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THE members of this Academy all belong to highly specialized branches of medicine. The unparalleled increase of scientific knowledge in modern times has inevitably led to the growth of specialism in every department. The day of the Admirable Crichton has passed for ever. It is futile to shut one's eyes to this fact, as is often done. On the contrary the position must be faced boldly, for specialism undoubtedly has its dangers, which must be studied and circumvented. It seems to me that the welfare of mankind in the immediate future depends more upon co-ordination of existing knowledge than upon the acquisition of new knowledge; and in many respects the former is the more difficult task—the latter is quite able to take care of itself, at any rate in the domain of the physical sciences.

Most of the papers and discussions which we hear at such meetings as this are of a highly specialized nature. An address such as that you have done me the honour to ask me to deliver is an opportunity for surveying a broader field, of attempting a synoptic view.

The reactions of every living animal, upon which its survival

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depends, are responses to the impacts of various forms of physical energy derived from its environment. In the lowest forms of life the response to any adequate stimulus is a crude tropism. Evolution to a higher plane in the animal scale is associated with, and indeed determined by, increased differentiation of the receptive organs and correspondingly increased differentiation of the resultant responses. In the higher animals the differentiation has led to the development of many receptors, far more numerous than the classical five senses of man. All these receptors are receptors of physical stimuli, whether derived from the outer world or from within the body. The receptors for mechanical stimuli are not confined to those of the tactile sense proper. In fishes the elaborate lateral line system responds to differences of pressure in the surrounding fluid medium, and hearing, both in fishes and higher animals, is but a further sublimation of response to rhythmical pressure changes in the surrounding medium. The proprioceptive receptors in the muscles, tendons and joints are but endogenous receptors of mechanical changes in tension of the parts. There are a host of chemical receptors—true chemical receptors in the mouth and on the body of fishes, almost atrophied to mere vestiges in man, further elaborated into taste and smell organs both in fishes and higher animals, for in both of these the actual stimulus is chemical. Many such occur in the organism itself, for hormones were first revealed as chemical stimuli, although their function does not end there. Perhaps the most remarkable of these are the chemical products of nervous activity which themselves act as stimuli in the synapses and end organs in the form of histamine, acetylcholine, etc. The receptors of radiant energy subserve responses to change of temperature, but the most "glorified heat spots" to use Sherrington's dramatic term, are in the retina and subserve vision.

The simplest response of the animal to a physical stimulus above the level of a mere tropism is reflex action. Here the stimulus excites an end-organ, gives rise to an afferent nerve impulse which is transmitted through one or more intercalary cells to an effector cell, an efferent nerve and an effector organ. Chemical activity seems to dominate every step in the process. In some cases it is definitely the intermediary between the stimulus and the nerve impulse; perhaps the best example is the pupil reflex to light where the optic nerve impulse is started by a photochemical substance, visual purple or other such. Every nerve impulse in every nerve is invariably associated with an electrical response, which is probably the manifestation of ionic activities and therefore chemical in character. The discovery of adrenaline, histamine, acetylcholine, etc., indicates that every synapse and every neuro-effector junction is the seat of chemical activity.

The fundamentally important part played by reflexes in even the highest animal economy has been exhaustively studied by Sherrington and his pupils. They have shown how, as the result of summation, facilitation, inhibition, and so on, the most complex and apparently purposive responses are brought about. Indeed they have done much to bridge the gap between the activities of the lower levels of the nervous system and those higher levels which subserve conscious life.

At some point in this chain consciousness arises. Of consciousness we have no criterion but our own individual experience. In man reflex acts are unconscious acts, but higher activities at any rate show some analogy to reflex acts. The constellation of physical stimuli arouses perception of an experience suffused with meaning, which in turn arouses a conation towards the appropriate response. It is probable that lower in the phylogenetic scale the reflex act is associated with a crude undifferentiated sentience.

