An Address ON THE PATHOGENESIS OF ACUTE PRIMARY GLAUCOMA.*

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GLAUCOMA is not a disease in itself, but rather a symptom-complex whose characteristic feature is increase in the tension of the eyeball. It was, however, the peculiar greenish reflex from the pupil that first attracted attention and suggested the name glaucoma. Centuries had to pass before William Mackenzie drew attention to the hardness of glaucomatous eyes. That was the first observation of real value in the study of glaucoma, and may be regarded as the foundation of all present-day knowledge of the subject.

When considered from the clinical standpoint glaucoma may be primary or secondary; primary when it is unassociated with any other disease in the affected eye, and secondary when the glaucomatous seizure arises as a complication of a pre-existing pathological condition. The attack is acute or chronic, according to the presence or the absence of congestion of the ocular blood vessels, but inflammation in the strict sense of the word never occurs during the course of acute primary glaucoma. Venous congestion is alone responsible for the severity of the symptoms, which vary greatly in degree in different cases. In the majority they are subacute and recurrent, but in a small proportion they may be described as fulminating. In these circumstances glaucoma is seen in its most tragic form—the onset, course, and termination being the incidents of a few hours. A single attack occurring with dramatic suddenness results in total and irrevocable loss of sight. Such a disaster is all the more overwhelming, because glaucoma usually affects both eyes, and although one may be attacked considerably in advance of the other, yet in a few desperate cases both suffer simultaneously.

SYMPTOMATOLOGY.

Acute glaucoma can be described as one of the emergencies of general practice, and in many instances it appears to come as a bolt from the blue. The patient goes to bed apparently in his usual health, but in the early hours of the morning is awakened by agonizing pain in the head, accompanied by feverishness, nausea, persistent retching, and bilious vomiting. The condition is so alarming that the family doctor is sent for in haste, and unless he knows well what he is about he may easily do the patient more harm than good. It is quite probable that no one will speak about the eye, because even although the failure in vision has been noticed, it has been tacitly assumed to be due to biliousness. The attention of the patient and of those surrounding him is occupied wholly as a rule with the severity of the pain in the head, the nausea, and the vomiting. The true nature of the condition, therefore, may be easily overlooked, and if the doctor is also deceived the result will be deplorable.

Acute glaucoma is not by any means a common disease. It may happen that a medical man has been many years in practice before he is called to treat a case. He ought, however, always to bear the disease in mind, and never to forget to examine the eye of a patient said to be suffering from a severe bilious attack. Every country doctor ought to be able to recognize acute glaucoma. There is not much difficulty in the diagnosis. The eye is tender and the patient shrinks from the slightest touch; it is hard, and said to feel too big for its socket. The bulbar conjunctiva

is congested and oedematous; the cornea is steamy and in many instances so insensitive that it can be touched without the patient's knowledge; the pupil is dilated, irregularly oval shaped, and irresponsive to light; the anterior chamber is shallow. At this stage of the examination the general practitioner must be on his guard not to misinterpret the significance of these signs and symptoms.

The chief local condition with which acute glaucoma is often confused is acute iritis; but the stony hardness of the eyeball, the dilated pupil, the shallow anterior chamber, and the loss of sight form a group of signs sufficiently diagnostic to prevent glaucoma from being mistaken for any other disease. Unfortunately, however, glaucoma and iritis are still confused by the unwary, and the consequences of such an error in diagnosis are deplorable, because the treatment for glaucoma is the opposite of that for iritis. It is well known that in iritis the vigorous use of atropine is imperative, but it is not so well known that if a mydriatic be instilled into an eye suffering from glaucoma the symptoms will be aggravated and the chances of recovery of sight will be materially lessened. There are few errors in diagnosis which are followed by such disastrous results.

Although the patient may never have consulted a doctor regarding his eyes until the onset of the acute symptoms, careful inquiry into the history of the case will usually elicit the fact that for weeks, months, or years he has suffered from transient attacks of dimness of vision. These attacks are often so fleeting that little significance is attached to them, and as a rule the patient does not think it worth while to mention them until something in the course of a medical examination recalls them to mind. The fact that such attacks are usually made light of and quickly forgotten makes it all the more necessary for the family doctor to be quick to appreciate and appraise at their proper value any remarks regarding eyesight made in a casual manner during the course of conversation.

