to changes in the thyroid secretion, which, as he supposed, found its way into the trachea.

In his conjectures concerning glands which in the natural state are so small as to be invisible, but when diseased become enlarged and are then seen scattered throughout the viscera and tissues of the body, it is not improbable that he is describing cases of generalized miliary tuberculosis. The assumed glandular origin of tubercles in the lungs suggested a relation to scrofula or

struma in which external glands were enlarged. The action of heredity is exerted through these glandular tubercles.

Varying conditions of humours, or, as we should say, secretions, at different ages are credited with powerful predisposing influence in the causation of phthisis. May there not be some truth in this? The varying activity and mutual relations of internal secretions, about which as yet we possess little accurate knowledge, have profound effects on the human organism, and who shall say that susceptibility to tuberculosis is not in some degree connected with these influences? The phthisical constitution or disposition is also attributed to changes in the humours or secretions of the body.

It seems, then, from the many-sided activities of Sylvius and from his important work on consumption, that Baker is justified in describing him as one of the great original thinkers of the seventeenth century, of the period that produced Harvey, Descartes, Leibnitz, and Malpighi.

Richard Morton was the author of two works, *Puretologia* and *Phthisiologia*, of which the latter alone concerns us now. He defines a consumption of the lungs as

an universal wasting of the parts of the body, caused by some distemper of the lungs, as a stuffing, swelling, inflammation and ex-ulceration of them, and thereupon it is attended with a cough, difficulty of breathing, and other symptoms of the breast, and accompanied with a fever, which at first is slow and hectic, afterwards inflammatory, and at last putrid and intermitting.

Morton clearly states his opinion that the formation of tubercles constitutes the first stage in the phthisical process. His belief in the great prevalence of tubercle and in the frequency with which spontaneous healing takes place has received striking confirmation in recent times. Morton distinguishes a special scrofulous variety of consumption in which

the blood by reason of its preternatural acrimony being, as it were coagulated, and so unable perfectly to unite the new Chyle to itself and the solid parts, is wont to throw it in a larger quantity than is convenient upon the glandulous parts . . . and what happens in other glandulous parts happens also in the lungs themselves, which are everywhere full of innumerable glandules, but of some more conspicuous ones, upon the windpipe and the branches of it, though in their natural state they are not so easily discerned: so that 'tis no wonder if those that have the King's Evil, who are frequently subject to glandulous swellings in other parts, are likewise many times affected with such kind of tubercles even in the lungs themselves.

But whether conscious or unconscious of a certain ambiguity in his description of this variety of the disease, he adds that the most certain diagnostic sign of this form "is to be taken from glandulous swellings in the external habit of the body accompanying of it, or at least preceding it." Morton says that this variety of phthisis was the commonest in his experience and furnished most cases of recovery.

In estimating the value of Morton's work we must consider his relation to Sylvius, although he makes no reference to the writings of the latter. The *Opera Medica* of Sylvius were published ten years before the appearance of Morton's *Phthisiologia*, and it is unlikely that Morton was unacquainted with the older work, as the reputation and authority of Sylvius were then so great. Morton adopts Sylvius's view of the glandular origin of tubercles in the most thoroughgoing fashion, and follows him in other points. Sylvius, as we have seen, was far in advance of all previous authors in asserting that tubercles were often found in the lungs of consumptive persons, and in attributing the formation of vomicae to the softening and suppuration of tubercles. Morton went still further and maintained that tubercles were found in the lungs in all cases of consumption, whatever its origin might be. But in the seventeenth century the word tubercle was used in the etymological sense and as yet possessed no specific pathological significance. Both Sylvius and Morton insisted upon the contagious nature of this disease, a view which had long prevailed and seems to have been held by Galen and Aristotle.

Thomas Willis deals very briefly with the subject, but he makes the important observation that the general belief that phthisis is a pining away of the whole body arising from an ulcer in the lung is untrue. In proof of this statement he says that he had opened the dead bodies of

men that had died of this disease, in whom the lungs were free from any ulcer, and yet they were set about with tubercles or stones or sandy matter throughout. "Wherefore phthisis is better defined as a withering away of the whole body, arising from an ill formation of the lungs." Waldenburg thinks that Willis may have intended to describe miliary tubercles by the term "sandy material."