We are accustomed to associate a particular sensation with the response of one of the higher so-called sense organs—touch with a tactile organ, hearing with the ear, vision with the eye, and so on. But just as a pure reflex is a physiological abstraction so is a simple sensation a psychological abstraction. It is true that in a given experience one sensation may be so predominant as to mask the complication produced by the others. Indeed, one sensation may be predominant in the life history of an animal, and upon it, its survival may appear to depend. Thus it is certain that in many animals such as the dog, the sense of smell is prepotent, and there is little doubt that one of the most important factors, if not *the* most important factor in the supremacy of the primates and man, was the development of the prepotency of vision. None the less the meaning of an experiential presentation—to use psychological language—is derived from the presentation as a whole, and this is an integration of all the sensations derived from all the incumbent stimuli. This “pluri-receptive summation and interference” (Sherrington) by means of which the reactions of receptors of different modality are integrated is a biological mystery. There is indeed a similar integration on a higher level than this perceptual plane, for the presentation as a whole forms a pattern (Gestalt) which possesses meaning which cannot be explained by the mere algebraic summation of its parts.

From these introductory remarks it will be gathered that the study of normal vision demands no small knowledge of physics, chemistry, physiology, neurology, and psychology. As you all know the study of clinical ophthalmology demands also a knowledge of general medicine and surgery, pathology and bacteriology.

The importance of physics is early impressed upon the student,

for, at any rate in the early part of his career, the correction of errors of refraction will be his chief source of income. He must therefore know a good deal about optics, for nature has ordained that the end organ of vision shall be constructed on the principles of a photographic camera. The curious psychological fact must have struck most teachers that medical students are inherently averse from mathematics. My own experience is that they will show an intelligent interest in geometrical proofs, but that they jib at an algebraical or trigonometrical expression. This is the more to be deplored in that opticians as a rule have had to submit to a much more intensive training in the theory of optics. I once expressed my regret to a distinguished physicist that many ophthalmic surgeons had a very elementary idea of the optics of retinoscopy. His reply was that one need not be a watchmaker in order to make good use of a watch. Admitting the cogency of this argument, the fact remains that the most efficient use of the ophthalmoscope, the slit-lamp, corneal microscope, etc., can only be attained by the thorough knowledge of the underlying optical principles. *Verbum sap.*!

The problem of visual acuity is primarily a purely physical problem and was first elucidated by astronomers. The discrimination of two points is simply the problem of the resolution of an optical instrument, and depends like it upon the formation of images by an approximately homocentric optical system with spherical and chromatic aberrations and diffraction at the margin of the pupil, and a receptive screen with a definite size of grain. But when all the physical conditions have been thoroughly established it is still found that the eye is a living organ and does not behave quite like a camera or a telescope. Though the physical conditions remain stationary the eye behaves differently in different circumstances. Thus it is found that there is a very much higher sensitivity to contour discrimination than to the resolution of two points of light. Whereas the former is of the order of a visual angle of at least 30 or 40 seconds of arc the latter is as low as 4 or 5 seconds of arc. This fact cannot be explained on purely physical grounds. The sensitivity of the receptive screen, the retina, and the mutual physiological inductive changes (contrast effects) which are set up in neighbouring areas of the retina result in a discriminative capacity which far exceeds that of any other sense organ in any animal. Fortunately for the physicists they discovered this fact empirically long ago and by means of the vernier applied it to their measuring instruments. Hence the extreme accuracy of physical measurements to which this form of discrimination can be applied, and their inaccuracy when it is not applicable, as in photometry. Physicists in their gibes at biological research often forget that their own criteria are themselves based on biological data.

The presence of an intermediary chemical activity between the physical stimulus and the nerve impulse in vision may be regarded as proved by the discovery and investigation of visual purple. It is true that this is positively proved only for scotopic vision *i.e.*, vision under dark adaptation and weak light. It is almost certain that the much more complicated phenomena of photopic vision under light adaptation and greater intensities of light are also due to photochemical intermediaries which have not yet been isolated. The activities of adrenaline, pituitrine and other hormones and of histamine and acetylcholine suggest that there is a chemical intermediary in all cases of nerve excitation.

The researches of Keith Lucas, Adrian, A. V. Hill and others have educed some fundamental facts in the chemistry and physics of the impulse in the nerve. Every nerve impulse is accompanied by rhythmical changes in electrical potential, and these are of the same nature irrespective of the type of nerve—whether motor, sensory, proprioceptive, etc. The response is of the all- or -none type, *i.e.*, a stimulus causes a maximum response or none at all, and there is a refractory state during which a stimulus of any strength is ineffective. Increase of intensity of the stimulus increases the frequency of the waves of response but does not affect their amplitude.

