FRACTURED RIB

Professor BYWATERS: Was there any evidence at necropsy of any metastasis in the fractured rib that might have given us an earlier clue to the diagnosis?

Dr. HEARD: There were very widespread metastases. I didn't examine that particular rib, but I expect it was affected.

Dr. COPE: What about this heavy intimal thickening, is it characteristic of asbestosis? Does it lead to pulmonary hypertension, or what happens?

Dr. HEARD: The gross intimal thickening of the pulmonary arteries that I showed was in the fibrous areas. Elsewhere there was only a little thickening. With this and the normal right ventricle, I doubt whether there was much in the way of pulmonary hypertension here.

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Drug Treatment of Disease**INFECTIONS OF THE EYE**

BY

ARNOLD SORSBY, M.D., F.R.C.S.*Research Professor in Ophthalmology, Royal College of Surgeons of England and the Royal Hospital, London*

Infections of the interior of the eye are grave emergencies and call for immediate and expert treatment. Relatively uncommon, they are seen after intraocular operations, perforating injuries, or in severe infections of the cornea. In contrast, infections of the outer eye are of daily occurrence. When the infection is bacterial in origin, treatment by antibiotics is generally efficacious, but virus infections still present a considerable problem.

The poor penetration into the interior of the eye of many of the antibiotics greatly limits the value of systemic administration of these drugs in the treatment of intraocular infections. Fortunately, subconjunctival injection of some of the antibiotics is a feasible procedure in expert hands and gives excellent results. For the external infections of the eye, local application is so eminently satisfactory, and so readily given, that neither systemic administration nor subconjunctival injections often need to be considered. The newer agents thus carry forward an older tradition of both ophthalmology and dermatology, in which local applications have always had a greater vogue than systemic therapy.

AVAILABLE DRUGS**Sulphonamides**

The classical sulphonamides are all highly insoluble. When sulphacetamide as a soluble sodium salt became available it was used widely as a local application in all forms of ocular infection, including infected corneal ulcers. Some of the claims put forward for sulphacetamide were untenable; the experimental and clinical results claimed for corneal infections due to *Pseudomonas pyocyanea*—organisms insensitive to sulphonamides—merely reflect the early and rather uncritical enthusiasm for the sulphonamides. It may be taken that the limited range of action of the sulphonamides, together with the fact that the sulphonamides locally are inactivated by pus and breakdown products of tissue, make sulphacetamide of little value in ocular therapeutics.

There is, however, an unquestioned place for the sulphonamides given systemically in treating some of the external infections of the eye; in ophthalmia neonatorum it is possibly still the agent of choice. The causative organism in ophthalmia neonatorum is commonly *Staphylococcus aureus*; a virus closely

allied to that of trachoma is responsible for another substantial group in which inclusion bodies can be found in epithelial scrapings taken from the conjunctiva; the gonococcus accounts for a relatively small proportion of the total—possibly as little as 20% or less in present-day series—and the pneumococcus accounts for a further substantial proportion. All these organisms are fairly readily susceptible to the modern sulphonamides in adequate concentration, so that most cases of ophthalmia neonatorum respond quickly to systemic administration.

Apart from ophthalmia neonatorum, and the somewhat similar purulent ophthalmia of adults, the sulphonamides systemically are useful in the after-treatment of septic affections in the lid and orbit dealt with surgically. In the treatment of intraocular infections the sulphonamides systemically are of little use owing to their poor penetration.

Sulphonamides administered locally are of value in only one disease: trachoma free from secondary infection. It is, however, likely that this isolated indication for the use of sulphacetamide has already been superseded by the greater efficacy of some of the antibiotics.

Antibiotics for Systemic Administration

Penicillin, streptomycin, chloramphenicol, and the tetracyclines are widely used systemically, and are all valuable as local applications in ophthalmology. The extensive use of penicillin ointment as a prophylactic measure after removal of corneal foreign bodies and after other minor injuries of the eye has greatly reduced the incidence of infected corneal ulcers and mucopurulent conjunctivitis. Ointments of penicillin and of chloramphenicol, as also of tetracyclines, are used commonly in the treatment of subacute and acute conjunctivitis, and of blepharitis, replacing almost entirely all the older remedies. Penicillin and streptomycin, being very soluble, can also be used as subconjunctival injections for infected corneal ulcers and intraocular infections generally, so that there is a broad field for the use of these agents in ophthalmology.

