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CLINICAL SCIENCE AND OPHTHALMOLOGY

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In the opening chapter of his recent book¹ Sir Thomas Lewis discusses the scope and methods of clinical science, and defines it as "that branch of medical science dealing with living human beings." My immediate purpose here is to indicate briefly how far a study of ophthalmology supports Lewis in this conception of clinical science.

It is generally admitted that observation without understanding and clear critical thinking is the chief obstacle to the scientific progress of clinical medicine. Such slipshod work is discredited in the laboratory, the incalculable gifts of which to medicine are discipline in scientific method, and training in the supreme importance of logical reasoning and the use of exact language in speaking and in writing. The nearest approach to laboratory training in clinical medicine is to be found in the study and practice of ophthalmology, because that subject offers a fine discipline in exact observation, in accurate measurement, and in precise statement. The eye, moreover, is easy of access, and can be examined very thoroughly; consequently it is a peculiarly favourable field for the study of disease at its onset.² The ophthalmic patient, too, is usually helpful, in so far as he is so much alarmed when he discovers anything wrong with his eyesight that he seeks medical advice with the least possible delay. When a patient consults an ophthalmologist he is, as a rule, suffering either from pain or from some disorder of the visual function. It will be convenient, therefore, to discuss our subject under these two headings.

Ocular Pain

Although pain cannot be measured by an instrument of precision, it is one of the most valuable symptoms of disease. It often saves time, therefore, to ask the patient at the beginning of the consultation if he is suffering pain. If the answer is in the affirmative the next question should be: How long has the pain been present? As pain is usually a danger signal, it ought to be investigated very thoroughly. It nearly always accompanies inflammation of the eye, but it may also be present without inflammation. Ocular pain may be described, therefore, as inflammatory or non-inflammatory.

INFLAMMATORY PAIN

This varies in character according to the site of the inflammation which is causing it. When the superficial structures of the eyeball are affected the pain is sharp and cutting, like a foreign body in the eye, and is aggravated by every movement of the lids. When the deep structures are implicated the pain is throbbing or gnawing, radiates along the branches of the trigeminal nerve, and is always most severe late at night or in the

early hours of the morning. Differential diagnosis can be carried further by studying the accompaniments of the pain, among which are the presence of secretion or of photophobia, variations in the size or in the reactions of the pupil, tenderness on pressure over the ciliary region, increase in intraocular tension, impairment of sight, and vomiting or nervous collapse. In short, an experienced ophthalmic surgeon will usually be put upon the right road to diagnosis after he has listened to the patient's description of the character of the pain, and has observed the signs accompanying it; but in every case, in order to avoid pitfalls, he will not neglect to make a careful systematic examination of the eyeball.

NON-INFLAMMATORY PAIN

The older ophthalmic surgeons grouped cases of non-inflammatory pain in and around the eye under the general heading "asthenopia." They examined the patient very carefully, and so little in the symptomatology escaped their notice that in the textbooks of the time we can read clinical descriptions of asthenopia which are full and accurate. But, in spite of so much laborious note-taking, these old-time surgeons must often have felt puzzled as they listened to a tale of terrible suffering and could discover so little in the eye to account for it. As they could not explain the causation of the symptoms their prognosis was pessimistic, and based entirely upon a general impression of personal experience.

In the fourth edition of his *Practical Treatise on the Diseases of the Eye* William Mackenzie³ wrote: "Asthenopia is an infirmity much more to be dreaded than many disorders of the eye which to superficial observation present a far more formidable appearance. The prognosis is on the whole unfavourable. It [the disease] has no tendency to wear itself out, and is probably incurable, although not likely to terminate in blindness." In clinical practice every patient suffering from ill-health must be treated, no matter how ignorant a doctor may be regarding the causation of the disease, and, as a rule, the less the doctor knows the greater the number of remedies prescribed. Consequently in the past asthenopic patients were submitted to so much drastic treatment, both local and general, that they must often have suffered grievously at the hands of their medical advisers.