Sydenham added nothing fresh to our knowledge of consumption, but he recommended daily riding on horseback as the principal assistant in the cure of this disease.

Bonetus, a contemporary of Sylvius and Willis, in his *Sepulchretum*, gives records of 150 necropsies of consumption from his own experience and from that of others. He regards phthisis as due to many different causes—ulcer of the lung, abscesses, scirrhus tumours, tubercles, vomicae. He speaks of tubercles as *tubercula glandulosa*, following Sylvius. Vomicae are closed collections of pus which resemble ordinary abscesses, but may be formed from tubercles. He seems to have described miliary tubercles in the following passage: "*Pulmonum parenchyma . . . duriusculum erat et multis quasi granulis instar steatomatum quae aliquid sebacei continebant, refertum.*"

Mangetus, who edited the *Sepulchretum* of Bonetus in 1700, added some further cases of phthisis, among which are included instances of generalized miliary tuberculosis; one case is summed up thus: "*Grandines pulmonum aliorumque partium cum phthisi.*"

Morgagni was so convinced of the contagious nature of consumption that he carefully avoided the dissection of those dead of this complaint. The cases which he describes in his great work *De Sedibus et Causis Morborum* seem to have been drawn from the records of his teacher Valsalva, who held similar views about contagion. Valsalva made the important observation that in all the cases he had dissected the ulcers and disease were in the upper part of the lungs. Morgagni considered that phthisis may be the result of the suppuration of tubercles, but he recognized other causes, and he accepted Morton's opinion concerning the connexion between scrofula and consumption.

Pierre Desault, a physician of Bordeaux, published his views on phthisis in 1733, four years before his death. In this work, which has great merit, he expresses himself very clearly. The causes of phthisis are divided into conjoint and antecedent. The conjoint cause is that whose presence sets up the disease and whose destruction leads to a cure. This cause he refers to as tubercles and concretions found in the substance of the lung and scattered through the different lobes. These concretions resemble hailstones and are of different sizes. From this description it is probable that Desault was acquainted with miliary tubercles.

All previous writers, both ancient and modern, with the exception of Willis, were agreed that the cause of phthisis is an ulcer of the lung. Desault rejects this view, relying on the results of his own experience.

Post-mortem examination of certain cases of phthisis which presented characteristic symptoms during life revealed a complete absence of ulceration, though the lungs were stuffed with tubercles. Phthisis is due to tubercles, ulceration of the lung is a secondary process. The symptoms of the disease precede the occurrence of ulceration and are therefore not due to ulceration, but to tubercles. He compares phthisis with scrofula (*écrouelles*), both of them chronic diseases. Phthisis begins with tubercles or tumours in the lung, scrofula with tumours in the neck. In both cases the tubercles or tumours become inflamed and suppurate. Suppuration of scrofulous tumours leads to the formation of ulcers which are slow to heal and can only be cured by destroying the tumours and the cause which produces them. The same is true of ulcers in the lungs resulting from the suppuration of tubercles. Both diseases in the stage of suppuration are contagious.

Desault believed that the contagion in this case, as in venereal disease, depends on the presence of worms. If we substitute micro-organisms for worms, there would be little to add even now to this statement, and in any case we may fairly credit Desault with a true prophetic instinct. The doctrine of "Phthisis ab Haemoptoe" advocated by Morton and nearly all previous authors is rejected by Desault, who says that this chapter in Morton's book should be headed "Haemoptoe a Phthisi," for haemorrhage is the result, not the cause of phthisis.

Young people between the age of 18 and 35 are most liable to be attacked by phthisis, as Hippocrates pointed out, but other ages are by no means exempt, for one meets with the disease in

persons at ages below and above these limits, though less frequently. The subjects of phthisis for the most part are:

1. Those with contracted alar chests.
2. Those with a phthisical parentage and hereditary disposition.
3. Those exposed to contagion (in which Desault is a firm believer). "Those who live with phthisical patients and wait on them may take the disease, though there be no hereditary disposition, for it is contagious. Thus wives who wait upon their phthisical husbands often contract the disease, and husbands who wait on their phthisical wives."

Desault was an enthusiastic supporter of the treatment of phthisis by horse exercise recommended by Sydenham, and he gives instances of the good results obtained by this means.