Suspicion should at once be aroused if a patient says that now and again he has seen objects through a fog, and that lights have appeared to be surrounded by rainbow-coloured rings. Inquiry will usually further elicit that while these symptoms are present there is a dull pain in the eye and forehead, and if it should happen that the doctor was consulted during one of these attacks he will remember that the eye was more or less red, hard to the touch, the cornea steamy, and the pupil dilated. If the examination be carried further by the use of the ophthalmoscope it will be seen that the retinal veins are enlarged and that the arteries pulsate as they pass over the optic disc. When the patient is kept under regular observation it will be discovered that the attacks are recurrent and vary in duration from a few minutes to several hours, while in the intervals the eye to all appearance is healthy. Recurrences become more and more frequent and protracted, however, until at length a state of increased tension is permanently established. In the majority of instances that sequence of phenomena is easily followed, but there is usually considerable difficulty in understanding the underlying cause of the condition.

The increased tension of the eyeball is not a disease in itself; it is only a symptom of a general condition, whose etiology is at all times very difficult to determine. When an eye is predisposed to glaucoma anything that depresses the action of the heart may determine a seizure, which in the majority of instances can be clearly traced to mental distress or moral shock, to the injurious influence of cold or of hunger, or to worry, sleeplessness, or fatigue. In many instances also there are present such associated conditions as anaemia, lithiasis, bronchitis, persistent constipation, or the suppression of some habitual discharge. Acute glaucoma occurs frequently in women at the menopause. Lagrange has defined glaucoma to be "a sick eye in a sick body," and Laquer says that everything "that dilates the pupil or debilitates the patient" may precipitate an attack. It is characteristic of the onset of the disease that the increase of tension is intermittent, but sooner or later it becomes permanent. By the time that stage is reached, however, the cause of the disease is usually obscured by its results.

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ETIOLOGY.

The earlier glaucoma can be detected, therefore, the more likely is its etiology to be discovered. No progress will be made with this quest, however, until the physiological mechanism whereby the intraocular tension is maintained in a state of health is properly understood, because without such knowledge it is not possible to detect the earliest aberration which transforms the physiological into the pathological. It must be borne in mind that there is no essential difference between physiology and pathology. No sharp line of demarcation separates the normal from the abnormal. By the recognition of symptoms, however, the trained clinician is able to detect the beginnings of disease, at a time when the morbid process giving rise to it is still on the borderland of the physiological. Function rather than structure is the foundation of the science of medicine. A physiological problem cannot be argued from the standpoint of pure anatomy without grave danger of falling into error. The special requirements of every organ necessitate certain modifications of structure, but the basis of vital activity is the same in every part of the body. The unification of both physiological and pathological processes must be recognized. If, for example, the etiology of acute glaucoma be sought for along anatomical lines the disease will inevitably seem obscure and mysterious; but whenever it is recognized that every vital process takes place through the walls of the capillaries, glaucoma is at once brought into line with other pathological conditions which are clearly defined and well understood.

The study of the etiology of glaucoma has passed through many phases. Hypotheses deemed important in their day have had, with the advance of science and the increase of knowledge, to be put aside; but they were useful at the time in so far as they paved the way to the acquisition of fuller knowledge. The tension of the eyeball depends upon the fluid content of the globe, and the theory generally accepted is that the intraocular fluids are derived from the capillaries of the ciliary processes,¹ and that in a state of health a close relationship exists between intraocular pressure and general blood pressure. It has also been demonstrated that, starting from their source, the intraocular fluids pass forward through the circumferential space, the posterior chamber, and the pupil to reach the angle of the anterior chamber from which they escape from the eye into the canal of Schlemm, through the filtration spaces in the pectinate ligament. When that mechanism is in proper working order the tension of the eyeball is liable to very slight variation, consequently the intraocular pressure resembles the general blood pressure in so far as both are maintained at a fairly constant level in the normal condition; but sudden and great variations are liable to occur in such morbid conditions as glaucoma and hyperpiesia. It must not be concluded, however, that high blood pressure is in itself an essential factor in the etiology of glaucoma. The two conditions frequently coexist, but the relationship is purely accidental and is not one of cause and effect. Arterial pressure must exercise a certain amount of influence upon the tension of the eye, but the important factor in the regulation of the intraocular pressure is the pressure in the capillaries. That being so, the clue to the pathogenesis of glaucoma is likely to be found by a study of the capillary circulation in the eye.

