THE BRITISH JOURNAL OF OPHTHALMOLOGY

MAY, 1935

COMMUNICATIONS

THE PATHOGENIC PROBLEM OF SO-CALLED CRITICAL ALLERGIC CONJUNCTIVITIS

(Specific sensitization—Non-specific sensitization—
Instability of organic colloids)

BY

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GENERAL pathology undergoes continual revision, required by the rapid progress made in our knowledge concerning humoral conditions. Familiarity with evolution of this kind is absolutely necessary in the special field which interests us. Advance in ideas dealing with anaphylaxis and immunity is incessantly presenting various angles of the pathogenic questions related to certain ocular disturbances. A close study of seasonal forms of conjunctivitis and crises intimately related to these conditions raises the questions of idiosyncrasy and anaphylactic sensitization.

1. *Historical.* A. *Clinical relations.*—Spring, or vernal, conjunctivitis was, for a long time, grouped with infectious forms of conjunctivitis. Writers of the last century, however, mention certain facts morphologically differentiating vernal from infectious conjunctivitis. In 1846, Arlt published three cases of gelatinous infiltration of the corneal limbus. Under the term perikeratic hypertrophy of the conjunctiva Desmarres presented, in 1847, bulbar changes identical with those described by Arlt and, in his clinical courses given in 1854, von Graefe described, accompanying

these perilimbal gelatinous infiltrations, pavement-like proliferations occurring in the tarsal conjunctiva.

Then ensued the bacteriological epoch. Since bacteriology revealed no bacteria and also since the current treatment of conjunctivitis was ineffective, some of the aetiological studies were directed toward essential tissue conditions (of the soil, or "terrain"). For example, Terson considered these forms of conjunctivitis related to arthritis, while Angelucci assigned them to a lymphatic constitution. Other investigations dealt with non-bacterial causes of irritation.

As early as 1872, Saemisch stressed the periodicity of the disease and Danvers noted resemblances between vernal conjunctivitis and hay fever. Schreiber, of Magdeburg, wrote: "It seems to me that the flowering season of grasses constitutes an essential factor in exacerbations of the signs of irritation. I have treated a farmer and his son, aged 10 years, the father presenting typical hay fever and the son vernal conjunctivitis, which was of recurrent type and invariably occurred when the father was affected with hay fever."

Horner and his pupil Vetsch observed analogies between spring conjunctivitis and the erythema of pellagra which occurs on parts of the skin exposed to sunlight. Schmeichler and Schiele actually termed spring conjunctivitis chronic solar eczema. Kreibich, of Gratz, noting the fact that thickening about the corneal limbus occurs in some lichenoid forms of aestival prurigo, called attention to the possible influence of the blue and ultra-violet rays of the spectrum. How far is the light-factor important? Is spring conjunctivitis produced by light, as solar erythema is, or as dazzling and blindness are caused by reflection from the snow? I merely touch upon these points. They gave rise to a remarkable expression, stated in 1907 by Axenfeld,¹ in his Report to the French Society of Ophthalmology, as follows: "According to the theory of light, the sensitizing factor is supplied by the human individual. It sensitizes in a way analogous with that of fluorescent substances, such as quinine sulphate, eosin or fluorescein, which sensitize to the action of the blue and ultra-violet rays. Further studies should, therefore, prove the existence of this sensitizing factor in the affected individuals."

B. *Experimental pathology*.—Experimental work has added certain data to clinical facts and the pre-existing hypotheses concerning the pathogeny.

von Szily,² in 1913, published a work on anaphylaxis as occurring in diseases of the eye. One chapter of this book reports experiments made by Wesseley, Colombo, Stanculéanu and Nita, Dold and Rados, who utilized the conjunctiva of the dog and guinea-pig for the introduction of proteins into the organism. Following

subconjunctival injections, or simple instillation, of horse serum in sensitized animals, these writers observed that the conjunctiva has the same absorbent capacity as that possessed by other mucous membranes and that it may give rise to reactions of anaphylactic nature.

At this same period, Weinberg and A. Julien³ presented papers to the Biological Society on the fatal effects occurring in horses following instillations into the conjunctival sac of toxins produced by ascarides. "These effects," they remark, "appear to be of anaphylactic character, the affected animals having been previously sensitized by the ascarides infesting and eliminated from them." In 1918, van Es and A. F. Schalck⁴ similarly reported, in the *Annals of the Pasteur Institute*, the results of studies undertaken to develop the anaphylactic nature of certain parasitic intoxications occurring in different animals.