The electrical responses which accompany stimulation of the retina are much more complex, as might be expected, since a chain of several neurones is involved. The study of the electroretinogram of late years, especially by Granit and his colleagues, has thrown much light upon the highly complex functions of the retina. In typical form the curve shows a latent period, a small negative change of potential (*a*); a sharp rise of potential (*b*); a gradual fall followed by a slow positive wave (*c*); and a positive rise (*d*), when the stimulus is removed. There is little doubt that these complex waves are the integration of at least three waves, one negative and two positive.

The Purkinje experiment proved long ago that the visual impulse starts in the neuroepithelial layer of the retina. It then passes through the bipolar cells to the ganglion cells whose processes end in the primary optic centres, whence another neurone carries the impulses through the optic radiations to the occipital cortex. It is attractive to regard the neuroepithelium as analogous to the epithelial end organ of a tactile nerve; the bipolar cell as a neurone of the first order analogous to the posterior root ganglion cell; the retinal ganglion cell as a neurone of the second order analogous to the mesial fillet; and so on. It must, however, be remembered that the retina and optic nerve are embryologically parts of the central nervous system, and there is now ample evidence to show that many of the functions of the retina can be best explained by bearing this fact in mind.

The evidence of the extraordinarily high discriminative capacity of the fovea shows that there is a strict dissociation of the impulses derived from neighbouring cones. The anatomical basis of this dissociation is found in the fact that each foveal cone has its own individual bipolar cell and ganglion cell—whereas in extra-macular regions several rods and cones form synapses with one bipolar cell, and several bipolars with one ganglion cell. At the same time there is evidence even in the macular region that summation of impulses can occur between neighbouring areas of excitation, and this is far more marked in peripheral regions of the retina. Thus it has been proved that such summation occurs by visual tests and also by the electrical responses in the retina and nerve. It was proved by Riccò and has been amply confirmed that the threshold stimulus in the macular area depends upon the quantity of light, *i.e.*, the same quantity of light may be concentrated in a small spot or spread over a larger area. The anatomical basis for the summation is to be found in the amacrine and horizontal cells of the retina. So far as foveal vision is concerned these facts appear to be contradictory, and can only be reconciled by physiological explanations. The minute discrimination of foveal vision demands an inhibition of the summation which occurs in different circumstances. All the facts of spatial induction (simultaneous contrast) prove the reciprocal action of neighbouring areas of the retina upon each other when stimulated; and that this reciprocal action takes place in the retina and is not at any rate entirely dependent upon activities in the higher centres is proved by the effects of such stimulation upon the electrical responses. We owe to Granit the most exhaustive experimental proof of the facilitation, summation, inhibition, etc., of impulses in the retina just as they were proved by Sherrington and his pupils to occur in the spinal cord.

That these facts are not merely of academic interest is shown by the complex phenomena of vision experienced in every day life. It is only as the result of recent experiments that we are obtaining some idea of the causation of the evil effects of glare in interference with visual acuity and the production of discomfort, headache, and so on. By the careful experiments of Stiles, a physicist at the National Physical Laboratory, a numerical criterion of the effects of peripheral illumination on central vision has been obtained.

The persistence of vision as the result of momentary stimulation by light shows that the retina acts differently from a photographic film. The response to a single short stimulus is a series of waves of sensation, several of which may in favourable circumstances rise above the threshold and give rise to recurrent vision. Repeated short stimuli give rise to flicker which fuses into a continuous sensation if the repetitions occur sufficiently often. It has

been found that the critical frequency at which flicker disappears is dependent entirely upon the brightness of the resulting sensation and is independent of the wave-length of the light. This is the Ferry-Porter law which holds good for central vision, but when the critical frequency of flicker for peripheral regions of the retina is measured under different conditions of central and peripheral illumination complicated results are obtained, as has been shown by the admirable experiments of Lythgoe and Tansley. All these results show the importance of reciprocal activities of various parts of the retina; and some of them seem to indicate that the activities initiated in the cones may have an inhibitory effect upon those initiated in the rods and vice versa.