Many of the old theories of the causation of glaucoma were based upon the hypersecretion of the aqueous humour; that hypothesis is open to serious objection. When the excretory channels in the corneo-iridic angle are in good working order any increase in the inflow of fluid is at once compensated by a corresponding increase in the outflow. The results of clinical experience, moreover, have demonstrated that when the secretion of the aqueous is excessive, this reciprocal arrangement is quite efficient in maintaining the normal tension of the eyeball. On the other hand, the pathological study of eyes enucleated as a result of secondary glaucoma has demonstrated that hardening of the eyeball is due, not to over-secretion of the intraocular fluids, but that it is the result of their retention. In almost every instance the filtration spaces at the corneo-iridic angle are closed and obstruct the outflow of fluids, which, being retained within

the eyeball, cause a gradual and progressive increase in tension.

Knies and Weber were among the first to suggest a retention theory for primary glaucoma similar to that generally adopted for the secondary form of the disease, and the epoch-making researches of Priestley Smith support their view. In the earliest stages of primary glaucoma, however, occasion for excision of the affected eye never arises, consequently before it is possible to obtain material for microscopic examination, the disease has advanced so far that, although end-results can be fully described, nothing whatever can be learned of the mode of origin. The opportunities for observation are not much more favourable from the clinical standpoint, because the family doctor rarely sees a case until the disease is fully developed. He has had no opportunity to note the subtle changes which have led up to the acute seizure on account of which he has been consulted. Nevertheless, it is the premonitory symptoms that ought to be carefully studied, because until the mechanism of their production is properly understood it is impossible to explain how it has come about that an eye apparently quite healthy in the evening is attacked by a formidable disease before morning. It is always assumed that the eye affected was predisposed to glaucoma, and from the anatomical standpoint such a predisposition undoubtedly exists.

Priestley Smith has demonstrated that eyes liable to glaucoma are smaller than normal, and, in view of the fact that primary glaucoma is a disease of late adult life, he has pointed out that, while the lens continues to grow throughout life, the size of the eyeball, after a certain age, remains stationary. In some instances, therefore, the disproportion between the bulk of the lens and the size of the globe becomes so pronounced that the circumferential space is obliterated. Whenever that occurs increase of pressure in the vitreous chamber pushes the lens forward, and closes the filtration angle by the approximation of the base of the iris to the posterior surface of the cornea. Retention of the intraocular fluids leads to the development of symptoms of glaucoma, and these will steadily persist so long as the drainage system of the eye remains blocked. If the circumferential space has been encroached upon gradually the eye can so far adapt itself to the altered conditions, and acute symptoms do not occur, but if, on the other hand, obliteration takes place suddenly signs and symptoms of acute congestive glaucoma at once arise.

The most meticulous study of the pathological anatomy of an eye that has been excised for glaucoma can, however, reveal nothing more than end-results. An examination of the eyeball can never by itself reveal the cause of the disease. The sick body, as Lagrange said, must also be considered, because, until glaucoma is brought into line with diseases whose etiology is well established, its pathogenesis cannot be properly understood. It is necessary in the first place, however, to recall the physiological principles which regulate the intraocular circulation and control the intraocular pressure. An essential postulate for the continuation of the circulation in the eyeball is that the arterial pressure be higher than the capillary, the capillary higher than the venous, and the venous higher than the intraocular. The capillaries, rather than the arteries, are the chief regulators of intraocular pressure: any obstruction to the venous outflow is of much more importance to the eye than high pressure in the arteries. This preponderating influence of venous obstruction is due, in all probability, to its immediate effect upon the capillaries. Any local interference with the venous circulation—ligature of the venae vorticosae, for example—will at once precipitate an acute glaucomatous seizure. When, however, the problem is put in its right setting and seen in its proper perspective, the behaviour of the capillaries is the one thing that is fundamental, both in physiology and in pathology. It is all-important, because the capillaries are not only the dynamic part of the circulatory system, but they also demonstrate the sum of the purposes for which circulation of the blood exists.