Such was the status of the question in 1921. At this period, so close to our own, the observations of experimental medicine were as if separated by an impermeable partition from the pathological facts which are now interesting us.

II. *Present work.* A. *Endocrine disturbances.*—The November number of *Arch. d'Ophthal.* (1922) contains⁵ two cases of conjunctival reaction, noted in the spring of that same year and occurring in individuals bearing different congenital anomalies which resembled each other because a metabolic disturbance existed in both cases, consisting of diabetes in one, and of myxoedema and hypo-ovarian phenomena in the other.

The endocrine disturbances present in these two cases constituted their principal feature of interest. The factor acting as antigen upon the conjunctival mucosa was identified and I concluded my comment on the cases by stating, in italics, "that a state of sensitization was fundamentally present, that it was related to disturbance of the endocrine functions and that the treatment of the given affection should be sought along these lines."

It is in this spirit that I have studied this condition. In other words, I have attempted to find the diathetic factor, hereditary or acquired, transitory or permanent, which determines this sensitization of the conjunctival mucosa. In the volume of the *Ann. d'Ocul.* for 1928 occurs a note⁶ referring to cases of spring conjunctivitis occurring in children at the prepuberal period. For me these cases were specially interesting because they showed the dependence of the ocular condition upon the psychic and sexual developments immediately preceding puberty and also because they showed the beneficial effects of opotherapy.

I supplied Madame Delthil⁷ with new cases, published in her thesis. One case was that of an American woman, some 40 years of age, affected with seasonal nasal and conjunctival crises ever since

undergoing a gynaecological operation producing uterine atrophy and almost complete amenorrhea. Another case featured similar disturbances, the patient in this case cohabiting with a cat since sudden and permanent arrest of menstruation at the age of 22 years.

A study of tuberculous allergy and its ocular manifestations shows clearly the allergic changes which the human organism may undergo through cosmic, climatic and meteorological variations under the action of the so-called "anergizing" infectious diseases, or under the influence of physiological variations in the humoral equilibrium as occurring in the hormonal crises of puberty, or of the menopause, or of the usual monthly phase of menstruation, or during pathological disorders in the activity of the endocrine structures.

However, it is by no means necessary to abandon sure and positive knowledge in favour of theories merely imagined. Only facts which are proven and unquestionable escape the risks of reasoning by analogy. All the cases whose essentials I have just pointed out have been published after having been followed up for a sufficiently long time and have the common conclusion as to the value of the sympathetico-endocrine abnormality and the interest inherent in opotherapy and hormonal treatment. Since 1922, the date of the earliest observations of non-infectious reactions of the conjunctiva, my attention has been essentially directed toward disturbances in the endocrine system.

B. *Sensitization*.—Anaphylactic sensitization, whose demonstration was possible after 1922, and supplied proof in place of mere hypotheses in ophthalmology, is another element which is common to all these cases. It permits non-infectious and non-bacterial reactions of the ocular conjunctiva to be placed in a special group, which includes affections like asthma or spasmodic coryza. The mucosae of the nose or the conjunctivae and respiratory tract are susceptible to the same pathological conditions. Since they are similarly exposed to similar influences, it is but logical to expect them to present similar, if not simultaneous, reactions. The association of these three types of reactions in the several mucosae is shown frequently in clinical work. As with the crises of asthma, those of the ocular conjunctiva are to be grouped with affections of anaphylactic nature, while some cases also show a relation between this group and urticaria and Quincke's disease. Still other cases, occurring more recently, have been subjected to the Prausnitz-Kutzner test for passive allergy.

C. *Experimental studies*.—Almost immediately following the clinical cases, experimental pathology has added arguments favouring interpretation of the facts as being of anaphylactic nature. In 1924, Alan C. Woods⁸ concluded from his studies that the eye shares in the anaphylactic mechanism occurring generally

within the organism and that a local sensitization exists which is more marked if the releasing injection is made locally. Working with guinea-pigs, Bret Ratner⁹ observed, in 1927, that if certain of the animals be previously sensitized and that if some of the latter be exposed to an atmosphere containing protein dust while others be injected parenterally with a liquid extract of these proteins, conjunctival hypersecretion appears in the animals of both groups, persisting for an hour and a half and sometimes still longer.