Recently it has been questioned whether it is justifiable to give any of these antibiotics for relatively minor infections. It is held that some patients may become sensitized, making the systemic administration

of the drugs hazardous in a future emergency. There is also the possibility of these agents producing local sensitization, so that local reactions are precipitated from subsequent systemic use, even if no severe systemic effects are observed. Though there is some question whether local application of an antibiotic can precipitate generalized sensitization, there is little doubt that local sensitization is a real problem. In consequence, there is at present a tendency to limit the local application of such antibiotics as are also given systemically. This tendency has been strengthened by the fact that penicillin-resistant *Staph. aureus* and Gram-negative bacilli are now so frequently present in infections of the eye that in any case it is questionable whether some other antibiotics more suitable to present-day conditions would not be better. It is for these reasons that considerable attention has been given of late to antibiotics that are used exclusively as local applications and have a wide spectrum.

Antibiotics for Local Administration Only

The outstanding antibiotic in this group is neomycin. It has an exceptionally wide range of action on bacteria, including penicillin-resistant *Staph. aureus* and many Gram-negative bacilli, among them many strains of *Ps. pyocyanea*. It is not particularly effective against the pneumococcus, but in the concentrations applied locally this limitation is not apparent. The polymyxins, too, are useful, but they are highly specific to some strains of *Ps. pyocyanea*, with little effect on other organisms, and are therefore to be used only against an organism known to be susceptible. Recently framycetin ("soframycin"), with a range of action almost approaching that of neomycin, has also received much attention; it is not effective against most streptococci nor against *Diplococcus pneumoniae*, two strains commonly met with in ocular infections. Bacitracin has also a fairly wide range of action, being effective against Gram-positive and Gram-negative cocci and most Gram-positive rods; it is, however, without effect on the common Gram-negative bacilli. For this latter reason bacitracin is generally used in combination with polymyxin. The exact possibilities of these various antibiotics still require critical assessment, but it would seem that neomycin ointment 0.5% can usefully replace most of the antibiotic preparations being applied locally.

Antibiotics and Corticosteroids

The specific therapy possible with the antibiotics calls for specific diagnosis—that is, it is necessary not only to establish that there is infection, but, where possible, to assess the nature of the infection on clinical or bacteriological grounds. This is particularly important for any reaction which does not readily respond to antibiotic therapy, for it is likely that the wrong drug is being given. To use the antibiotics with their specific effect on tissues that are merely inflamed and not infected is both irrational and ineffective. Antibiotics do not control an iritis, which is an inflammation of the eye, nor glaucoma with its inflammatory reactions; nor do they control allergic reactions of the lids, conjunctiva, or interior of the eye, for here again there is no infection. The inflammatory diseases of the eye are a complex chapter, and gratifying results can sometimes be obtained by the use of the corticosteroids.

To combine the corticosteroids with an antibiotic, as is a common practice, is to convert two useful agents

into one bad compound and to indulge in blunderbuss therapy of a particularly objectionable type. Infections are readily controlled by suitable antibiotics and do not require corticosteroids, the use of which may in fact hinder recovery by spreading such infection as is not controlled. Likewise inflammatory reactions of non-infectious origin, which can be controlled by corticosteroids, do not need antibiotics, whilst such inflammatory reactions as are not controlled will not be influenced by antibiotics, which may add their own quota of irritability to an already damaged tissue. There are indeed rare instances in which an inflammatory reaction also shows secondary infection; here the combined use of the two agents by an expert may be justified.

CLINICAL APPLICATIONS

1. Bacterial Infections of the Outer Eye

Ophthalmia Neonatorum

Treatment can be either by the sulphonamides systemically or by penicillin locally. Sulphonamide therapy is less exacting on the nurse, while treatment with penicillin gives more rapid control. Occasionally the two methods need to be combined in a slowly yielding case; there is, however, no need to use these procedures in combination as a routine. Whichever method is used, a swab is taken for bacteriological examination, the eye is irrigated with some bland lotion, such as half-normal saline at room temperature, and, where facilities are available, a drop of adrenaline 1 in 1,000 is instilled and a scraping of the palpebral conjunctiva is taken for examination for the presence of inclusion bodies. In all cases a drop of atropine sulphate 1% is instilled, followed by a drop of medicinal paraffin. The subsequent management differs with the two methods.

SULPHONAMIDE THERAPY

(1) A tablet (0.5 g.) of sulphadimidine, or of sulphamerazine, crushed into powder is given by mouth in a teaspoonful of water or milk. Alternatively a stock mixture can be used.