Bryson,² in the early days of the James Mackenzie Institute for Clinical Research, was the first to suggest that the

capillaries play the predominant role in all vital activities, and that the other parts of the vascular system are controlled by them and are subservient to their requirements. On several occasions he has brought forward clinical evidence in support of his views, and the truth of his hypothesis has been proved by many laboratory workers, among whom Krogh, Lewis, and Dale deserve special mention. These observers have demonstrated that the capillaries act independently of the other parts of the circulation; that they are called into use only as they are required, and that there is an enormous reserve of shut-down capillaries in an organ while it is resting. The capillaries and the cells associated with them may be said, therefore, to act together as a physiological unit. When the feeding time for a cell is due the capillaries associated with it open at the right moment, and after sufficient nutriment has been supplied they close down. This nutritional process goes on intermittently so far as individual cells are concerned, but constantly over the body as a whole. The result is that blood is sent round at the call of the different cells, while the utmost economy is practised in its distribution. This regular fluctuation of the capillaries is the basis of all vital activity.³ It explains why it is that separate parts of an organ work in shifts—some of the component cells being in action while the others are resting, and vice versa. If all the capillaries were to open up simultaneously it is common knowledge that they could contain more than the whole of the blood in the body, and the animal would bleed to death into its own capillaries, because, stagnation having taken place, circulation would cease.

It is generally agreed that the tissue fluids come from the blood plasma by dialysis through the walls of the capillaries, and Duke-Elder has demonstrated that the intraocular fluids obey the same physico-chemical laws. He believes, therefore, that the aqueous humour is a dialysate, and has brought forward evidence to prove that it is neither a secretion nor a filtrate. His work has put the physiology of the intraocular circulation into line with the circulation in the body as a whole. That does not mean, however, that there are no local differences in special organs, but Duke-Elder believes that the apparent anomalies are to be explained by the difference in the permeability of the capillaries. Each organ has its own needs, and possesses within itself physiological adaptations for the purpose of satisfying its requirements. In carrying out this process the permeability of the capillaries is one of the most important factors, permitting only the right quantity and the proper quality of nutrient fluid to be dialysed from the blood plasma.

In the eye the capillaries are very impermeable, relative to those in other parts of the body. While, as a rule, the tissue fluids are dialysed at a pressure of from 1 to 2 mm. Hg, in the eye dialysis takes place under a pressure of about 25 mm. Hg. The aqueous, therefore, is comparable to the tissue fluids, both as regards its origin and its metabolism, but it differs from them qualitatively in proportion to the relative impermeability of the capillaries. In the eye the special arrangements may be described as a "biological adaptation to keep the intraocular fluids as far as possible optically homogeneous." That is to say, that a simple modification of the same physiological process which regulates the function of the capillaries in all the other parts of the body is sufficient to secure the transparency of the dioptric apparatus of the eye. That physiological arrangement is an apt illustration of one of the main contentions of this paper—namely, that although peculiarities of structure are necessary for the architecture of the different organs of the body, yet it is one and the same physiological process which regulates and controls their vital activities.

The first departure from health in the eye is indicated by dilatation and increased permeability of its capillaries, but except in the case of direct injury the cause of this must be sought for in the general health of the patient rather than in the eye itself. The eye is not only in the body, it is also of the body: that is the key to the proper understanding of the glaucoma problem.