All the confusion and the regrettable ignorance concerning asthenopia arose as a result of want of knowledge of physiological optics; but a new era in the history of the disease was about to dawn. Helmholtz, working in a little room in the anatomical department of the University of Königsberg, was inventing optical instruments and creating a new science. Donders, a professor both of ophthalmology and of physiology in the University

of Utrecht, was studying the same subjects from the standpoint of clinical ophthalmology. When these men began their work nearly all that was known of the subject could be summarized in very few words: concave glasses improved myopia and convex glasses presbyopia, the selection of the one or the other being arrived at for any given case, as a result of crude empiricism, much as a child suffering from asthenopia might discover by accident that he got relief from his symptoms by wearing his grandfather's spectacles. There was no real knowledge of the subject until Helmholtz and Donders settled the much-disputed question of the accommodation of the eye for varying distances.

The results of all this observational and experimental work were made public in 1864, when Donders¹ published his epoch-making book on the *Anomalies of the Refraction and the Accommodation of the Eye*. It was then demonstrated for the first time what is understood by the terms "refraction" and "accommodation," how abnormalities and the changes due to age are brought about, and how errors of refraction are neutralized by suitable lenses. That was a tremendous advance in knowledge, and it was due largely to the fact that Donders was an ophthalmologist as well as a physiologist. He was therefore in a very favourable position to utilize the discoveries in the laboratory in such a manner as to make the physiological mechanism underlying the symptomatology of asthenopia intelligible to ophthalmologists, and to put the prescription of spectacles upon a scientific basis.

Clinical science can show few more brilliant examples of a satisfactory solution of a pressing medical problem. So long as asthenopia was studied exclusively by the observational method the disease meant nothing more to an ophthalmologist than a miscellaneous grouping of a number of symptoms the physiological causation of which was not understood. Such knowledge, however, is only a cloak for ignorance, encourages the assumption of an air of finality regarding the whole subject, and conceals the need for research. Much of this apparent complacency arose because ophthalmologists were so familiar with the symptoms that they concluded they knew all about the disease. Clinical science is not so easily satisfied. It aims at correlating function with structure, and thereby seeks for the inner meaning of signs and symptoms. It follows, therefore, that the study of the mechanism of the production of symptoms must always go hand-in-hand with critical investigations into the causation of disease, and the motive power behind research is always the hope of discovering a remedy for the relief or the cure of the patient.

When symptoms are studied with that end in view clinical observation and research in the laboratory ought always to go together. Mackenzie² insisted that there must be no cleavage between research in the ward and research in the laboratory. There must be no attempt at domination on either side. Donders was able to accomplish so much because he combined in his own person the dual role of ophthalmologist and physiologist, and it follows that if the best progress is to be made a clinician should always be a physiologist in his own special line of investigation. But that does not mean that he will never require the assistance of an expert. He ought, however, always to be in a position to direct and supervise the laboratory investigations. The problem to be solved originated in the wards, consequently the clinician must be the judge of the kind of information required for its solution. Clinical science suffers when research work in a laboratory, whether physiological, pharmacological, or pathological, is carried on without the guidance of the clinician who is seeking the help. A chance meeting and a brief conversation between the two workers is not enough. It is as important for the laboratory worker

to be a frequent visitor to the wards as it is for the physician to visit the laboratory. The closer their collaboration the better for the future of clinical medicine.

Disorder of the Function of Vision

From a physiological point of view the characteristic feature of vision is the reception of light by the retina. It is usual to compare the eye with a camera, and the retina with a photographer's plate. As far as it goes the analogy is perfect, because an image of an external object is formed on the back of the eye in the same way as it is formed on the photographic plate. From this point onwards, however, the analogy breaks down, because a single exposure to light exhausts the sensitivity of the plate, and, as it has within itself no power of renewal, it is useless after it has been used once. Moreover, a photographer knows that if he is to do good work he requires plates sensitized for different intensities of light. The difference in the behaviour of a photographic plate and of the human retina is due to the fact that from beginning to end the plate is governed by physical laws, whereas in the retina the physical stimulus of light has released a new type of activity, which is known as a "physiological response." When the eye is exposed to light a loss of sensitivity takes place in the retina similar to that which takes place in the photographic plate; but the loss is much less rapid, and if the patient is kept in the dark a fresh liberation of visual purple brings about a renewal of sensitivity. This function of the retina is called "adaptation to light," and is fundamental in the economy of vision.