D. *Clinical confirmation.*—Clinical cases being rapidly added to those already mentioned are also of great interest. Among these must be included those of Lehrfeld,¹⁰ in 1925, who noted five cases of vernal conjunctivitis, occurring in young people. He made skin tests in these cases with different proteins, some of the tests proving positive for ordinary fruits and vegetables, while others were positive for the proteins of hair and plumage of domestic animals. One of the interesting publications of Pasteur Vallery-Radot¹¹ reports true conjunctivitis replacing, and occurring at the time of, dyspnoeic crises in a case of asthma. Morenas¹² reports a striking case of conjunctival reaction accompanying the presence of oxyuris, compares it with a similar case obtained from the German literature and concludes as follows: "How can these facts be interpreted otherwise than as manifestations of verminous anaphylaxis?"

E. *The syndrome of so-called critical allergic conjunctivitis.*—These various labours have finally permitted the emergence of very exact ideas and the isolation of a definite and special syndrome. The latter presents the following characters:—

1. *Its nature* consists of pruriginous cutaneous or mucous reactions. They appear and cease abruptly, thus assuming the character of crises.

2. *The conditions under which the syndrome occurs* consist of identical climatic, seasonal or environmental circumstances.

3. *Pathological associations.*—A frequent co-existence or alternation of other anaphylactic signs, including dystrophic conditions, such as endocrine syndromes, developmental disturbances or disorders of puberty or of the menopause.

4. *Absence of infectious signs and the histological changes commonly occurring in follicular conjunctivitis.*—Bacteriological examinations are negative. Smears show no including cells, but a larger or smaller number of eosinophilic cells.

5. *Sensitization tests.*—Cutaneous or intradermal reactions are positive. So also is the Prausnitz-Kutzner test for passive allergy.

6. *Reactions to treatment and medication.*—Adrenalin and ephedrin act immediately and temporarily. Cessation of the action of the antigen acts immediately and durably. Opotherapy acts slowly and favourably. Desensitization is effective.

As with experiment, clinical medicine shows that two types of critical conjunctival reactions may be distinguished. To the first type belong reactions perhaps indicating local sensitization, since the crises occur always at the same site. Reactions of the second type are local and alternating or associated with other manifestations of the same morbid group, but are very variable in relation to the clinical syndrome of which they form a part (asthma, urticaria, Quincke's disease, etc.) and cannot be assigned to local sensitization.

Summary of the data

a. The individuals whom I have studied are dystrophic and attention is drawn to the effects of the dystrophies upon humoral equilibrium. In the cases I present, I note as far as possible the criteria of haemoclastic and blood-vascular changes.

b. The disorders in question are determined by sensitization to various antigens. In many cases this sensitization appears specific.

c. The sensitization mentioned cannot be identified with experimental anaphylaxis without explanation of certain contradictory facts which constitute problems in themselves, as follows:—

1. Why does the anaphylactic crisis never here immunize against a fresh anaphylactic shock?

2. Why do not slight and successive contacts (necessarily occurring in pollen anaphylaxis, for example) establish in medical anaphylaxis a state of resistance comparable to that shown by Bersredka in experimental or serum anaphylaxis?

3. Is there not often a contradiction between what we know of tact of a mucous membrane or the skin with some general substance anaphylaxis proper and cases in which frequent and repeated contact suggests a mode of anaphylactic sensitization, although here there is not the incubation phase required for the production of the anaphylactic sensitization?

The complexity of these problems renders definition of certain basic ideas desirable, the usage and parallel descriptions for which they are employed requiring exact knowledge of the meaning of the terms anaphylaxis, allergy, receptivity, sensitization and idiosyncrasy. Three facts, of experimental nature, provide here the bases of definition:—

1. The anaphylactic phenomenon.
2. Protein shock.
3. Colloidoclastic shock.

1. *The anaphylactic phenomenon*.—An animal, injected for the first time with a heterologous albumin, in itself perfectly harmless, and left for some 10 days in repose for incubation, dies suddenly when receiving a minute dose of the albumin previously injected. Such is the phenomenon described for the first time by Charles Richet and Portier.

