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THE STORY OF SHIPYARD EYE*

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The title of this lecture sounds rather mysterious, suggesting the adventures of a one-eyed pirate who sabotages shipyards. In fact, this account does have much in common with a detective story: it is replete with mystery, mistaken identity, a missing phial of poison, and the final dénouement in which the hero of the beginning of the story turns out to be the villain.

My story begins 70 years ago, in 1889, when several Austrian ophthalmologists (Fuchs, 1889) described a new disease entity under various names. The illness consisted of an acute conjunctivitis with extreme oedema of the conjunctiva, pain, photophobia, and lacrimation, followed by superficial erosions of the cornea, and finally by deeper, opaque subepithelial corneal infiltrates located just beneath Bowman's membrane. These unique opacities were round, located mainly in the centre of the cornea, and they persisted for up to two years. If the opacities were large or numerous enough they seriously impaired vision. Systemic manifestations of illness were lacking.

In the next 40 years many reports appeared in the medical literature indicating that this illness was worldwide. Epidemics involving thousands of persons were described in Asia and sporadic cases occurred in European countries. Controversies arose among ophthalmologists regarding the possible identity of similar disease pictures, and many suggestions were made concerning the possible aetiology of the illness. However, bacteriological studies remained inconclusive. Wright (1930), who observed some 3,500 cases in Madras, suggested a viral aetiology and transmitted the typical disease to volunteers by means of filtered conjunctival washings.

During the summer of 1941 a very large outbreak (more than 10,000 cases) occurred in Hawaii, at the Naval shipyards of Pearl Harbour. Soon thereafter the illness made its appearance on the West Coast of the United States. Several thousand cases were diagnosed, most of them workers in shipyards. Members of their families and other close contacts were rarely affected. Hogan and Crawford (1942) studied 125 patients in detail and coined the name "epidemic keratoconjunctivitis," abbreviated as E.K.C. However, the popular name "shipyard eye" was attached to the disease, and this name persisted even when the illness spread to other industries across North America in 1941-2, seriously hampering war production. By then

exhaustive studies had ruled out a bacterial aetiology, and the apparent infectious nature of the illness made a search for causative viruses mandatory.

Search for a Virus

Techniques for virus isolation were well advanced at that time. Perhaps the most intensive search for a specific virus was made by Dr. Murray Sanders and his associates. They inoculated material from infected eyes into embryonic mouse brain in a Maitland-type tissue culture. After several passages in that medium the intracerebral inoculation of mice resulted in neurological symptoms and death. The virus was stated to be also fatal for rabbits and some monkeys, and to be neutralized by sera from several E.K.C. patients, but not by antisera to the viruses of herpes simplex, lymphocytic choriomeningitis, or Theiler's mouse encephalomyelitis. The inoculation of one volunteer resulted in acute conjunctivitis but no keratitis. The publications by Dr. Sanders and his group appeared in 1943 (Sanders and Alexander, 1943; Sanders *et al.*, 1943). Dr. Sanders went off to war, and the virus gained admission into textbooks as the "virus of epidemic keratoconjunctivitis."

The Missing Phial

We now come to the missing phial of poison. After the second world war several virologists wanted to examine the "virus of E.K.C." They searched for a strain of Sanders's agent in various laboratories, refrigerators, and dry ice cabinets, but alas—the virus had disappeared. Only a single tube labelled "Virus of E.K.C.," perhaps originating in Dr. Sanders's laboratory, could be discovered. It was carefully examined by Ruchman (1951) and by Cheever (1957), who noted to their dismay that it was actually a strain of St. Louis encephalitis virus. Sera from patients who contracted E.K.C. in 1951 contained no antibodies to this agent (Ormsby and Fowle, 1954). Competent virologists failed to recover a virus from the 1951 outbreaks of E.K.C. by Sanders's technique, although latent mouse viruses were occasionally activated in the course of mouse passage. To confound the confusion there were scattered reports from several countries describing the "isolation of the virus of E.K.C." It was difficult to accept these reports, because the descriptions of no two of these viruses resembled each other, and the agents appeared to be too fragile to permit their transportation from the discoverer to other investigators. At that point our group felt that perhaps it would be best to discard the accumulation of myth, fiction, and hearsay and take a new look at the aetiology of E.K.C.