Cullen did not make much advance on the views of Sylvius and Morton. Tubercle is the commonest of many causes of consumption. The lung may contain tubercles without any symptoms for a time, but finally the tubercles suppurate and lead to phthisis. Tubercles are small swellings resembling indurated glands. Phthisis is common in persons of scrofulous parentage. Cullen assumes the existence of a disposition to the disease in certain individuals. Some cases that cough up calcareous matter, with or without blood, recover, others die. Asthma frequently terminates in consumption. Cullen did not favour the contagious origin of the disease.

William Stark, who died at the early age of 29, deserves special mention for his excellent work on the morbid anatomy of phthisis. His *Clinical and Anatomical Observations* were not published till 1788, eighteen years after his death. Tubercle is described as follows:

In the cellular substance of the lungs are found roundish firm bodies, named tubercles, of different sizes, from the smallest granule to about half an inch in diameter; the latter often in clusters. The tubercles of a small size are always solid, even those of a large size are frequently so; they are of a whitish colour and of a consistence approaching nearly to the hardness of cartilage; when cut through the surface appears smooth, shining, and uniform. No vesicles, cells, or vessels are to be seen in them, even when examined with a microscope, after injecting the pulmonary artery and vein.

This description shows that he was familiar with miliary tubercles though he does not use that term. He then traces the development of vomicae from tubercles and their communication with the air passages. Near the larger cavities the pulmonary vessels are suddenly contracted and the bronchi are thickened. The upper and posterior parts of the lung are first and most affected. Stark gives what I believe is the first account of an aneurysm of the pulmonary artery, measuring 1 in. by $\frac{1}{2}$ in., opening into a vomica in the lung with a slit on one side of it. The patient died of haemoptysis.

Matthew Baillie, at the end of the eighteenth century, gave an admirable description of tubercles in the lungs to which little has been subsequently added. He believed that tubercles arise in the cellular tissue of the lungs, and are not glandular in origin, as no glands exist in the lungs, "and on the inside of branches of the trachea, when there are follicles, tubercles have never been seen."

Tubercles are at first very small, being not larger than the heads of very small pins, and in this case are frequently accumulated in small clusters. The smaller tubercles of a cluster probably grow together and form one larger tubercle. The most ordinary size of tubercles is about that of a garden pea, but they are subject in this respect to much variety. They adhere closely to the substance of the lungs, have no peculiar covering or capsule, and have little or no vascularity. When cut into, they are found to consist of a white, smooth substance, possessing a firm texture, and they often contain in parts a thick curdy pus. In cutting into the substance of the lungs a number of abscesses is sometimes found, from tubercles of a considerable size having advanced to a state of suppuration. In the interstices between these tubercles the lungs are frequently of a solid texture, from the cells being in a great measure obliterated. The texture of the lungs on many occasions, however, round the boundaries of an abscess, is perfectly natural. . . . When tubercles are converted into abscesses, phthisis pulmonalis is produced, one of the most destructive diseases in this island.

Baillie described tubercles in other organs, but he did not offer any explanation concerning their relation to similar disease of the lung.

The great work of Bayle, in the early part of the last century, marks the commencement of a new era in the conception of phthisis. He divided the disease into several classes—tuberculous, granular, ulcerative, melanotic, calcareous and cancerous; of these the tuberculous is the most

common. This artificial classification, including tuberculous and non-tuberculous affections, did not long survive. Bayle's description of tubercles does not differ in essentials from that given by Baillie. The smallest tubercles he calls miliary. These are opaque or yellowish, and tend to suppurate and break down to form an ulcer.

Bayle's criterion of tubercle was an opaque or cheesy substance. Tubercle may be encysted on non-encysted, nodular or diffused. What Baillie called scrofulous matter Bayle called tuberculous. Like Baillie, he assumed a close connexion between scrofula and tubercle. In addition to tubercles, certain transparent hard miliary nodules were described in the lungs; these, which he called miliary granulations, were distinguished from miliary tubercles by the fact that they never became opaque or cheesy. From their hardness and translucency Bayle regarded them as of the nature of cartilage. The simultaneous appearance of tubercles in various organs of the body convinced him that the explanation was to be found in a common cause, and he attributed this dissemination to a tendency to the production of tubercles, a tuberculous diathesis or disposition. This diathesis was the common cause of tuberculous phthisis, which is a general disease, and for this condition the term tuberculosis was first employed by Bayle. The conception of a tuberculous diathesis had a profound influence on contemporary thought, and for fifty years after Bayle's death its effects could still be traced in medical literature. It needed the touch of genius to dispel the mists that obscured the relations of phthisis to tubercle, and this was supplied by Laënnec's masterly treatment of the whole subject. Laënnec proclaimed the doctrine of the unity of phthisis. All phthisis is tuberculous.