(2) Sulphadimidine in doses of 0.25 g. is continued every six hours. If sulphamerazine is used the administration has to be at intervals of eight hours.

(3) Local treatment, during the first day in cases with profuse discharge, consists of irrigation every three hours with saline solution; as a rule there is no need for further irrigation on the subsequent days. After irrigation medicinal paraffin is instilled as a precaution against the sticking together of the lids.

(4) The sulphonamide is continued for 48 hours after clinical cure.

With this treatment swelling of the lids generally subsides within 12 hours of beginning treatment; purulent discharge disappears within 24 hours. Cases due to the virus of inclusion blennorrhoea respond as readily as those due to bacteria.

PENICILLIN THERAPY

(1) The preliminary measures are completed by the instillation of a drop of penicillin in a concentration of 10,000 units per ml. into the conjunctival sac.

(2) The baby is now placed on the nurse's lap, while another nurse sitting near by instils one drop of penicillin solution, 10,000 units per ml., into the conjunctival sac every minute for 30 minutes. Irrigation is not needed, as pus does not form to any extent. Such thin mucoid discharge as is present can be ignored, or, if it clings to the lid margin, wiped away with moist pledgets of cotton-wool.

(3) At the end of this time there is invariably no pus and generally little or no discharge. The eye, however, is still moist, the lids are still swollen, and the lid margins tend to be sticky. The baby is returned to its cot, and instillation of penicillin drops is continued six times at five-minute intervals, followed by a similar number of instillations at intervals of half an hour, one hour, and two hours. This gives a total of 22 hours' treatment. Many cases require no further attention.

(4) In some babies the lid margins still tend to remain sticky. It is advisable in such cases to continue with penicillin at intervals of two hours until the eye is dry, when treatment is carried on for a further 12 hours.

With either method severity itself is not a significant factor in the duration of treatment. Frequently, mild cases take longer to clear than do moderate or severe cases, and equally often severe cases show remarkably gratifying response within a very short time, the sensitivity of the infecting organism rather than the severity of the reaction determining the course. With either treatment there are occasional cases with an unsatisfactory response in so far as moistness of the conjunctiva and sticky lid margins persist, and sometimes some oedema of the fornices or even a slight discharge. Such cases are best treated by changing the method or combining the two methods. When relapses occur, it is only exceptionally that the condition is as severe as it was initially, and it responds readily to a further course of treatment. Where corneal haze develops or a corneal ulcer threatens, expert advice should be sought.

Purulent Ophthalmia in the Adult

Local penicillin therapy differs in no way from that given for ophthalmia neonatorum. Systemic sulphonamide therapy is also as for ophthalmia neonatorum, except that full adult doses of the sulphonamide have to be given—for example, an initial dose of 2 g. of sulphadimidine or sulphamerazine with a maintenance dose of 1 g. at intervals of six or eight hours.

Muco-purulent Conjunctivitis

Most cases will respond to penicillin ointment 1,000 units per gramme, instilled at intervals of one to two hours for two to three days. In all cases it is advisable to take a smear for bacteriological control. If the clinical response is poor, some other antibiotic should be tried in the light of the sensitivity test: chloramphenicol ointment 1.0%, or one of the tetracyclines in ointment form of 0.5 to 1.0%, or an ointment containing 10,000 units polymyxin and 500 units bacitracin per gramme, or neomycin ointment 0.5% may be necessary. Sulphacetamide ointment, though widely used, is of limited or no value.

Blepharitis

In blepharitis, cleansing of the lid margins with some solution such as borax or bicarbonate lotion is still essential before applying ointments containing an antibiotic. Penicillin ointment 1,000 units per gramme applied three times a day is adequate in most cases, but ointments of either chloramphenicol (1.0%), the tetracyclines (0.5 to 1.0%), or neomycin (0.5%) will do as well. Some cases do better on painting of the lid margins with liquor tinctorium B.P.C. at night for a month or so.

2. Virus Infections

The greatest contribution chemotherapy and the antibiotics have made to ophthalmology probably rests

with their effect on trachoma—the largest single blinding disease in the world as a whole. Local application of sulphonamides has proved a highly effective measure and there is now much evidence that chlortetracycline may give even more rapid results.

The following simple procedure in the management of trachoma has been found effective:

(1) Oral administration of full doses of sulphathiazole or sulphadimidine for 10 days.