Interference with the circulation of the blood through the eyeball and the consequent alterations in the composi-

tion of the intraocular fluids are the outstanding features of acute congestive glaucoma, and in every instance loss of tone in the wall or the capillaries is responsible for the onset of an attack. Of the predisposing causes, in addition to the small size of the eyeball, the most important is the wear and tear of life, with its cumulative autointoxication and its vascular degenerations, while among the causes directly precipitating an attack may be mentioned over-excitement, crushing misfortune, sorrow and bereavement, excessive fatigue, prolonged exposure to cold, repeated indiscretions in diet, or a bout of drinking. It is almost certain that glaucoma cannot occur in anyone who is quite healthy. Doubtless in many instances the disease reveals itself with appalling suddenness in one who is apparently healthy, but in every case of that kind a careful scrutiny of the patient's medical history will disclose symptoms, both local and general, which, though regarded as trivial at the time of their occurrence, were really premonitory of something much more serious. It is difficult to detect the earliest signs of failure in the delicate physiological mechanism for keeping the tension of the eyeball at a normal level. These must, however, be intimately associated with an alteration in the behaviour of the capillaries which regulate intraocular pressure, and the truth about glaucoma will not be known fully until all the factors governing the circulation, both of the blood and of the fluids within the eyeball, have been clearly demonstrated.

It is known that the body contains two groups of substances mutually antagonistic—a histamine group, acting as dilators of the capillaries, and an adrenaline group, acting as contractors. During life there must be a constant give and take between these two groups in the effort to maintain equilibrium, which is readily disturbed in one or other direction by the influence of hormones. Whenever one of these groups gains ascendancy over the other disturbance in the capillary circulation occurs sufficient to place the patient in the borderland of the pathological. Dale and his associates have made a careful study of histamine,⁴ and have demonstrated that when this substance is injected intravenously into a living animal it causes such extreme dilatation of the capillaries that the blood stagnates and at the same time the capillary walls become so permeable that oedema of the tissues occurs from loss of blood plasma. Those changes may become so extreme that the circulation is brought to a precariously low point by depletion of the central vessels. When such circulatory disturbances are general throughout the body secondary shock arises, but when they are localized in the eyeball acute glaucoma supervenes. Both in acute glaucoma and in secondary shock, therefore, the underlying cause is the same, and from the pathological point of view one condition may be regarded as analogous to the other.

To sum up, it is probable (1) that the first stage in the pathogenesis of glaucoma is a disturbance in the capillary circulation leading to a general dilatation accompanied by increased permeability of their walls; (2) that the condition is brought about by the action of a toxin which upsets the delicately balanced mechanism controlling the function of the endocrine glands, and thereby interferes with the normal action of the sympathetic nervous system.

One of the earliest symptoms of glaucoma—one that occurs before increased tension in the eyeball has become permanently established—is dulling of sensitivity to dim light and delay in dark adaptation.⁵ This failure in light minimum is due to interference with the function of the layer of rods and cones of the retina, which derives its nourishment from the choriocapillaris. Whenever these nutrient capillaries lose tone the blood stagnates, the rods and cones suffer, and the light sense becomes disordered.

Although severe congestive changes and oedema of the ocular conjunctiva are such outstanding characteristics of acute glaucoma, they are neither primary nor essential to the attack, but are secondary to the changes which have occurred already in the capillaries. The glaucoma is fully established before the surface of the globe has become congested; but unless the patient has consulted

his doctor during a premonitory attack, the disease is very seldom seen in this early stage.⁶ That, however, is the time when it can be studied in its simplest form, because a premonitory attack differs from genuine glaucoma only in so far as it passes off quickly. The pathogenesis of both is the same. The congestive changes are something superadded to a pre-existing condition, and it is not difficult to understand how they originate. The increased dilatation of the capillaries and the increased permeability of their walls cause great interference with the intraocular circulation. An increasing obstruction is therefore offered to the return of the blood by the veins, and whenever stagnation occurs acute glaucoma supervenes. The phenomena seen in the eye resemble what occurs in the thrombosis of blood vessels in other parts of the body—acute pain, vascular congestion, oedema, and loss of function. The gravity of an attack is in great measure determined by the severity of those secondary vascular complications. The chief stress is felt at the corneo-iridic angle, where the circulation can be said to be strangulated, and the state of the eye may be compared to a hernia which has become strangulated. In both instances danger is extreme until the strangulation is relieved.