The visual phenomena to which we have already referred show that the eye must be an efficient optical instrument. That this may be so the media through which the light passes must be transparent, and the curvature of the cornea must be kept constant. In order that the latter requirement may be fulfilled the pressure of the fluid contents of the eye must be kept practically constant and above the atmospheric pressure, so that the walls of the globe may be kept in state of tension. The transparency of the media demands that the cornea and lens shall be free from blood vessels, and therefore some mode of nutrition independent of proximity of blood vessels shall be provided. Since the nutrition of the lens and vitreous depends upon the intra-ocular fluid a stagnant fluid at constant pressure, which would suffice to keep the tension normal, will not suffice to keep these structures healthy. Movement of some kind or other must occur in this fluid.

The theory of the formation of the intra-ocular fluid which has held the field up to recent times is the filtration theory which is specially associated with the name of Leber. Clinical observation and experiments on animals seemed to prove that no process of true secretion occurs, and that the facts are adequately explained by the difference between the intracapillary and intra-ocular pressure. It is not to be supposed that the earlier investigators ignored other possibilities, such as the importance of osmotic changes. For my own part, after reviewing all the evidence available at the time, I always taught my students that the facts appeared to be "not inconsistent with" the filtration theory. Evidence has accrued of recent times to show that osmotic interchange is more important than was once thought. Much of this evidence depends upon minute physical and chemical measurements which are perilously near the border line of experimental error. I am always rather suspicious of chemical weighings carried to four places of decimals! At the same time it must be admitted that our knowledge of colloid chemistry has increased so much that the body of evidence in favour of the intra-ocular fluid being a simple dialysate

is much stronger than it was. Perhaps one of the strongest arguments is the greater concentration of chlorides in the aqueous as compared with the blood plasma, for on the dialysation theory one would expect negatively charged ions to be driven through the capillary walls in order to maintain thermodynamic equilibrium with positively charged colloid ions (proteins) in the blood.

The natural enthusiasm which these results merit and have received tends to obscure the rôle which filtration plays in the process. For though these biophysical and biochemical reactions must now be admitted to be fundamental to the process of lymph formation they are completely explanatory—if that—of only static conditions. Under those conditions the intra-ocular pressure represents the resultant of the intracapillary pressure (say, 50 mm. Hg) minus the difference between the osmotic pressures of the aqueous and plasma (30 mm. Hg) *i.e.*, 20 mm. Hg. But the intra-ocular pressure is never static. It follows passively normal changes in the blood-pressure due to pulse and respiration. It undergoes large rises due to activity of the extrinsic ocular muscles and the movements of the lids. Large changes in the general blood-pressure are accurately reflected in it except in so far as they are modified by local vasomotor and chemical effects. If, however, the general changes persist, as in cases of hyperpiesis, compensation occurs and the intra-ocular pressure resumes its normal level. Convection currents are also set up in the anterior chamber owing to the difference in temperature between the iris and cornea.

Hence the atomic and molecular changes which have been proved to occur are associated with molar changes which alter the hydrostatic conditions. These are specially marked under abnormal conditions. If the aqueous is evacuated, *e.g.*, by paracentesis, the capillaries dilate, their walls become more permeable and filtration of fluid takes place. The fluid thus formed more nearly resembles the blood-plasma in containing more protein than the normal aqueous. If again the eye is massaged the intra-ocular pressure falls. Seeing that this pressure is dependent upon the volume of the contents of the globe and the other conditions are not materially altered, the fall of pressure must be due to the mechanical expulsion of fluid from the eye. Cases of secondary glaucoma indicate the chief site of exit, for in them the angle of the anterior chamber is blocked. There can be no doubt that the rise in intra-ocular pressure which occurs in secondary glaucoma is due to blockage of this "filtration angle," whereby the aqueous is denied free access to the canal of Schlemm.

It has been shown that if the intra-ocular pressure is raised so as to exceed that of the venous pressure the veins collapse. This results in a reflex rise of arterial pressure so that the circulation is restored. The process may in some cases be repeated until the

intra-ocular pressure is equal to the arterial pressure, and the circulation stops. The canal of Schlemm, however, is a venous channel in the substance of the cornea, and therefore does not collapse even when the intra-ocular pressure is moderately raised. Filtration can therefore occur through its inner wall—unless the latter is rendered impermeable by adherent iris, etc.—and an exit is thus provided for the excessive fluid and the normal intra-ocular pressure is restored. The meridional fibres of the ciliary muscle are inserted anteriorly into a scleral “spur.” There is reason to think that when this muscle contracts on accommodation it pulls the spur backwards, thus tending to keep the canal of Schlemm open.