(2) Mechanical expression of the follicles and of the contents of the fornix under local anaesthesia. Only rarely is brossage needed. If necessary, expression is repeated after 7 or 14 days.

(3) The conjunctival surface thus treated is painted immediately with 30% sodium sulphacetamide solution. Such painting is continued once daily, and sodium sulphacetamide ointment (6%) is instilled three times daily. These procedures usually ensure a relatively clear fornix and tarsal conjunctiva within a fortnight. Some follicles and some infiltration of the fornix may still remain, but the characteristic feature of this stage is the moistness of the eye. Under continued daily painting and the application of ointment, all follicles disappear and the fornix becomes more normal. The eye rapidly becomes dry.

A dry eye, however, is not necessarily healed trachoma, though in most cases nothing need be done, for spontaneous healing will now occur. The continued use of sulphacetamide ointment is helpful in consolidating the results of treatment. Scarring is minimal with this treatment; the tarsal conjunctiva remains remarkably supple and shows a pearly tinge.

In trachomatous countries, fresh cases of trachoma without marked complications are readily controlled by the instillation of chlortetracycline ointment 1.0% twice daily on three consecutive days once a month for six months.

Apart from trachoma and the virus type of ophthalmia neonatorum already discussed, the sulphonamides and antibiotics are of little value in any of the established virus infections of the eye such as dendritic ulcer, disciform keratitis, and herpes ophthalmicus. These are all viruses of the herpes group, which are particularly resistant, and it is likely that the sulphonamides and antibiotics are effective only against the larger viruses of the rickettsia type, which have an extracellular phase of existence in addition to their normal existence as intracellular parasites. In herpes ophthalmicus, treatment of the secondary infection by local application of penicillin cream (1,000 units g.), or neomycin ointment 0.5% is of inestimable value in cutting short what would normally be a prolonged and disabling affection. It is possible that one form of epidemic keratoconjunctivitis seen in some years is also susceptible to chloramphenicol ointment 1%, but most virus conjunctivitis (characterized by watery rather than mucopurulent discharge) and keratitis are still beyond treatment.

3. "Chronic Conjunctivitis"

"Chronic conjunctivitis" presents a difficult aetiological group. Many cases are not infective but congestive, being part of a chronic congestive condition of the eye as a whole from causes including possibly chronic glaucoma and irritability from uncorrected refractive errors or from exposure to dust and fumes. Some cases are part of a diffuse follicular reaction, possibly infective in origin in some instances. Rarely, an undoubted chronic infection like tuberculosis is responsible. Not infrequently a chronic inflammatory

condition of the conjunctiva is maintained by chronic dacryocystitis and occasionally by a fungus infection of the canaliculi or a virus infection of the lid margin of the verruca type. There is therefore no treatment readily available for "chronic conjunctivitis" until adequate differential diagnosis is carried through. The persistent application of antibiotic ointments is likely to add the irritation of the drug to the existing conjunctival trouble.

4. Infected Corneal Ulcer

In no ocular condition has the changing status of the antibiotics been so striking as in the treatment of infected corneal ulcers. Ten years ago most infected corneas were rapidly and gratifyingly controlled by subconjunctival injections of penicillin. In recent years such treatment has generally given disappointing results, as the organisms often responsible for corneal infection to-day are either penicillin-resistant *Staph. aureus* or Gram-negative bacilli—in all probability, as already indicated, because prophylaxis against penicillin-sensitive organisms is highly effective.

In addition to the classical serpiginous ulcer of the cornea, with its undermined edges and hypopyon reaction, there is frequently seen to-day what has been called a proteolytic corneal ulcer, in which appearances are nearer those of a corneal abscess. Clinically these types of corneal infections are distinct, and penicillin treatment is likely to be effective against the serpiginous type, while subconjunctival injection of 0.5 g. neomycin on two or three successive days will be needed for the proteolytic type. An infected corneal ulcer is a serious disorder, and the proteolytic type inadequately treated is particularly disastrous. The management of such cases is therefore a matter of expert handling. A fuller account on this and other issues raised in this article is given elsewhere (Sorsby and Ungar, 1960).

REFERENCE

Sorsby, A., and Ungar, J. (1960). *Antibiotics and Sulphonamides in Ophthalmology*. Oxford Univ. Press., London.