The effects accompanying the death of the test animal appeared highly striking to the earlier observers. Almost immediately after receiving the so-called releasing injection, the animal presents convulsions, posterior-tract paralysis, vomiting, diarrhoea and death. During this dramatic laboratory episode, examination shows marked humoral changes. The blood becomes suddenly incoagulable, the leucocytes disappear from the peripheral circulation and the blood pressure declines. This blood-vascular crisis constitutes the humoral proof of anaphylactic shock.

The fact has thus been established that, instead of immunizing, the first injection of a harmless substance such as albumin confers upon an animal organism permanent sensitization after a period of incubation. As expressed by Charles Richet, a memory of the first injection remains for ever. This test likewise proves that, under certain conditions, a substance harmless in itself may become lethal. Such are the phenomena of anaphylaxis and anaphylactic shock.

2. *Protein shock*.—Now, is humoral shock anything new and extraordinary? Has nothing of the kind ever been observed in the past by physiologists? Biedl and Krause, Arthus, and Nolf have shown that, during the past half-century, the records of the physiologists prove that identical effects have been observed following intra-venous injections of tissue extracts, egg-white, peptone or any heterologous albuminoid. The test animals died in the same way as with modern tests. The same humoral crises occurred (decline in blood pressure, incoagulability of the blood and diminution of the leucocytes in the peripheral blood) and the same clinical signs (convulsions, posterior-tract paralysis, vomiting and diarrhoea) were noted preceding sudden death.

Anaphylactic shock thus presents nothing very extraordinary. As Arthus expressed it, the shock appeared as a manifestation of *proteotoxy*, that is, as a sign of intoxication assignable to some specially toxic property of the albuminoid molecule, designated by Charles Richet in anaphylaxis as *apotoxin*. However, anaphylaxis continued to remain fundamentally interesting.

The discovery of Richet consisted in the proof that humoral shock may be fatal without any previous sensitization, but that it must be produced under such conditions by the *intravenous* injection of a large dose of the heterologous albumin, while the same effect may occur by the *subcutaneous* injection of a very

minute dose, provided the test animal be sensitized some days before with an inoculation of the same substance, not at all toxic in itself.

3. *Colloidoclastic shock*.—Fernand Widal proceeded to examine the question of toxicity. Clinically, any form of intoxication has specific characters peculiar to each of the known toxins. Veronal poisoning is unlike that produced by mercuric chloride or strychnine. Now, do substances essentially harmless as far as known, such as organ extracts, peptone or egg-white, really become toxic under certain conditions? And, if they do become toxic, should they not produce the same toxic disturbances and organic changes?

Charles Richet had shown the relations between anaphylaxis and immunity by proving that, when an individual has overcome the releasing injection he may then with impunity receive injections of enormous quantities of the substance which should theoretically prove fatal, the shock having suddenly annulled the state of anaphylaxis. How could this fact be reconciled with the idea of intoxication and what was known of intoxication?

Such were the major reasons for causing Widal to doubt the existence of toxicity in the problem. He approached the experimental problem by suggesting to his more intimate associates that, at the moment of the releasing injection, some *physical* action must occur within the organism capable of returning to the normal immediately or almost immediately after being created. Experiments were, therefore, undertaken under his direction attempting at first to produce states of humoral shock with substances other than heterologous albumins, which were at the same time quite atoxic. These tests showed that abrupt injection into the veins of a substance like an isotonic solution of sodium bicarbonate or chloride produces a shock indistinguishable from protein shock. Such sudden intravenous injection produces changes in the coagulability of the blood, diminution of the leucocytes in the peripheral blood, a shiny appearance of the blood and this humoral shock is followed first by a chill and then by a marked rise in temperature, and vomiting or even diarrhoea may occur. A decisive advance had thus been made.

Among these special conditions which he was so capable of interpreting, a study of paroxysmal haemoglobinuria supplied Widal with a new argument. In the crises of haemoglobinuria produced by exposure to cold, he showed that the haematuria was determined by something other than haemolysis. He observed that urticaria often develops while the individual is being chilled, that there is always a chill followed by rise in temperature, rachialgia and vomiting, and that these clinical signs of shock are inseparable from the humoral and haemoclastic crisis characteristic of shock.