The permeability of the capillaries is increased in inflammatory conditions, *e.g.*, iridocyclitis, and a plasmoid lymph, rich in protein, is formed. This causes a rise in intra-ocular pressure, and there can be little doubt that, since in these cases the filtration angle is not otherwise obstructed, and is indeed generally abnormally open, the high tension is due to the difficulty of filtration of the large moleculised colloid proteins into the canal of Schlemm.

Many other facts might be adduced to show the importance of filtration in the maintenance of normal and the relief of abnormally high intra-ocular pressure. Neither dialysation nor filtration, nor both together, suffice to explain all the facts of normal and abnormal intra-ocular pressure. The dialysation theory has to fall back upon the variable permeability of the capillary walls in the various tissues of the body to explain the differences of lymph-pressure and constitution; and this variable permeability is at present only explicable on teleological grounds.

The long established explanation of the mechanism of secondary glaucoma depends upon the application of the filtration theory to the anatomical conditions found in these cases. Even the most ardent advocates of the osmotic theory of the formation of the intra-ocular fluid regard the so-called “filtration angle” of the anterior chamber with the canal of Schlemm as the principal site of exit of the fluid and in general concur in the accepted view for secondary glaucoma. The very ingenious theory of Priestley Smith for the explanation of primary acute glaucoma also involves blockage of the exit channels. The constriction of the circumferential space in the hypermetropic eye by the continued growth of the lens is insufficient in itself to bring about the crisis, which is said finally to be due to venous congestion of the ciliary processes. Recent biochemical work tends to lend support to this exciting factor, for it has been shown by Dale and others that histamine-like bodies are found normally in many tissues of the body and are produced readily by antidromic impulses in nerves (*cf.*, Lewis’s “triple response” in the skin). These bodies produce dilatation

of the capillaries, and are liberated by all forms of radiant energy. Duke-Elder has shown that the histamine-like response can be obtained in the albino rabbit's iris by stroking it and that the more widespread axon-reflex is abolished by cocaine—a typical example of the triple response.

Priestley Smith's theory, however, does not explain the not infrequent cases of acute glaucoma in myopic eyes, and fails entirely to explain cases of chronic glaucoma. No one with wide experience of the latter disease can be satisfied with the tentative explanations which have been advanced. The treatment of such cases by trephining, etc., has been founded upon the theory of blockage of the filtration angle, and in spite of its crudity and empirical nature is fortunately successful in preserving vision in a large proportion of cases. There are other cases in which it quite unexpectedly fails. There are, moreover, many cases in which increased intra-ocular pressure is never proved, and the presumption that it occurs is merely a slavish adhesion to current dogma. I have had rare cases of deep cupping in both discs, with full fields and normal visual acuity persisting for several years, yet eventually developing paracentral scotomata and finally constriction of the nasal fields. One must conclude that chronic glaucoma is not a single entity but embraces cases in which the aetiological factors are different.

Recent biochemical researches on histamine and similar metabolites and on the nature of the vitreous suggest possibilities which only further research can prove or disprove. Specially interesting in this connection is the chronic primary glaucoma associated with epidemic dropsy met with in India. In the 1934-5 epidemic 1,695 cases were treated in Calcutta (Kirwan). Although the disease is regarded as due to feeding on stored, par-boiled rice, it is quite different from beri-beri, and cannot be regarded as a deficiency disease. The interesting fact from the present point of view is that Kirwan found evidence of large amounts of histamine or at any rate an "H-substance" in the aqueous humour of a large proportion of the 23 cases he was able to examine. The albumin in the aqueous was also increased so that the ratio of albumin to globulin, which is normally 0.44 to 1.0, was in the ratio of 2.3 to 1.0, the crystalloids remaining normal.

I shall refrain from further discussion of these metabolites in this connection because I must confess that the independent variations in the calibre of the capillaries which have been proved by Krogh and others have introduced further complexity in estimating the hydrostatic conditions in various parts of the vascular system.