The initial cause of glaucoma may be traced to the injurious action of a toxin of the histamine type. It is probably of biochemical rather than of bacterial origin, and is manufactured in the course of defective metabolism due to persistent constipation, hepatic insufficiency, or renal inadequacy. There is, however, little difference in the action of a biochemical toxin and one of bacterial origin. Both cause dilatation of capillaries with increased permeability of their walls.

AN ANALOGY.

A good example of the action of both forms of toxin is seen in a comparison of acute glaucoma with acute glomerulo-nephritis. The ciliary processes in the eye and the glomeruli in the kidney show many features in common. The chief function of both is to dialyse fluid through the walls of capillaries, and the dialysate in both eye and kidney contains every substance present in blood plasma. There is this difference, however, that the quotient varies according to the osmotic pressure of the blood and the degree of permeability of the walls of the capillaries. With those reservations the aqueous humour may be taken as a type of every dialysate, and if the eye were supplied with a tubular arrangement similar in function to that in the kidney, the aqueous, after passing through it, would be turned into urine. Moreover, while the reaction of the normal aqueous is almost neutral, in glaucoma it is distinctly alkaline.⁷ A change in the osmotic pressure and a diminished hydrogen-ion concentration of the blood permit an excess of sodium to pass through the walls of the capillaries. Archer found that the sodium content of the blood is diminished in glaucoma, and that observation is in harmony with the generally accepted statement that in nephritis there is a deficiency of sodium bicarbonate in the blood. Those changes lead to increase of pressure in the capillaries followed by damage to their walls, which become so permeable that they allow particles of protein to escape. The normal aqueous contains the merest trace of albumin, but Troncoso has demonstrated that in glaucoma it is present in appreciable amount. Albuminuria of the aqueous is due, therefore, to the same pathological process which gives rise to the presence of albumin in the urine, and if the eye were not specially protected by the great impermeability of the capillaries of the ciliary processes the presence of protein in the aqueous humour would be of frequent occurrence.

These widespread changes in the capillaries and in the veins must cause great increase in the size of the organ affected, and as both the eye and the kidney are enclosed within a firm capsule, increase of tension readily supervenes. When that occurs a state of glaucoma may be said to exist both in the eye and in the kidney—the abnormal pressure causing blindness in the one and suppression of urine in the other. In neither organ can function be restored until the abnormal tension is diminished, and,

in the last resort, that can be accomplished by performing iridectomy in the eye, and by stripping the capsule in the kidney.

PRINCIPLES OF TREATMENT.

The rational treatment of glaucoma is based on a knowledge of the same physiological principles which are so helpful in the study of its etiology. It is not possible, however, to attempt in this paper anything more than a brief and general discussion of the problem. In considering the pathogenesis of glaucoma, it has been stated that histamine and adrenaline are mutually antagonistic, and that when the histamine group of toxins predominates increased intraocular pressure arises, and will persist and become permanent if the noxious cause cannot be removed. The physiological antidote to all poisons of the histamine type is adrenaline,⁸ which consequently is the rational treatment whenever capillaries are over-dilated and their circulation obstructed. When administered artificially adrenaline restores the circulation and prevents loss of fluid through the walls of the capillaries by improving their tone. A retrobulbar injection of about 3 to 6 minims of a 1 in 1,000 solution within a few minutes reduces the tension of a normal eye. In primary glaucoma it has a similar effect, and in some instances its use has brought about a cure of the disease. The use of adrenaline must, however, be carefully safeguarded locally. It is a very powerful mydriatic, and by dilating the pupil to the maximum might readily cause serious complications by pushing the iris into the corneo-iridic angle, thereby obstructing still further the escape of fluids from the eye. Its use, therefore, must always be preceded by energetic instillation of eserine drops to keep the pupil contracted. Treatment by adrenaline is, moreover, usually ineffective in very acute cases of congestive glaucoma, it being powerless to relieve the secondary complication due to thrombosis at the venous exits.⁹ In these circumstances the first thing to be done is to relieve the stranglehold at the corneo-iridic angle. Sleep is Nature's cure for glaucoma, consequently the first indication in every case is to relieve pain—by the administration of morphine hypodermically, the continuous application of heat to the eye, free leeching of the temple, and eserine instillations to keep the pupil contracted. The general condition of the patient also demands attention. At the outset a calomel purge, followed, in three hours, by an alkaline saline draught, is always helpful, and ought to be repeated if necessary. The fact that intraocular pressure can be lowered by producing a hypertonic state of the blood has led Duke-Elder, following previous observers, to recommend the intravenous injection of 50 c.cm. of a supersaturated saline solution. The tension falls as a result of abstraction of fluid from the eye, but, as the treatment interferes with the whole fluid traffic of the body, it must be used with caution lest dangerous symptoms supervene from too rapid a fall in the general blood pressure.