MEDICAL ENZYMOLOGY FIRST EUROPEAN CONGRESS

[FROM A SPECIAL CORRESPONDENT]

The First European Congress in Medical Enzymology was held in Milan on March 28 and 29 under the presidency of Professor LUIGI VILLA. The congress was attended by well over two hundred participants from the countries of Western Europe, representation from Germany and Italy being particularly strong. In his opening speech, Professor VILLA pointed out that the extensive information from enzyme investigations in the clinical field had reached a stage where some synthesis and assessment of results was essential if further progress was to be made.

Enzyme Specificity

T. BÜCHER (Marburg) emphasized the similarity between the assessment of the meaning of patterns of serum enzymes and that of the cytological patterns of classical histology. He illustrated this point by his investigations of the locust. The various tissues of this species show remarkable specificity of enzyme pattern, especially in those of the muscles of flight as opposed to those of the muscles for jumping. The high respiratory rate of the flight muscles could be correlated with dissociation of carbohydrate breakdown and anaerobic energy production, two mechanisms normally closely associated in other muscles. He also described the

close correlation between the histological development and the acquisition of enzymes by flight muscles during the five successive moultings.

B. HESS (Heidelberg) described his work on the heterogeneity of lactic dehydrogenase, as shown by electrophoresis and by chromatography on treated cellulose. The physical constants of the enzymes prepared from various tissues were different, and suggested that enzymes might be organ- or tissue-specific. He considered that, until this specificity has been more widely investigated, results of clinical enzymology must be interpreted on an empirical basis, a view also strongly supported by C. H. GRAY (London), who discussed the difficulties of interpretation in relation to the problems of correlating enzyme activity with enzyme concentration; errors due to instrumental inaccuracies and to inadequate extraction from tissues were also described.

Pregnancy Changes in Leucocytes

A. VANNOTTI (Lausanne) had extended earlier cytochemical observations of different enzymes in the various leucocytes. He had made microchemical determinations of the enzymes in cell populations containing various proportions of the different kinds of leucocyte, and by mathematical analysis derived the amounts of enzymes in the polymorphs, lymphocytes, monocytes, or eosinophils. Proteolytic activity was much greater in the polymorphs than in the lymphocytes; on the other hand, the monocytes possessed higher glycolytic and proteolytic activity, respiration, reducing power, and esterase activity than the polymorphs. Striking changes were observed in pregnancy, in which the leucocytes showed a great increase in alkaline phosphatase activity with a decrease in aerobic and anaerobic glycolysis. Similar but less marked changes occurred during the menstrual cycle, and Vannotti thought they might result from hormonal action, but such changes were also observed in tuberculosis. Very young cells of the myeloid and lymphoid series could synthesize porphyrins, but, on maturation, the synthesis stopped at the porphobilinogen stage.

G. W. LOEHR (Marburg) had investigated the enzyme content of the platelets in thrombasthenia, a disease in which there is a failure of clot retraction; he found a deficiency of some enzymes of adenosine triphosphate and perhaps of magnesium ions, all of which seem to be necessary for the contraction of a contractile protein isolated from the platelets.

Enzyme Patterns in Liver Disease

E. and F. W. SCHMIDT (Cassel) had studied a large number of enzymes in the serum of a variety of diseases of the liver, and attempted to relate their results with Bücher's hypothesis that the irregular distribution of enzymes in the subcellular particles of the liver was responsible for the "deformation" of the pattern of enzymes during their passage from the damaged cell into the blood-stream and extracellular fluid. M. J. H. SMITH (London) considered that the enzyme pattern in liver disease is of little diagnostic value, and thought that the results must be essentially empirical; on the other hand, repeated estimations would be very valuable in following the progress of hepatic disease. However, L. DEMEULENAERE (Ghent) thought that transaminase estimations were of great diagnostic value, although admitting that normal values did not exclude hepatitis. F. DE RITIS (Naples) agreed that there was abnormality of serum enzymes during acute hepatitis, but thought that the change was not necessarily an expression of necrotic hepatic lesions.

Defective Erythropoiesis

N. DIOGUARDI (Milan) had made a very complete study of numerous enzyme activities, as well as adenynucleotides and lactic and α -keto acids, in the red cells and plasma in various disturbances of erythropoiesis. He called changes limited to a single enzyme or to several enzymes of the same chain "elective lesions" as opposed to "general lesions," in which there were changes in the enzymes concerned with a variety of metabolic pathways. Examples of elective lesions were the enzyme deficiencies of acatalasaemia,