The work done on the vitreous has been almost as revolutionary as that done on the intra-ocular fluid. Like it I do not think it is

as revolutionary as appears at first sight. It may be considered as proved—at any rate for the sake of argument—that the vitreous is a gel, and that the fluid which constitutes the sol is in every respect identical with the aqueous. The latter fact conforms with the filtration theory. It is stated that the greater concentration of micellae at the periphery, etc., is in itself sufficient to account for the “structure” which has wrongly been described as a hyaloid membrane; and that similar concentrations and coagulations elsewhere account for slit-lamp and histological “structures” which have been described in the interior of the vitreous. It is to be remembered, however, that the foetal vitreous originates from definite structures derived from the retina, and is full of blood vessels derived from the central artery of the retina and comprising the hyaloid artery and veins. It can scarcely be doubted that the fibres of the suspensory ligament are permanent relics of embryological structures and are not due simply to micellar aggregations. Normally the hyaloid vascular system disappears and the vitreous gel which replaces it is an inert non-vascular jelly nearly resembling the jelly-like material which is formed by the degeneration of the granulation tissue of a so-called Meibomian cyst.

So far as the non-ionised constituents and the albumin and globulin in the vitreous are concerned they are in identical proportion with those in the aqueous. The vitreous, however, also contains a mucoprotein and residual protein, and it is upon these that its behaviour as a gel depends. The investigations of Baurmann, Redslob, Duke-Elder, and others have shown that these proteins have two iso-electric points at about pH 4 and pH 9, and it is upon these that the turgescence and deturgescence of the vitreous gel depends. The maximum change of volume of fresh vitreous gel occurs at about pH 8 to 9, and consequently we may expect that the volume of the vitreous is increased if the fluid contents are abnormally alkaline. Investigations of the alkalinity of the blood in chronic glaucoma have led to conflicting results, but it can scarcely be doubted that the considerable pressures exerted by a swollen vitreous may be an important factor in the pathogenesis of glaucoma.

The crystalline lens, like the vitreous, is a non-vascular organ, and like it is not susceptible to inflammation, so that the old terms hyalitis and phakitis imply ignorance and should be discarded. The chief pathological condition met with in the lens is cataract, and clinical observation over many years has led to the accumulation of a vast body of information as to the types of cataract and the concomitant conditions under which they occur. None the less our ignorance of the fundamental causation of cataract is abysmal. There can be little doubt that the solution of the

problem depends upon the discovery of the normal metabolism of the lens and the factors which lead to its upset. Hence it is not surprising that a large amount of attention has been devoted to the biochemistry of the lens, and the remarkable advance which has been made in biochemical methods of recent years has led to the revelation of many facts which cannot but be of fundamental importance in spite of the fact that they cannot at present be co-ordinated into a satisfactory theory.

The most important chemical constituents of the lens are the salts and proteins. Spectroscopic examination reveals many metals, of which the most important are sodium, potassium, and calcium. The potassium content diminishes with age, but the calcium is relatively constant (Adams). The normal lens contains more potassium than sodium, the reverse of the aqueous. It contains more potassium and phosphorus, less sodium and chloride, and the same amount of calcium as blood serum. The proteins consist of euglobulin, and α -, β -, and γ -crystallins. β -crystallin is soluble in water and decreases with age, a factor in the normal process of sclerosis of the nucleus of the lens. The crystallins are rich in tyrosine, cysteine, and leucine—amino-acids which tend to form melanins on exposure to ultra-violet light, thus accounting for the normal and pathological pigmentation of the lens.

Owing to the absence of a blood supply the lens is dependent for its metabolism on an autoxidation system which has been proved to be identical with that which occurs in muscle (Hopkins). It is carried out by means of a reversible oxidation—reduction reaction, the catalytic agent of which is a cysteine-like substance, probably identical with the glutathione found in muscle. This substance contains an SH group, which on oxidation changes into a SS group. Thermostable substances, of which the chief is probably β -crystallin, effect reduction of this product (SH=SS).

In senile cataract the potassium almost disappears, and the calcium may be eight times the amount of the normal (Adams). The total protein and β -crystallin are diminished. α -crystallin is most easily precipitated and is peculiarly sensitive to precipitation by calcium (Tsuji); its coagulation is probably the chief cause of the opacity in cataract. Glutathione diminishes and finally disappears. In senile cataract there is no significant change in blood-sugar, as compared with the increase which is concomitant with diabetic cataract, nor in the calcium content, as compared with its diminution in tetany and parathyroid cataract.