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In December, 1954, a seaman (Trim) came to our clinic at the University of California in San Francisco suffering from intensely painful red eyes for 12 days. The illness had started on board ship several days after his departure from an Oriental port, with an "inflammation" in the right eye, and had spread to the left eye about four days later. On examination he exhibited a very severe conjunctivitis with pseudomembrane formation and enlarged pre-auricular nodes. A few days later he developed the typical subepithelial corneal opacities of E.K.C. (Fig. 1). The nurse

FIG. 1.—Subepithelial corneal infiltrates in patient Trim 99 days after onset of eye symptoms (artist's drawing). Reproduced, by permission, from *Amer. J. Ophthalm.*, 1955, 40, 203.

FIG. 2.—Subepithelial corneal infiltrates (clinical photograph) typical of epidemic keratoconjunctivitis in nurse of patient Trim. Reproduced, by permission, from *Amer. J. Ophthalm.*, 1955, 40, 203.

who took care of him also contracted E.K.C. 10 days after her initial contact with the patient, and eventually developed typical opacities (Fig. 2).

Adenovirus Type 8

Scrapings were taken from the conjunctivae of our patient (Trim) and inoculated into tissue cultures of strain HeLa cells. After an unusually protracted period of incubation these cultures yielded a cytopathogenic virus, subsequently established as the prototype of adenovirus type 8 (Jawetz *et al.*, 1955). Up to the present time some 100 strains of this agent have been isolated all over the world, all from the eye, and with rare exceptions all

from typical cases of E.K.C. Acute and convalescent serum specimens obtained since 1952 from patients with E.K.C. regularly exhibited a rise in neutralizing antibodies for adenovirus type 8.

A serological survey was conducted in several countries where E.K.C. had recently occurred. Among 132 patients carrying the diagnosis of E.K.C. 80% had antibodies to adenovirus type 8 in a serum dilution of 1:10 or greater. Among 106 individuals of similar age and place of residence who had no history of clinical E.K.C., only 8.6% had such antibodies. These findings pointed strongly to a constant association between adenovirus type 8 and typical E.K.C. (Hanna *et al.*, 1957). It was, of course, desirable to establish a similar serological pattern for patients who had contracted E.K.C. prior to 1952. Regrettably, properly stored serum obtained in the 1940s from patients with active clinical E.K.C. has not been available. Regrettably, also, the titre of neutralizing antibodies to adenovirus type 8 declines rapidly in man, so that diagnostic levels are not usually encountered more than two years after the onset of clinical E.K.C. (Jawetz *et al.*, 1956). Thus we have been unable to diagnose by retrospective serology the aetiological agent involved in the E.K.C. epidemics of the early 1940s.

Final proof for the aetiological role of adenovirus type 8 in E.K.C. came from the inoculation of volunteers. Mitsui *et al.* (1957) regularly produced E.K.C. by the instillation of adenovirus type 8 grown in tissue culture into the eyes of volunteers, provided they possessed no specific antibody to that virus. Conversely, neutralizing antibody concentrations of 1:20 or greater in the serum protected volunteers against disease after experimental inoculation. Such antibody was, at times, present as the result of clinical or subclinical infection in the past, or it could be induced artificially by repeated subcutaneous injections of active adenovirus grown in tissue culture. Specific neutralizing antibodies protected against challenge infection with either infectious material from fresh cases of E.K.C. or with laboratory-grown adenovirus type 8 (Mitsui *et al.*, 1959).