Humoral shock may thus be produced not only by an injection of an isotonic solution of sodium chloride, but by merely chilling the individual. The resulting shock should not be, and could not be, distinguished from proteotoxic or anaphylactic shock or from the effects attributed to the apotoxin of Charles Richet.

In broad lines, such are the points which enabled Widal to affirm that specificity in a living being largely depends upon an individual condition in the humours created by colloids and that anything capable of altering this colloidal specificity is likely to produce the signs of a shock which may be termed *colloidoclastic*.

As soon as Richet's work became generally known, many theories were presented assigning various pathological syndromes to anaphylaxis. Such haste showed the universality of the discovery. However, I can scarcely believe that a real relation was established between experimental and medical anaphylaxis in publications other than those of V. Hutinel, in 1908,¹³ Lesné, Dreyfus and Charles Richet, Jr.,¹⁴ in 1911, on alimentary anaphylaxis, F. Widal on anaphylactic reactions in urticaria¹⁵ and asthma,¹⁶ in February and July, 1914.

A historical date was that of the case of asthma in a sheep vendor studied by F. Widal, Lermoyez, Abrami, Brissaud and Joltrain. By simply shutting up the man in a stable with his sheep a crisis of asthma was produced in the man, preceded by intense haemoclastic or colloidoclastic shock. As he had asserted the year before in connection with paroxysmal haematuria, Widal¹⁷ showed that, in urticaria as in asthma, identity of these several types of shock depends solely upon a physical process, since the shocks occur under a wide variety of conditions, and that this process consists in a sudden upsetting of equilibrium in the blood plasma. "Many disturbances," he wrote, "heretofore assigned to intoxication, and others whose mechanism is not yet known, correspond very probably to sudden colloidal disequilibrium."

The cases of conjunctivitis alluded to above should be grouped with the studies made upon urticaria, Raynaud's disease, asthma and spasmodic coryza. The element of sensitization is evident in all these conditions, and colloidoclastic phenomena are frankly characterized. In most of my cases sensitization is of specific character, the conjunctival crisis being produced at will by the same antigen. Some of the cases, however, raise another question. For example, a patient whose case was imparted to Madame Delthil, experienced ocular disturbances for the first time while making a garment from American wool and the so-called "angora" wool. The symptoms recurred whenever she wore this garment. She had positive cuti-reactions with this wool and other samples

like it. The symptoms ceased only when she ceased to handle wool and woollen garments.

Possibly the case was one of incipient sensitization. Does it not bring up, in a different form, a question raised by the cases reported by Widal, Abrami and Jacques Lermoyez,¹⁸ in which a crisis of coryza or asthma could be produced by a dose of aspirin, but for which intolerance developed after the first ingestion of the substance? Here the intolerance occurred under conditions such that it is not possible to consider this idiosyncrasy due to sensitization to aspirin.

I have recently observed a nine-year-old child who had a very evident conjunctival crisis, accompanied by suffocative signs, both being developed while the child was playing with a Siamese cat. The child often played with ordinary cats, but never presented and never presents now any such effects from contact with them. On careful investigation, we have proved that only the Siamese cat produces the crisis of asthma, coryza, and conjunctivitis, and have found that the child had known of no other cat of this species. The question arises whether this case is one of sensitization or of idiosyncrasy.

The problem of idiosyncrasy and its relations with the state of the organic colloids has remained unsolved for a long time. A particle of colloid appears ultra-microscopically as a group of molecules. Each of the latter contains numerous atoms, which form a complex whole. The complexity of the molecular structure permits a vast number of chemical combinations capable of being represented by stereo-chemical diagrams or formulae and also allows a huge variety of biological reactions. According to the place occupied by each atomic group with reference to the central nucleus, the essential part of the colloidal particle, various substances are or are not capable of combining with the colloidal complex.

Armand Gautier has taught that any substance must be capable of a stereo-chemical relation with some element of an organism in order to act upon that organism. Without such a relation, which may be considered geometric, between an organism and a medicinal agent, for example, no combination, and consequently no medicinal action, can occur. Speaking of such a combination, Fischer said that it is like the fitting of a key in a lock, an accord having occurred between the heterologous substance and the molecules forming the proper organic colloid. These facts show how the problem of idiosyncrasy is linked with the colloidal pathology which we are considering and how this problem extends widely beyond the earlier conception of anaphylaxis.