Biochemically the essential factor in cataract is the coagulation of the proteins, and many important factors in this process have been discovered in recent years. In general, coagulation of proteins occurs in two stages; (a) denaturation, probably by hydrolysis, whereby the colloidal system becomes more labile; (b) agglu-

mination. Any form of radiant energy—heat, luminous, ultra-violet, radium—can cause coagulation. Ultra-violet rays alter the permeability of the lens capsule (Duke-Elder), diminish the efficiency of the autoxidation system (Adams), and render the proteins more vulnerable to variation in hydrogen ion concentration and salt concentration, *e.g.*, calcium (Burge). Changes in the capsule cause alteration in osmotic pressure and hence in concentration of electrolytes. Deformation of the fibres leads to mechanical strains. Further, the lens proteins are organ specific, especially α - and β -crystallins, but investigations of their serological properties have proved contradictory. The relative parts played by these factors in the development of various types of cataract are obscure, and have not yet led to any satisfactory prophylactic or therapeutic results.

Apart from the experimental production of cataract in animals by various forms of radiant energy it is easily produced in rabbits by administration of naphthalene and other allied poisons; dinitrophenol, for example, used for slimming, has produced posterior cortical cataract in girls. The occurrence of cataract in tetany, due to parathyroid deficiency when correlated with the excess of calcium in cataractous lenses, suggests a definite association with the rôle of calcium in metabolism. Bourne and Adams found that the blood calcium was fundamentally unchanged by prolonged naphthalene dosing in rabbits. Yet they have shown conclusively that the blood calcium may determine the effect of naphthalene on the eye; for an oats and cabbage diet, which prevents naphthalene cataract, causes a high blood calcium, and is associated with the deposition of crystals, probably calcium oxalate, in the retina; whereas a bran and carrots diet causes cataract and toxic symptoms in conjunction with naphthalene, and is associated with a low level of blood calcium. Recently Yudkin and Arnold have produced cataract in albino rabbits by administration of lactose or galactose, the latter being the more potent; this can be explained by disturbance of calcium metabolism.

I think I have given sufficient examples to show that laboratory experiments have materially advanced our knowledge of the physiology and pathology of the eye. Many other advances of a similar but more general nature doubtless have a distinct bearing on ophthalmological problems. Thus Tansley and others have proved conclusively that vitamin A is essential to the metabolism of visual purple. It is easy to produce night-blindness in rats by deprivation of this vitamin in their diet; and indeed, Charpentier, working with Granit, has used these animals for the purpose of analysing the electroretinogram. E. Mellanby's researches have shown that avitaminosis produces widespread changes in the nervous system, especially in the afferent nerves

and this may have a bearing on the aetiology of retrobulbar neuritis, whether as a manifestation of disseminated sclerosis or not, and possibly upon the aetiology of some lesions associated with the trigeminal nerve. It is by no means improbable that the metabolism of the eye structures is profoundly modified by disturbances in the internal secretions of glands, such as the thyroid, pituitary, adrenal, and the genital glands. Polyhormonic preparations have, indeed, been recommended as a cure for incipient cataract by Siegrist and others. Most competent observers have pronounced this method of treatment as a complete failure. In spite, too, of the immense amount of work which has been done on immunology the practical results must be regarded as disappointing. *Parturiunt montes, nascetur ridiculus mus.* We may all agree that vaccine treatment is often beneficial, and sometimes curative, but there is a lamentable discrepancy between the frequency of its application and the successful results.

These advances in knowledge have by no means been neglected by clinicians, and praiseworthy attempts have been made to apply them to clinical problems. Great ingenuity and great perseverance have characterized these efforts. Only too often enthusiasm has outrun discretion, and the earlier reports of startling success have been followed by discouragement and ultimate admission of failure—or more commonly, silence. For my own part I am convinced that the future advance of ophthalmology, and indeed of medicine in general, can be attained only by persistent pursuit of these more purely scientific efforts correlated with careful and equally truly scientific clinical observations.