Some Peculiar Properties

In laboratory studies of several strains adenovirus type 8 exhibited some peculiar properties which set it apart from other types of the adenovirus group. When grown in a variety of cell strains in tissue culture the yield of infective virus was invariably very low, never exceeding 300 tissue culture infective doses (TCID₅₀). Extracellular virus was extremely stable, persisting at room temperature for weeks. Only a portion of the inoculated virus was adsorbed on to cell sheets, yet there was no evidence to suggest that certain cells were much more resistant than others. In spite of the low yield of infective virus the total antigenic mass in such tissue cultures was high, when estimated as complement-fixing antigen.

While this test admittedly detects mainly a soluble antigen, distinct from the infective particle, it seemed probable that it reflected the total amount of virus synthesis in culture. If this assumption is correct most of the virus produced in culture is non-infective. The ratio of infective virus to complement-fixing antigen in cultures of adenovirus type 8 (200 TCID₅₀/ml. and 160–640 units antigen/ml.) was quite different from that usually encountered with type 4 (3,000 TCID₅₀/ml. and 80–320 units antigen/ml.). Thus it was reasonable to assume that infective virus constituted only a minute fraction of the total antigenic mass produced in the course of viral growth. The question naturally arose whether the non-infective antigenic material, the postulated non-infective virus, might account for some of the biological peculiarities of adenovirus type 8.

It is quite possible that non-infective antigen interferes with the adsorption of infective virus on to susceptible cells, or with infective virus production after adsorption. This might account for the uniformly low infective titres of type 8 encountered in many laboratories. If non-infective antigen were capable of combining with specific antibody it might effectively compete with infective virus for available antibody molecules in virus-serum mixtures. This might explain the extremely narrow range of virus concentrations—usually only threefold to tenfold—which can be employed in serum-neutralization tests (Jawetz *et al.*, 1958). This odd behaviour of adenovirus type 8 in the laboratory makes one wonder whether similar features might be exhibited in human infections and might, perhaps, account for the curious epidemiological pattern of E.K.C.

The Diverse Epidemiology of E.K.C.

Several puzzling aspects of the epidemiology of E.K.C. have been noted in the past (Thygeson, 1948). In most

outbreaks in the Western world, particularly in the United States, Canada, and Britain, the disease was sharply limited to adult workers in certain industries—for example, shipyards—with only negligible spread to members of their immediate families, in spite of close and protracted contact. Other outbreaks centred around hospitals where eye surgery was performed, or offices of ophthalmologists. There appeared to be virtually no subclinical infection in the population at large, and E.K.C. was not seen in children. Neutralizing antibodies were encountered in only 4–5% of persons who lived in the area of a recent epidemic but had not themselves suffered from the disease.

In Oriental countries, particularly Japan, the epidemiological pattern seemed to be quite different (Tanaka, 1957). E.K.C. was not principally an industrial disease. As pointed out by Mitsui *et al.* (1955), children were commonly infected. They developed a systemic illness with fever, respiratory or gastro-intestinal symptoms, and a pseudomembranous conjunctivitis, but no keratitis. Sporadic cases in adults often occurred in families with infected children. Subclinical or mild infection appeared to be relatively common. Between 25 and 33% of the general population had a significant antibody titre to adenovirus type 8. How can one explain such different epidemiological behaviour of the same virus in different parts of the world?

The Virus in Action

We had an opportunity to get a glimpse of this virus in action when a member of our group contracted an accidental infection with adenovirus type 8 in the laboratory.

This 41-year-old technician and five other persons had handled adenovirus type 8 in routine laboratory procedures for from two to four years without ever developing clinical or serological evidence of infection. The accidental contamination probably occurred while she injected, repeatedly, large volumes of infective tissue culture fluids into rabbits. Soon thereafter she had a severe and entirely typical attack of E.K.C., involving both eyes and leading to the unmistakable subepithelial corneal opacities. She was closely observed clinically during the entire course of illness, and conjunctival scrapings for virus isolation as well as serum specimens were obtained frequently. All her close contacts were also examined. The results of these observations were remarkable. In spite of the extremely pronounced inflammatory response and chemosis, persisting for several days, only minute quantities of infective adenovirus type 8 were recovered from the patient's eyes. Only on the first day of each eye's involvement could more than three tissue culture infective doses be collected. During the remainder of the two weeks of acute eye involvement virus was isolated with great difficulty, requiring one or more blind passages in tissue culture.