Tuberculous matter may be developed in the lungs and other organs under two principal forms: that of isolated bodies and that of infiltrations. Whatever be the form under which the tuberculous matter is developed, it presents at first the appearance of a grey and semi-transparent substance, which becomes by degrees yellow, opaque, and very dense. It then softens, gradually acquires a liquidity about equal to that of pus, and, being expelled through the bronchi, it leaves in its place cavities commonly known as ulcers of the lung, and which I shall designate by the name of tuberculous excavations.

He then describes miliary tubercles and Bayle's granulations and shows that transitional forms connect the two, proving that the latter are only an early stage of the former.

There is no other difference between them than that which exists between the green fruit and the ripe. All cheesy matter is tuberculous, even that which is sometimes seen in cancerous growths. Inflammation plays no part in the production of tubercles, which may develop in any organ of the body, and are to be regarded as new formations. Scrofulous glands are tuberculous. Haemoptysis is never the cause of phthisis, but is always the result of disease already established. Tubercle, wherever situated, is connected with a certain disposition, but "the real cause, like that of all diseases, is probably out of our reach."

These views met with strong opposition on the part of some of Laënnec's own countrymen. Thus Broussais, accepting the tuberculous nature of phthisis, regarded tubercle as the result of irritation and inflammation of the lung, pleura, or bronchi, reverting to the standpoint of the seventeenth century, when the Hippocratic tradition still largely prevailed.

Andral took up a somewhat different position. While he embraced the idea of a tuberculous diathesis, he denied that tubercle is a new formation. According to his conception, caseous or tuberculous material represented inspissated secretion in the small bronchi and lung, which gradually becomes more compact and ultimately suppurates. The common causes of phthisis are pneumonia, pleurisy, catarrh, or haemoptysis, occurring in persons with a tuberculous diathesis. He supported Bayle's view that miliary granulations are distinct from miliary tubercles, and considered that they represented discrete areas of alveolar inflammation.

Louis, by his elaborate pathological and clinical observations, gave strong support to Laënnec's views. Rokitansky put forward a theory of a tuberculous crasis, dyscrasia, or blood change depending on a hyperinosis. He regarded scrofula and tuberculosis as identical. In England Laënnec's doctrine in the main was generally adopted.

Until nearly the middle of last century pathological

views were based almost entirely on naked-eye observations. But about this time the microscope began to be employed with important results, and numerous observations were made on the histology of tubercle. Lebert described certain small cells or tubercle corpuscles which were pathognomonic of tuberculous material. Reinhardt disputed the specificity of these cells and showed that similar appearances may be presented by pus corpuscles. William Addison regarded tubercle as consisting of epithelial cells derived from the white corpuscles of the blood.

Virchow, in his great work, *Die Krankhaften Geschwulste*, essayed to revolutionize the whole doctrine of tuberculosis:

Miliary tubercle is the only criterion of what is tuberculous. Caseation, though a common change in tubercles, is not a specific process; it may occur in new growths and is often the result of inspissated pus. This transformation is a necrobiosis and is allied to other forms of degeneration. In pulmonary phthisis inflammation is the chief factor and may terminate in caseation. . . . Tubercle plays a subordinate part. The cells of tubercle resemble the cells of a lymphatic gland. Tubercle is a heteroplastic lymphoma, its seat is the connective tissues of the body. Scrofula is not a specific disease, but a manifestation of a general vulnerability of tissue and proclivity to disease. Heredity is recognized as a potent factor. What is inherited is a certain disposition or vulnerability, not the disease itself.

Niemeyer applied Virchow's views in their most extreme form to the clinical history of phthisis, which he divided into two groups—miliary tuberculosis and chronic caseous pneumonia.