For it must be carefully borne in mind that scientific research is a method and a mode of logical thought vitalized by intuition and imagination. Though many, perhaps most, of the outstanding discoveries of science have been made in the laboratory, scientific research is emphatically not the perquisite of the laboratory. If such were the case astronomy could not be classed among the sciences in spite of the fact that it owes so much to laboratory discoveries. The physical processes which underlie most biological problems are so complex that few of these are solved by what I have elsewhere termed the "synthetic" method. The fact that a cataract can be produced by the application of radiant energy does not solve the problem of cataract. We learn most about cataract by clinical observation and experimentation, *i.e.*, by accurate correlation of the relationship of complex conditions. Just as psychological problems are rarely explicable upon a purely neurological theory, so biological problems are rarely solved by purely physical methods. Both modes of approach can be made truly scientific, and the scientist should admit that his scorn of empiricism is not wholly justified.

Every case which we are called upon to treat is a biological problem, and we are paid fees for the express purpose of investigating these problems. Whether we do so scientifically or not is a matter of method; and whether we make any great discovery or not is not even solely a matter of scientific training, but depends also upon inborn factors in the observer, such as imagination and intuition. For intuition, unscientific as the concept appears to be, surely plays a large part in scientific discovery. How did Gonin get the idea of sealing up the holes in a detached retina? If it was pure chance he is still to be credited with the discovery that only in those cases in which the holes were sealed up the retina became attached.

Discoveries have indeed been made as the result of action upon entirely false premises. Such was von Graefe's discovery that iridectomy affords a cure for acute glaucoma. He first performed the operation on the theory that iridectomy, often performed in those days for optical purposes, reduced the normal intra-ocular pressure—a wholly erroneous observation.

Our knowledge of the physiology of the normal intra-ocular pressure is still very scanty, and that of pathological increase of tension still more so, yet considerable success has been obtained in the treatment of chronic glaucoma by the many drainage operations which have been devised. If, as I think, they are all very crude methods of dealing with a little understood pathological condition, they at least have the pragmatic sanction that they are often successful in retaining sight. They remind me of Michael Foster's criticism of electrical stimulation of the brain, which he compared to playing the piano with a broomstick.

While we must all be profoundly dissatisfied with the utilitarian results of the application of biochemical and other forms of more "purely" scientific research, and also with the groping advances of hit-or-miss empiricism, we may yet rest assured that unmistakable progress has been made in our knowledge of ophthalmological problems and in our treatment of diseases of the eye. It is not given to everyone to be a biophysicist, a biochemist, a physiologist, or indeed, a pathologist. For such it is encouraging to know that he also can do useful research work; and it is still more important that all who have to deal with patients should be thoroughly trained in clinical methods, and that their clinical training should not be limited to their own speciality.

Recent numbers of the *Archives of Neurology and Psychiatry* have contained a valuable series of papers on the training of the neurologist and the psychiatrist. The arguments which apply to neurological training apply equally to ophthalmological training; and I cannot do better than quote the words of my colleague,

Dr. F. M. R. Walshe :—"So I believe," he says, "that while technical methods of investigation and experimental studies have now to be included in the essentials of a complete neurologic training, clinical observation remains the foundation of neurologic medicine and on it all else must be built. Only the adequately trained clinical observer can evaluate the relationship of the results of laboratory and other technical methods of investigation to the symptoms of disease presented by the individual patient, for it is the individual that is the material of our study, be it remembered, and not an abstract thing called 'disease.'"

The importance of the training and acumen of the observer is admirably expressed in the words of your great authority on medical education, A. Flexner. He writes, "There is a widespread impression that the scientific quality of medical education and practice is in some fashion dependent upon the part played by the laboratory. This is not the case. Science is essentially a matter of observation, inference, verification and generalization. Not only is the part played by the active senses the essential criterion of science; one may go further, the vast and complicated paraphernalia of science are merely means of extending their scope."

I have no hesitation in stating that in my opinion clinical medicine is better taught, and therefore better practised, in England and the United States than in any other part of the world; and this is largely, if not chiefly, due to the fact that British and American students have not only freer access to the hospital patient than in other countries, but are compelled by careful note-taking themselves to investigate the signs and symptoms of disease and to exercise their own wits in arriving at a plausible diagnosis.

INTRACAPSULAR CATARACT EXTRACTION*

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THE problem of intracapsular cataract extraction is not a new one. There is a considerable amount of literature on the subject, much of which is controversial; thus Appleman¹, in discussing a first series of 100 cases, regards the method as being an ideal procedure; de Grosz² reminds us that the further results of intracapsular removal must be followed up for many more years and

* Abstract of Paper read at the Manchester Meeting of the North of England Ophthalmological Society, October, 1936.