The human eye is capable of adapting itself to almost any intensity of illumination; and the changes in sensitivity proportionate to the brightness of the light keep the retina functioning so steadily that a marvellous equability of sight is maintained in spite of the changes in lighting conditions, which are occurring constantly in the course of a day. The reaction of the eye to varying intensities of light will depend upon the health of the retina, and, if that be so, we might obtain an index of normality if it were possible to measure the time required for the recovery of loss of sensitivity after exposure to light. The retina, moreover, owing to its extreme delicacy of structure, is peculiarly susceptible to pathological influences, consequently an index of morbidity might also be obtained by similar measurements. To secure a quantitative measure of the light sense the patient must be kept in a dark room for at least half an hour before the examination. A special photometer is necessary, but the results will not be reliable unless preliminary precautions are taken to ensure dark adaptation of the retina beforehand. A quantitative examination of the light sense must of necessity, therefore, take up much time, and probably the tedious nature of the examination is responsible for so little attention having been paid to the light sense in ordinary clinical work.

It is possible to learn a great deal about both the light and the colour sense, however, by listening quietly to an intelligent patient as he describes his visual symptoms; and after he has told his story the ophthalmologist will learn still more by skilful cross-examination, supplemented by a careful scrutiny of all the signs and symptoms. Of course, any information regarding the light sense gleaned in this way is only qualitative, but the results of a clinical examination are usually sufficiently suggestive. If further information is required the ophthalmologist can take the patient to a laboratory, where a complete investigation can be made with the assistance of a physiologist.

The feeblest light capable of causing a sensation is the "light minimum," and the smallest increase in brilliancy of one of two lights is the "light difference." These two

are not interchangeable; each has its own clinical significance, but any disturbance in either guides us to the retina. Increase in light minimum is evidence that its receptor or functioning system is at fault—layer of rods and cones; while increase in light difference incriminates its conducting system—inner layers of the retina with the ganglion cells and nerve fibres. The rods and cones are the functioning units in the eye like the muscle fibre in the heart or the glomerulus in the kidney. That is important, because the first step in estimating the danger of derangement of function in any organ is to determine its functioning unit. The capillary supply⁶ is of equal importance, and in the retina both receptor and conducting systems have each their own separate blood supply. The rods and cones are supplied by the choriocapillaris through the choroidal vessels, and the ganglion cells and inner layers of the retina are nourished by the capillaries associated with the retinal blood vessels. As the functional activity of every organ depends upon the quality and quantity of the blood circulating through its capillaries, and as the primary function of the eye is the reception of light, variations in the light sense ought to yield clinical results of the first importance.

Increase in Light Minimum

The light minimum is always disordered in diseases which interfere with the circulation in the choriocapillaris, thereby disturbing the nutrition of the rods and cones, and preventing the normal regeneration of the visual purple. The following are some examples.

An elderly man complains that he is unable to read his newspaper with comfort by ordinary daylight, and that for a considerable time past he has had steadily increasing difficulty in working in the evening. He thinks he requires a change of spectacles. He admits, however, that long before he had any trouble in reading he had noticed that when passing from a well-lighted room into comparative darkness he felt so blind for a time that he was very uncomfortable. He does not realize that he suffers from any colour defect, but remembers that quite recently, when taking a country walk, he saw cornflowers growing in a field, and was surprised to observe that they had lost their blue colour and appeared to be black. He is quite healthy, and says he never needs a doctor, but on cross-examination he admits that for the past year or longer he has known that he has had to be more careful, both in eating and in drinking, because he is now liable to slight discomforts, which he attributes to indigestion. He complains of black spots floating in front of his eyes, and says he is sure they are due to "liver."

It is found on testing that in a good light vision, both for reading and for distance, is almost equal to the normal standard, and objective examination of the eyes reveals nothing more than slight congestion of the fundus with a characteristic lack of translucency in the ophthalmoscopic picture. The urine contains crystals of oxalate of lime, and there is a want of a proper ratio between the output and the specific gravity. There is little disturbance in blood pressure, but it tends to be somewhat higher than normal.