In spite of those conservative means of treatment, however, ocular hypertension may persist, and in these circumstances operation will be required. The sole object of operation is to reduce the tension of the eye and to prevent the recurrence of hypertension. No operation can be said to be a cure for glaucoma, in spite of the fact that thousands of sufferers, who would otherwise have been blind, have been enabled to retain their sight by the aid of one or other of the various operative procedures that have been introduced since von Graefe discovered the value of iridectomy.

The aim of every operation for glaucoma is to establish a filtering cicatrix which will act as a safety valve through which excess of fluid can escape from the eye during any recurrence of high tension. This immediate end may be successfully attained, but nevertheless the disease may progress. The treatment of the patient himself, therefore, must always be considered to be as necessary after, as it was before, operation.

I am greatly indebted to the following books of general reference. Priestley Smith: *Pathology and Treatment of Glaucoma*, 1891. V. Morax: *Glaucome et Glaucomateux*, 1921. Elliot: *A Treatise on Glaucoma*, 1922. Duke-Elder: *Recent Advances in Ophthalmology*, 1927. Thomas Lewis: *The Blood-vessels of the Human Skin and their Responses*, 1927.

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PROFESSOR CALMETTE'S STATISTICAL STUDY OF B.C.G. VACCINATION.

BY

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IN the January issue of the *Annales de l'Institut Pasteur* Dr. Calmette publishes an article¹ on the statistics and results of his method of prophylactic inoculation from July, 1924, to December, 1927. Dr. Calmette's earlier report² was subjected to some little criticism both in the editorial columns of the *British Medical Journal*^{3, 4} and from individual writers^{5, 6}; recently Dr. Monod⁷ has expressed the hope that the latest report might allay the doubts that had been expressed as to the sufficiency of the statistical evidence.

Briefly, the objections which were urged against the earlier report were these: (1) that the enormous rate of mortality from tuberculosis said by Dr. Calmette to apply to the children of the tuberculous, or to children exposed to massive infection, in the first year of life was deduced from inadequate data or depended upon misinterpretations of published literature, and did not agree with such evidence as that of Kjer-Petersen and Ostenfeld⁸; (2) that the positive evidence of a statistical kind supplied by Dr. Calmette was ambiguous.

Thus, with respect to the first objection, I pointed out that Weinberg's very careful statistical study had been misrepresented; that, far from supporting the suggestion that anything like 25 per cent. of the children of the tuberculous died of tuberculosis in the first year of life, Weinberg's figures were in reasonable agreement with those of Kjer-Petersen and Ostenfeld, Bergman,⁹ and Dörner,¹⁰ making the rate of mortality of the order of 5 to 10 per cent. rather than of 25 per cent. With respect to the second objection, I showed that the data handled by Dr. Biraud, who used an adequate method of analysis, became so scanty within a few months of birth that it was difficult to have great confidence in the inferences—*prima facie* favourable—which appeared to be deducible from them.

An attentive study of Dr. Calmette's latest paper leads me to think that its distinguished author has either not read or not understood the criticisms of his former report, because, to put the matter quite plainly, this new paper repeats and even exaggerates former inaccuracies while introducing statistical errors peculiar to itself. I take first the contention that Dr. Calmette has again misrepresented the published work of other writers. Of Weinberg he writes under the heading *Mortalité par Tuberculose des nourrissons de zéro à un an nés et élevés en milieu bacillifère*:

"D'autre part, une statistique (déjà ancienne, mais portant sur un grand nombre d'enfants) publiée par Weinberg, avait établi qu'à Stuttgart, de 1873 à 1889, la mortalité des enfants de zéro

à un an par tuberculose était due : pour 30, 53 p. 100 à la mère tuberculeuse; pour 29, 88 p. 100 au père tuberculeux; pour 31, 92 p. 100 à la fois à la mère et au père tuberculeux."