Thus it became evident that in this patient, as in tissue cultures, very little infective virus was released and hence she did not transmit the agent to others. Indeed, her husband, four children aged 7–12, and several close associates remained uninfected both clinically and serologically, although she used no aseptic precautions whatever during the earliest days of profuse lacrimation when the largest amount of infective virus was recovered. Because of the small quantity of material in conjunctival scrapings it was unfortunately not possible to assay for

non-infective antigen. However, this accidental infection suggested that the amount of infective virus produced in the adult eye was insufficient for spontaneous transmission of E.K.C., and that special circumstances were required to produce infection at all. Among these, direct inoculation of the eye by fingers, instruments, or solutions, and a relatively concentrated inoculum appeared important. The eye is probably the only portal of entry which permits the establishment of symptomatic infection by adenovirus type 8 in adults. Subcutaneous injection of the highest available concentration of infective virus (as undiluted tissue culture fluid) into volunteers failed to induce clinical disease (Mitsui *et al.*, 1959).

A Possible Explanation

All these threads of evidence may now be woven into the following tentative explanation for the diverse epidemiology of E.K.C.

The adult is not highly susceptible to adenovirus infection, the eye being the sole portal of entry and the principal susceptible tissue. Infection is likely to occur only if a large inoculum is placed direct into the eye. Infection of the adult yields very small amounts of infective virus, so that spontaneous transmission is improbable. Spread from one adult to another must therefore depend on direct transfer of virus from one eye to another. The individual most likely to accomplish such a transfer appears to be a nurse or physician engaged in examining the eye. The extreme stability of extracellular adenovirus aids the persistence of infective virus in ophthalmic solution or on instruments. Thus E.K.C. in the Western world appears to be largely an iatrogenic disease. Because of the low spontaneous transmissibility of the infection, antibodies and immunity are infrequent in the general population. Thus virtually all persons exposed to the manipulations of an eye physician are susceptible to infection, and should he disseminate virus an explosive outbreak ensues. The shipyard, with its chemical and mechanical irritants, brings many workers to the dispensary, where doctor or nurse may inoculate them with adenovirus type 8. Epidemics of "shipyard eye" continue to occur. This pattern appears applicable in the United States, Great Britain, and Canada, and is well supported by factual evidence.

For Oriental countries such as Japan an alternative epidemiological pattern may be proposed. Small children appear to be relatively susceptible to adenovirus infection. They may commonly develop a systemic illness with only minor involvement of the eye. It is possible—but needs to be established—that the yield of infective virus from children is much higher than from adults. Thus a child might spread the agent effectively to other children (possibly through respiratory or gastro-intestinal excretions) and to adults. When childhood infection is prevalent a mechanism exists for the endemic maintenance of the infection in the population. In such circumstances the dispensary may play only a minor part in the spread of the disease. While much of this hypothesis is entirely speculative, some facts in its support are established now. Childhood infection is common in Japan; children are commonly the first members of the family group to be infected (Mitsui and Jawetz, 1957); between one-fourth and one-third of the population have antibodies to adenovirus type 8, suggesting a high endemic level of infection. The

systemic nature of the childhood infection and its prevalence suggest that it can be acquired spontaneously by routes other than eye-to-eye transmission. However, we lack information about the quantity and route of virus excretion in the child and the precise nature of its transmission.