Any form of pneumonia may terminate in phthisis, but in most cases it is a chronic catarrhal pneumonia which leads to caseation and excavation. Haemoptysis may set up a caseating pneumonia and is a common cause of phthisis. Miliary tuberculosis is seldom a primary affection of the lung, but is generally secondary to ulcerative pneumonia or to a caseous lymphatic gland. Phthisis is not a specific disease and is not hereditary. A congenital vulnerability and a tendency to a luxuriant growth of cells are the distinguishing marks of this disease, and in this sense there is a connexion between phthisis and scrofula.

This profession of faith, supported by the great authority of Virchow, found much favour in Germany. But in France and England the great majority of physicians held firmly to Laënnec's doctrine of the unity of phthisis.

In 1857, when discussions about tubercle were still chiefly concerned with histological details, Buhl came forward with the important statement that generalized miliary tuberculosis is the expression of an infection of the blood originating in a caseous focus situated in a lymphatic gland, in the lung, or in some other part of the body. This was the first attempt to explain tuberculosis on the basis of infection, and constitutes a landmark in the inquiry.

Seven years later Villemin made known the results of his memorable researches on the experimental production of tuberculosis in animals. Rabbits and guinea-pigs inoculated with miliary tubercle, caseous matter or phthisical sputum, invariably developed tuberculous lesions in the serous membranes, lungs, and other organs. In certain animals, such as dogs, cats, and sheep, inoculation was unsuccessful. Control inoculations with other material, such as cancer or anthrax, invariably failed to produce tuberculosis.

Villemin concluded from his experiments that tuberculosis is a specific inoculable disease, and he compared it with virulent maladies like small-pox, syphilis, and glanders. These conclusions were disputed at first on the ground that tuberculous lesions could be produced experimentally by the injection of non-tuberculous material. But, after much controversy, the truth of Villemin's views was universally acknowledged.

In 1867 William Budd, basing his opinion on geographical and epidemiological considerations, enunciated the view that phthisis is a zymotic disease like typhoid fever, and that its propagation is determined by infection. But all doubts as to the infective nature of tuberculosis were removed by Koch's famous announcement in 1882 of his discovery of the tubercle bacillus. The facts concerning Koch's brilliant research, and the overwhelming proofs adduced by him in support of his conclusions are too well known to need recapitulation here. But we may pause a moment to pay homage to the genius of Laënnec, who conceived the doctrine of the unity of phthisis; to Villemin, who supplied the first experimental evidence of the truth of this view, and to Koch, who isolated the infective

micro-organism, cultivated it outside the human body, and demonstrated its pathogenic action on the lower animals.

Koch's discovery having furnished the most complete confirmation of Laënnec's doctrine, non-tuberculous caseous pneumonia, which had long figured prominently in German writings, was now given a decent burial. Many elaborate and artificial classifications of phthisis shared the same fate. The old terms "consumption" and "phthisis" began to pass out of use, and "tuberculosis"—a term which we owe to Bayle—was generally adopted. Some of Koch's most enthusiastic supporters were at first prepared to explain everything in the natural history of the disease by infection with the tubercle bacillus, and to throw all ideas of heredity and disposition to the winds. The temperate and judicial statements of Koch himself are in striking contrast with the attitude of these extremists.

In his monograph, *The Etiology of Tuberculosis*, published in 1884, Koch admits that "although a good many of the phenomena classed together under the head of 'predisposition' may be referred to simple and easily explained conditions, some facts still remain difficult or impossible to interpret, compelling us for the present to accept the view of a varying liability." He further agrees that tuberculosis is hereditary in the sense that a predisposition is inherited. Careful statistical investigations by Pearson supply strong confirmation of the existence of an hereditary disposition. This question has been very ably discussed by Bulloch and Greenwood, who concluded that "the many workers who have dealt with the problem of inheritance and infection during the last few years have failed to achieve any real solid advance from the classical position."

In Koch's opinion the main, if not the only, source of pulmonary tuberculosis is the dried sputum of tuberculous patients, which reaches the lungs through the air passages. Villemin had expressed similar views. The aërogenic origin of the disease has been disputed, but the rival view which regards pulmonary tuberculosis as enterogenic has received less support than the former.