This passage repeats the misrepresentation to which attention had already been drawn. The figures quoted are not for the mortality from tuberculosis, but from all causes, and, at the same epoch, the death rate in the first year of life of children of mothers who were not tuberculous was as high as 23.82 per cent. The present misrepresentation is rather worse than that of the first report (p. 210), because there the attribution of the mortality to tuberculosis was not quite so explicit.

Of Kjer-Petersen and Ostenfeld's recent work (again in the section dealing with mortality from tuberculosis in the first year of life), Dr. Calmette writes that they

"n'ont enregistré, pour 245 nourrissons suivis par eux, qu'une mortalité de 7,7 p. 100 de zéro à un an. Mais il faut remarquer d'abord que les 245 nourrissons dont il s'agit ne comprennent pas seulement des enfants nés de mères tuberculeuses, mais aussi et surtout des enfants qui ont simplement été en contact, pendant une période plus ou moins longue, avec un tuberculeux."

The mortality rate of 7.7 per cent. in Kjer-Petersen and Ostenfeld's series is the rate of mortality from all causes—namely, 19 deaths among 245 children, and of these 19 deaths only 12 were assigned to tuberculosis. The complete specification in the paper is as follows. Tuberculosis: 3 from tuberculous meningitis, 5 from pulmonary tuberculosis, 1 from abdominal tuberculosis, 1 after operation for tuberculous disease of the ear, 2 from generalized tuberculosis. The other deaths were thus classified: 1 cholera, 1 influenza and inflammation of the lung, 2 measles and inflammation of the lung, 3 inflammation of the lung. If we assume that the last three were really instances of tuberculous infection we shall reach 6.1 as the percentage death rate from tuberculous disease.

The authors set out their categories quite clearly, and one finds that 101 of the children had the mother or both parents tuberculous, and of these 101 children 4 died of tuberculosis, while the remaining 8 deaths from tuberculosis occurred among the 116 children whose fathers only were tuberculous. In other words, these data show a higher incidence of fatal tuberculosis upon the children of tuberculous fathers than upon the children of tuberculous mothers.

The fundamental importance of Kjer-Petersen and Ostenfeld's paper depends on the fact that it is based upon data compiled on statistically sound lines. Their means of access was the tuberculosis station of Copenhagen. They obtained a record of all births from July 1st, 1919, to June 31st, 1925, to families with at least one case of open tuberculosis, and they have excluded from the series instances where the child was born at least a month after a tuberculous father's death, or was isolated from the mother during the first year of life; that is, their data should give a maximal incidence for the class of population concerned. I shall return to the point later; at present I am merely describing Dr. Calmette's treatment of his sources. It is, I think, evident that no reader of his report who had not had access to Kjer-Petersen and Ostenfeld's paper (the locus of publication of which is not given by Dr. Calmette) could have formed a just impression of what these authors actually did.

The next example of Dr. Calmette's literary researches is even more interesting. On page 7 of the report under notice we are told that:

"Margarete Roepke, dans un tableau qui résume l'histoire de 78 enfants, trouve une mortalité de 30.8 p. 100 pour les nourrissons en contact avec des malades arrivant à la période ultime de leur tuberculose; de 25 p. 100 lorsqu'il s'agissait de lésions avancées, tandis que la mortalité était nulle lors des contacts avec des formes légères de la maladie."

Dr. Calmette does not actually give a reference to the locus of publication of M. Roepke's paper, but there is no doubt that the paper in question is that printed on pages 252-263 of vol. 54 (1923) of the *Beiträge zur Klinik der Tuberkulose*. The source of the above-quoted statement of Dr. Calmette is in fact the following table, which I have taken from Frl. Roepke's paper (p. 260), the only change I have made being to translate the letterpress into English.