By this rapid review of facts interpretation of which we are seeking I wish to point out that, starting with experimental anaphylaxis

and having collected clinical cases in which sensitization seems unquestionably present, and having sought to learn what distinguishes auto-anaphylaxis, or spontaneous anaphylaxis, from the anaphylaxis of Charles Richet—I repeat that I beg to make it clear that there are cases in which sensitization appears native, constitutional, diathetic and quite independent of proved sensitization.

The conclusion of this survey is necessarily provisional. However, it is to the effect that pathological disturbances exist which are caused by sensitization, or susceptibility, of which the fundamental humoral test consists of colloidoclastic shock, a sign of the diathetic instability of equilibrium in the organic colloids. At present, this special susceptibility assumes three aspects, as follows:—

1. Specific sensitization, due to anaphylactic sensitization, similar to experimental anaphylaxis.
2. Specific sensitization produced allergically, in a way not resembling experimental anaphylaxis.
3. Non-specific sensitization, corresponding to diathetic instability of colloidal equilibrium and forming another group of allergic reactions.

Medical conceptions and theories are fated to be subjected to practical verification and therapeutic tests more immediately than is the case with other scientific productions. I have no need to defend such proofs. I need only allude to desensitization, constituting a test of sensitization, and to Ravaut's ideas¹⁹ on secondary cutaneous sites of allergy, stated in connection with eczema and the Bruno Bloch phenomenon. These ideas have added fresh arguments to the general idea of sensitization.

I wish to close this discussion by mentioning the results obtained by acting upon the organo-vegetative nervous system by the treatment of endocrine disturbances. There are many reasons for considering of main importance the relations which have been shown to exist between the colloidoclastic diathesis and alterations in the endocrine functions. Therapy is already taking advantage of this point, considering that a relation between effect and cause exists.

In May, 1922, Widal, Abrami and L. de Gennes²⁰ and, again, Widal and Abrami²¹ published a case in which crises of asthma were cured in a myxoedematous patient and again, in May, 1924, reported similar success in a case of hyperthyroidism. These facts may be grouped with details of a case of complex pluriglandular disturbances following surgical castration, reported in 1922. Here castration accompanied the typical paroxysmal syndrome occurring in the conjunctiva, and opotherapy acted beneficially both upon the ocular affection and the glandular conditions. The cases of mine which were published in Madame Delthil's thesis justify

the following conclusion : Recent studies have shown the influence of the organo-vegetative nervous system and of the glands of internal secretion in spring conjunctivitis. This affection occurs sometimes in adults, combined with disturbances in endocrine function, but it is more especially an affection of childhood and puberty which, contrary to other anaphylactic conditions, has a tendency to disappear as the equilibrium of the organism becomes established.

If it be true, as Renan wrote, that "scientific specialists do the most effective work toward mental progress," the study of certain blood-vascular conditions of the eye and certain critical changes in ocular tension have already shown that, in this phase of scientific effort the tasks of the specialists have a share in the general problem of biology. In closing, I beg to allude to what Ed. Joltrain²² said, in 1933, in the *Presse Médicale*, with reference to emotion as a factor of humoral equilibrium, as well as to the discussion carried on during the preceding year by the Paris Ophthalmological Society²³ upon visceral pain associated with glaucoma. These brief comments serve to indicate that the new pathology, founded on the work of Fernand Widal, opens an unbounded prospect to specialized work.

The variety of clinical syndromes which this creative mind has pointed out for our study includes, for example, painful acrocyanosis, oedema, pruritus, erythema, paroxysmal dyspnoea, haematuria and other affections of the general kind which are such as to impress us with the inevitable necessity of revising ophthalmological syndromes in accordance with the fresh light emanating from Widal's views.

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TRACHOMA—RECENT ADVANCES AND THE PRINCIPLES OF PROPHYLAXIS*

BY

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A DISCUSSION of the social and legal measures which may be taken in different countries to reduce the incidence of trachoma, and to relieve the suffering and disability it causes, may be prefaced by a definition of what is meant by trachoma, and by a summary of the recent advances in our knowledge of the disease.

Trachoma is a specific contagious disease of the conjunctiva

* A report by A. F. MacCallan, President of the International Organization against Trachoma, read on April 3, 1935, at the Annual Meeting of the Organization held in London on the invitation of the Ophthalmological Society of the United Kingdom.