The fundamental disturbance in this case is an increase in the light minimum. Experiments have demonstrated that there is "a fairly consistent increase in the light minimum with age,"⁷ but obviously the patient here, although he may be close to the boundary line, has gone beyond the physiological limit. His symptoms are due primarily to the wear and tear of life with its cumulative auto-intoxications, which, from the clinical standpoint, are the result of prolonged functional disorder of the liver⁸ and renal inadequacy. They depend, therefore, more upon the general make-up of the patient than upon external causes. Nowadays we are apt to forget the influence of the constitution on metabolic processes, and to look for an external cause to explain the occurrence of every symptom. In the case just described the patient's disabilities are due not so much to manifest

ill-health as to a failure on the part of his constitution to adapt itself to his mode of life. It is not easy to demonstrate toxic substances in the blood, but the results of treatment by eliminant remedies are so satisfactory that the existence of some such cause working from within may be assumed.

An increase in light minimum is one of the earliest symptoms of primary glaucoma.⁹ That is a very important observation, because it proves the existence of a morbid process affecting the functioning unit of the retina through its blood supply, and denotes the onset of the disease before its more characteristic signs and symptoms have revealed themselves. There is no essential difference in processes which are physiological and those which are pathological, and disturbance of light sense thresholds are at their onset on the borderland between health and disease. When a doctor, in the course of his daily work, meets a symptom with which he is not familiar he is very apt to look upon it as of morbid significance, whereas with larger experience he will discover that it may also occur in the healthy. Mackenzie⁵ used to say that a symptom of disease in any organ is nothing more than the sensations that can be produced by over-exhaustion of the same organ in a state of health, and that the evidence of morbidity lies in the prematurity of its occurrence.

Like the fleeting attacks of dimness of vision and the appearance of rainbow-coloured rings surrounding a light, increase in the light minimum is a transient symptom, and on that account is easily overlooked and forgotten. Transient symptoms cannot, however, be studied too closely. They have an importance peculiarly their own, because when the patient can provoke them at will they are a perfect illustration of the experimental method of research, for the symptoms are the results of experiments performed by Nature herself in the laboratory of the patient's own body.

The onset of glaucoma is usually associated with some exalted state of mind—joyous or grievous—and as it is known that emotional disturbances and biochemical processes are very closely interrelated, it is easy to understand how toxins, circulating in the blood supplying the choriocapillaris, can inhibit the functioning of the rods and cones and interfere with the manufacture of an adequate supply of visual purple. Gjessing¹⁰ relates the case of a man who, as regularly as he drank a large cup of strong black coffee before breakfast, "saw rings of colour when he lighted his pipe" and suffered from other symptoms premonitory of glaucoma. In this case the coffee was probably the exciting cause of the disturbances of metabolism—a local manufacture by the tissue cells of a histamine-like substance—underlying the production of the initial symptoms of glaucoma. If that be granted, it affords a rational basis for their onset.

Night-blindness may be a patient's chief complaint. In ordinary daylight he suffers no inconvenience, but as soon as twilight sets in he sees so badly that to all intents and purposes he is blind. The symptom is pathognomonic of retinitis pigmentosa, in which disease pathological changes occur in the bacillary layer of the retina, destroying the rods and cones and preventing regeneration of the visual purple. In some cases of night-blindness, however, an ophthalmoscopic examination reveals nothing abnormal, and it is in these cases that the recognition of the symptom—night-blindness—is of very great assistance in diagnosis.

The disease may be hereditary and congenital, and is often discovered accidentally. The parents have no suspicion that there is anything wrong with their child's sight until they notice that if he is out of doors after sunset he becomes so blind and helpless that he may have to be carried home. When night-blindness occurs in

adults, without the appearance of pigmentary changes in the retina, it is usually the result of dazzling light, over-fatigue, and malnutrition. Dietary factors, which are in essence chemical factors, have an important influence upon nervous structures. Hippocrates recommended liver as a cure for night-blindness; and recent experimental research has demonstrated that the symptom can be produced in animals fed on a diet deficient in vitamin A, but that it disappears whenever cod-liver oil is added to the dietary.

In retinitis pigmentosa, however, the disease is steadily progressive, and the field of vision becomes more and more restricted until at length sight is blotted out completely. The retinal arteries are much contracted, and so much reduced in calibre that an insufficient supply of blood reaches the capillaries. It occurred to Royle¹¹ that in retinitis pigmentosa the choriocapillaris would be starved of blood, and that the rods and cones would in consequence suffer from want of nourishment. He thought that permanent vaso-dilatation of the ocular blood vessels produced by division of the thoracic sympathetic trunk at the level of the second thoracic ganglion would so alter the conditions underlying the disease that substantial benefit might be obtained. He has operated on several cases of retinitis pigmentosa by this method with such gratifying results that further experimental research is clearly indicated. Young,¹² when commenting on Royle's work, says: "It would seem that a similar effect might be obtained by a similar operation higher up—in the neck; it would hardly seem justifiable to employ the more difficult procedure of thoracic section when the sympathetic trunk higher up in the neck can be so much more easily and readily exposed." The original Claude Bernard experiment appears to secure all that is necessary.