The relation of human to bovine tuberculosis had engaged the attention of Villemin, who concluded that the two diseases were different. But Klebs and later workers, including at first Koch himself, regarded them as identical. This was the prevailing view, though doubts were expressed by individual writers, until 1900, when Koch made the startling announcement that further experiments had convinced him that human and bovine tuberculosis are distinct diseases, and that pulmonary tuberculosis is invariably due to infection by bacilli of human origin.

In spite of numerous researches on the alleged morphological and cultural differences exhibited by tubercle bacilli of the human and bovine type, no general agreement has been reached. But that there is a difference in the pathogenic effects on animals there seems to be no doubt. Inoculation of bovine bacilli is followed by an acute general tuberculosis, whereas when human bacilli are employed the effects are limited to a local tuberculosis at the site of inoculation, or to a comparatively mild and chronic form of infection. In 1903 Behring proclaimed the opinion that infection of infants by the milk of tuberculous cows is the chief source of pulmonary tuberculosis. Further investigation, however, has confirmed the truth of Koch's view that pulmonary tuberculosis is invariably due to infection with tubercle bacilli of the human type. This question has been fully discussed by Bulloch in his Horace Dobell lecture delivered before the College in 1911.

Records of autopsies at hospitals show that in a large percentage of all dead bodies—70 to 90 per cent.—arrested tuberculous lesions are found in the lungs or other organs. It is clear, therefore, that the number of persons that recover from the infection greatly exceeds the number of those that succumb. Man is evidently more resistant to tuberculosis than the ordinary laboratory animals, though less so than animals like the cat, dog, sheep, horse, and ass. Koch has pointed out that in the human subject a temporary immunity is often manifested, periods of partial or apparently complete recovery alternating with phases of active infection.

There seem then to be intermediate grades of immunity in man contrasting with the complete immunity of certain animals. By analogy we may infer that these different grades of immunity in man and the lower animals depend on defensive arrangements which are similar in kind and

vary only in degree. We can hardly doubt that the explanation of these differences is to be found in biochemical variations at present imperfectly understood.

Hereditary disposition may be explained on similar lines. These considerations illustrate the importance of the part played by the soil in which the germ of tuberculosis is planted. This fact had not escaped the acute observation of Villemin, who insisted on the interdependence of two factors in tuberculosis—the virus and the "*milieu organique*."

A further study of the soil or "*milieu organique*" is the most pressing need for the better understanding of the pathology of tuberculous infection. This inquiry is intimately connected with the explanation of immunity, a subject bristling with difficulties. In recent controversies concerning the relative importance of phagocytosis and chemical action of the body fluids we seem to witness a renewal of the old contest between the cellular and humoral pathologists. But in spite of the immense amount of research devoted to the study of immunity no general conclusion has yet been reached. This need not surprise us in view of the complexity of the problems involved.

When the infectious nature of the disease had been finally established by Koch, great results were anticipated from the application of this knowledge to the prevention of tuberculosis. But, so far, the results have been disappointing.

The death-rate from phthisis had been steadily falling for a number of years before the discovery of the tubercle bacillus, and no accelerated reduction has taken place in recent years. Furthermore, since the Great War began in 1914, there has been a steady rise in the phthisis death-rate, the causes of which have yet to be worked out. A recent paper by Brownlee on the epidemiology of phthisis pulmonalis, based on statistical tables of the death-rates at different ages in different districts, raises points of great interest. His conclusion is that there are at least two types of phthisis: one especially affecting young adults, and one middle age. The type affecting middle age seems to have been the chief type in London for more than 200 years. Sydenham's statement that the usual age at which death from phthisis occurs is between 15 and 30 is taken directly from Hippocrates.

When Morton, who gives the actual ages of phthisis deaths, is consulted, it is found that a very large proportion of cases are over the age of 30. Further, investigation has shown that the young adult type, which is the prevailing one in Ireland and Shetland, spreads independently of environment, being as common in the more healthy parts of a district as in the unhealthy, while the amount of middle age phthisis is correlated to the unhealthiness of a district.