Conclusion

Thus I have come to the end of my story of shipyard eye. At present adenovirus type 8 unquestionably causes epidemic keratoconjunctivitis, and it may well be the sole cause of this disease in its typical form. Thus it is proper henceforth to support the clinical impression of E.K.C. by laboratory evidence of infection with adenovirus type 8—either by virus isolation or by the demonstration of a rise in specific neutralizing antibody titre. The mythical “virus of epidemic keratoconjunctivitis” or “Sanders virus” of textbooks may be discarded—the poison phial is lost for ever. Finally—in North America and Great Britain at least—the hero of the beginning of the story, the eye physician, is the villain at the end. It is he who spreads the virus among his patients in shipyard, office, and hospital, and who is responsible for outbreaks of the disease in the Western world.

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“The previous year was disappointing enough, but the year under review has been the most frustrating in the 21 years’ history of the Nuffield Department of Anaesthetics. Any scientific investigation, and much of the routine work, in the ‘temporary’ accommodation of this, the first of the Nuffield Medical Departments, has been made almost impossible by the distractions of noise and dust from the contiguous new buildings which are being erected in accordance with the policy of catering for undergraduate clinical teaching. This miserable state of affairs was verified by visits of three of the Nuffield Trustees and the then Chairman of the Board of Governors of the United Oxford Hospitals. In the department there are posts for four graduate assistants, for which hitherto there has always been competition. A year ago all four assistants tendered their resignations. Dr. Epstein was persuaded to continue, but even at the time of writing this report conditions have not improved sufficiently to attract inquiries from suitable candidates for the other posts. Owing to the fact that there was no suitable accommodation, the visit to Oxford of 20 Continental anaesthetists organized by the British Council had to be restricted to an inspection of the respiration unit—and a sight-seeing tour of the city.”—*Oxford University Gazette*, March 6, 1959.

DIURETIC EFFECT OF STEROID THERAPY IN OBSTINATE HEART FAILURE

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“A creaking door hangs longest.”—ANON.

Clinical experience in the relief of heart failure has evolved an effective therapeutic routine, the roots of which are buried in herbal folklore, its branches growing into the realms of biochemistry and endocrinology. The beneficial effect of bed rest, digitalis administration, diuretic therapy, and a low-salt regimen have proved the efficacy of this routine, but in oft-repeated or long-continued congestive heart failure this treatment may become ineffective. The clinician is dispossessed of his traditional remedies and the patient succumbs with unrelenting dropsy.

The inadequacy of treatment in late-stage heart failure has become apparent with increasing frequency since antibiotics, by reducing the hazard of intercurrent infection, have prolonged the lives of cardiac patients, allowing heart failure to continue its variable course and eventually to persist as a permanent state. That intractable heart failure is capable of responding to routine therapy following the administration of prednisone has been shown by Muller *et al.* (1956a) and by Gutner *et al.* (1957). Their results, however, were not uniformly successful.

It is the purpose of this paper to describe a rationale for the success of prednisolone therapy in patients with obstinate heart failure.

Heart Failure

When the heart fails, the inability of the cardiac output to satisfy the metabolic demands of the tissues (Altschule, 1938) initiates circulatory adjustments attempting to correct this deficiency. The cardiac output is augmented by a compensatory increase in circulating blood volume which results from an independent variation of renal excretion of sodium and water, at times even at the expense of the tissue fluid tonicity (McCance, 1936; Leaf *et al.*, 1953; Weston *et al.*, 1953). Initially a primary retention of sodium occurs, with water retention a secondary phenomenon. Since sodium predominates in the extracellular space, fluid accumulates in this compartment, thereby increasing plasma volume (Gibson and Evans, 1937; Berson, 1954), venous pressure, and interstitial fluid volume, manifested as oedema. The haemodynamic principles of the “backward failure” hypothesis (Hope, 1832) largely determine the distribution of this excess fluid in either the peripheral or the pulmonary circulation. The ultimate clinical picture is also influenced by such factors as the character of the heart lesion, salt and water intake, physical activity, local tissue metabolism, and therapy.

These principles, however, cannot be applied to all patients with heart failure. Hollander and Judson