Increase in Light Difference

A patient in this group sees best in a dull light. He is easily dazzled in bright light; a whitish-yellow mist rises like a cloud in front of the eyes and prevents him from seeing clearly. Towards sunset this sense of dazzling disappears, and he usually says spontaneously that he always sees best in the evening. When he meets his friends on the street in broad daylight he has much difficulty in recognizing them, and when he does see them he is shocked by their appearance—all healthy colour seems to have left the skin of the face, which looks like that of a corpse. The colour sense is obviously disordered, and the patient may remove all doubt on that subject by saying that when he is golfing he has no difficulty in seeing the white flags on the outward course, but that he cannot distinguish the red flags as he approaches the homeward greens; or, if he is a billiard player, he says that in certain positions round the table he has great difficulty in seeing the red ball.

That account of colour-blindness given so spontaneously by the patient can easily be confirmed by an examination in the consulting room. The defect, usually equal in both eyes, is called a central scotoma, because it is confined to the centre of the field of vision. The colour of a small disk of red or green paper cannot be distinguished in the line of direct vision, but is recognized at once in the periphery of the field. This central blindness for red and green is pathognomonic of increase in light difference, and is in sharp contrast to blindness for blue so characteristic of the presence of increase in light minimum. To anyone suffering from increase in light difference a bunch of sweet peas seems to be made up entirely of blooms of a blue colour: the hue of the reddish flowers is not recognized. As the disease progresses these colours assume a metallic lustre; red is said to glitter like gold and green to look like silver.

Clinical experience has taught us that these symptoms are due in a very large proportion of the cases to over-indulgence in tobacco and alcohol, but they also occur in those who have never smoked and have been life-long total abstainers. In every case, smokers and non-smokers alike, some toxic cause is active, but up till now all the efforts of the laboratory worker have failed to isolate individual toxins from the blood. Clinicians, however, still believe that the quality of the blood is intimately associated with metabolism, and that when there is derangement of metabolism, toxins quickly find their way into the circulating blood.

The patients are usually from 40 to 60 years of age, and both eyes are affected equally and simultaneously. The diagnosis must always be made from a careful examination of the symptoms, rather than from any ophthalmoscopic appearances which can be said to be characteristic. One of the most striking features of toxic amblyopia is the great contrast between the apparent gravity of the symptoms and the absence of any distinctive lesion which can be discovered with the ophthalmoscope. The prognosis is favourable; but the time required for recovery must be measured by months rather than by weeks.

Conclusion

In conclusion, let me repeat that when the functioning unit of the retina is affected the primary function of the eye suffers, and there is always danger of blindness; but when it is the conducting system of the retina that is chiefly at fault the prognosis is much more favourable. The extreme delicacy of the layer of rods and cones renders them very susceptible to every pathological influence, and when attacked they are very easily destroyed. The inner layers of the retina are more resistant; but when the noxious influence is sufficiently virulent they also are destroyed, and atrophy of the optic nerve is the result. The broad distinction between a lesion of the functioning unit and one of the conducting system applies to other organs as well as to the eye, and serves as a reliable guide both in prognosis and in treatment. A physiological study of the light sense enables us to make this distinction very easily in the eye, because in an individual patient a lesion of the receptor or functioning system of the retina is accompanied by increase in the light minimum, whereas a lesion of its conducting system is accompanied by increase in the light difference. The one cannot see in the dark; the other is very easily dazzled by bright light.

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J. Baumann (*Orvosi Hetilap*, December 8th, 1934) reports the discovery of a new gonadotropic substance occurring in the urine during pregnancy. In sexually mature rats this new preparation effects strong luteinization and development of the corpora lutea, but shows a temporarily negative effect on the development of the follicles. It does not produce the characteristic features of the Aschheim-Zondek reaction in infantile rodents, and is thus seemingly a different substance from the previously known gonadotropic products of the urine.