The explanation suggested is that phthisis is not one disease, but a mixture of at least two allied diseases, an explanation to which the recent discoveries regarding typhoid fever furnish an analogy. In one form of phthisis the chief death-rate occurs between the ages of 20 and 30 years, in a second form the maximum death-rate occurs between the ages of 45 and 50 years. This hypothesis does not, in the present form, explain the occurrence of phthisis at high ages observed in Wales and Cornwall. It is possible that the senile form is due to the same organisms as that which causes the young adult type. It is well known clinically that many persons develop phthisical lesions in their youth which apparently heal, while later in life a recurrence of the disease or a new infection leads quickly to a fatal issue. No district by itself gave any clue to the meaning of the phenomenon of phthisis at the later age observed in Wales and Cornwall. Light on this type was obtained from the statistics showing the susceptibility to phthisis in different occupations. It was found from these data that a very marked susceptibility to phthisis at later ages was shown by coal miners, though the total amount of phthisis occurring among them was very small.

A study of the phthisis death-rate in England generally during the last sixty years shows a great reduction at all ages. This is most marked at the age period 20 to 25 years. At the middle and later ages the fall has not been nearly so marked. The result has been to raise the mean age at which death from phthisis occurs. No completely satisfactory explanation of this fact is possible at present. The figures available suggest that an epidemic of "young adult" phthisis culminated about the middle of last

century, since which date that form of the disease has markedly diminished. It is to be hoped that further investigations on these lines will enable Brownlee to clear up some of the questions raised in his valuable paper.

If we look back and review the progress of knowledge we see how Laënnec's great generalization was foreshadowed by the work of Richard Morton. For Morton was the first to point out that consumption is in all cases associated with the presence of tubercles in the lungs. Thomas Willis had previously broken away from the Hippocratic tradition that phthisis and ulceration of the lung are convertible terms.

Sylvius, their great contemporary, whose influence must have powerfully affected both Willis and Morton, had not taken up such a definite position himself, though, as already shown, he had made important contributions to the pathology of consumption. His views on the fluctuating activity of the humours or secretions of the body, and their relation to consumption, find their counterpart, at the present time, in the temporary immunity which Koch discerns in the course of many cases of tuberculosis. The mutual relations of the different humours or secretions advocated by Sylvius, and the modern development of the doctrine of the endocrine glands, provide another illustration of the well known fact that no great discovery is made without some previous preparatory work. Again, though the conception of tuberculosis as an infection first took definite shape in consequence of the experimental work of Villemin, we know that a belief in the contagiousness of consumption can be traced back as far as the time of Galen and Aristotle.

Let us not forget the debt we owe to the ancients. "Vixere fortes ante Agamemnona multi." How true was Elijah's outburst—"I am not better than my fathers."

THE ADVANTAGES OF INTRAMUSCULAR INJECTIONS OF SOLUBLE CINCHONINE SALTS IN SEVERE MALARIAL INFECTIONS.

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MEDICAL MEN practising in highly malarious countries find that severe plasmodial infections constitute an important cause of death, but one which is entirely preventable by early recognition and active treatment. In the most severe infections quinine by the mouth may be powerless to avert a fatal issue, as in cases reported by me last year in this JOURNAL¹ in a paper on the suitability of soluble salts of quinine and cinchonine for intravenous injection. I have for long advocated the prompt intravenous injection of soluble quinine salts in such dangerous cases, and in the paper referred to I advised the acid hydrobromide as the least toxic salt for this purpose. Captain R. Knowles, I.M.S., has since confirmed my conclusions, and reported prompt and favourable results from its use in the severe and dangerous bilious remittent malaria met with in Assam, in some of which quinine by the mouth could not be retained, and the patients' lives were in danger.²

The disadvantages of the intravenous method, especially in tropical countries with few highly trained medical men, are, first, that many doctors are insufficiently acquainted with the simple technique of giving intravenous injections, so the measure is liable to be postponed until too late; and secondly, unless the injections are given very slowly, it is possible to cause sudden death of the patient by the full doses of 10 to 15 grains of the drug required in the severe infections under consideration. The latter danger can be averted by injecting very slowly, or by dividing the dose into two equal parts with an hour or more between the two injections.

In my former paper I pointed out that cinchonine bi-hydrochloride and cinchonine acid hydrobromide intravenously in rabbits are very slightly less toxic than the corresponding quinine salts, while they are even more soluble than the latter, and I suggested that they would be worth trying intravenously in malaria. MacGilchrist³ found that the sulphate of cinchonine orally was slightly more efficient in malaria than the sulphate of quinine, but