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RETROLENTAL FIBROPLASIA A PROBLEM OF PREMATUREITY

BY

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Retrolental fibroplasia may lead to blindness in infancy, and it is the gravity of this possible outcome that makes its study so urgent a problem. The disease has been the subject of a large number of papers in the American literature since Terry's first report (1942), in which he recognized it as a condition occurring in premature babies, leading to the formation of an opaque vascularized membrane behind the lens of both eyes, usually with gross visual defect and searching nystagmus. The subject has as yet received little attention in the medical press of this country, but there is reason to believe that the disease is making its appearance here in the same curiously uneven and unpredictable manner as in the United States and, more recently, in other countries.

A team drawn from the Oxford Eye Hospital, the paediatric department of the United Oxford Hospitals, and the Nuffield Laboratory of Ophthalmology has been concerned in a joint investigation since June, 1950.

Diagnosis of Cases

Early in 1950 we started routine ophthalmic examination of all premature babies of low birth weight born in Oxford, in the hope that some clue to the nature of the disease might be gained from observation of the condition as it developed, and later because of the possibility of treatment.

It is unlikely that retrolental fibroplasia occurs in infants weighing over 5 lb. (2.3 kg.) at birth, so this was our dividing line. All infants weighing 5 lb. (2.3 kg.) and under at birth are examined at the discretion of the paediatricians, larger and healthier children within a few days of birth, and small weakly babies, unable at first to tolerate the handling involved in an ophthalmic examination, after several weeks. After the first examination infants are seen every week while in hospital. They are usually discharged on reaching a weight of 5 lb. (2.3 kg.) and are then followed up at special clinics at the Eye Hospital. Generally a baby will be seen fortnightly until it is between 3 and 4 months old, and then monthly until 6 months of age, when it is discharged from supervision if no signs of the disease have appeared. If any suspicious feature is seen in the eyes, particularly retinal vascular dilatation of marked degree, the infant may be examined at shorter intervals.

The examinations are all made by an ophthalmologist, and the infant is held by a nurse experienced in this work. General anaesthesia is unnecessary, though a comforter is invaluable. The pupils are dilated with

During recent years industry has paid increasing attention to colour coding of danger points in factories to indicate high voltage lines, toxic gases, and obstructions such as low doorways and steps; the British Standards Institution considered the possibility of preparing a uniform "safety" colour code. However, following an inquiry by the Royal Society for the Prevention of Accidents it has now been decided to abandon the idea. Examination showed that a distinction must be made between a safety colour code and an identification code—the one being broadly to classify and give warning of types of hazard by colour and the other primarily to identify the contents of cylinders and so on. It was found that many colours had traditional meanings which were not reconcilable with their identification value—for instance, green CO₂ containers are not consistent with the concept of red for danger. Also, since anything up to 8% of the population is thought to be to some degree colour-blind, the application of a colour system can in no way be universally effective.

homatropine 1% combined with cocaine 2% instilled into the eyes half to one hour before examination, and repeated if necessary. It is almost always possible to see far out to the retinal periphery; on two occasions only have we found it necessary to steady the eye with conjunctival fixation forceps, after using a drop of local analgesic.

There are certain differences between the ophthalmological appearances of the infantile and the adult eye. Unless these are appreciated confusion is likely. The infantile optic disk is always extraordinarily pale and the central fundus often has a patchy distribution of pigment. The retinal periphery constantly has a peculiar oedematous-looking greyness, gradually merging into the pinkness of the posterior fundus. These appearances have been seen in both full-term and premature babies, and they gradually disappear during the first weeks of life.

Early diagnosis of the disease is not easy. Many of the preliminary stages seem to develop gradually from conditions which are apparently normal in the infant. The grey zones in the retinal periphery appear to be a constant feature of the infantile eye. Only observation week by week, or even from day to day, makes it possible to be sure that this appearance is normal and not increasing.

The periphery of the infant lens is often doubly refractile, and this may lead one to suspect a detachment of the retina when in fact there is none. We are sure that diagnosis of the disease cannot be made without the presence of a retinal detachment or thickening, or of some retrolental mass near the periphery. In addition to these signs engorgement of the retinal vessels and formation of "fans" of new vessels from the retinal vessels, often coming forward into the vitreous in front of the thickened or detached retina, are important diagnostic points. We do not regard retinal vascular dilatation alone as sufficient to warrant a diagnosis of retrolental fibroplasia.

Treatment with A.C.T.H.

Reports of the results of treatment with A.C.T.H. and cortisone show no general agreement. The small number of cases in the series treated and the unpredictable course of the disease make evaluation of treatment difficult. The organization of vitreous opacities is probably responsible for the final cicatricial changes, and it is in preventing the formation of this fibrous tissue that A.C.T.H. may be expected to exert its effects. In Woods's (1950, 1951) experience with 10 treated cases, the results of the use of A.C.T.H. were unfavourable. Fitzgerald *et al.* (1951) treated three cases with A.C.T.H., with unfavourable results, and three cases, in the late glaucomatous stage of the disease, with cortisone locally, with results of doubtful significance. On the other hand, the experience of Reese and Blodi (1951a) has encouraged them to continue the use of A.C.T.H. In 14 of their treated cases the disease either regressed or was arrested, while the disease progressed in six out of the eight untreated cases under their care during the same period. Scheie *et al.* (1951) treated five cases, and concluded that treatment with A.C.T.H. is worth further trial.

In a personal communication from Dr. Perera and Dr. Day, of New York, in November, 1950, we learned of their early experience with A.C.T.H. We were fortunate in obtaining a supply of the drug for treatment of a case in December, 1950. Since then five further cases have been treated.

We gave A.C.T.H. by intramuscular injection to the six cases in four doses daily, totalling 20–25 mg. When re-

actions caused anxiety, each dose was divided and given in two parts with a 10-minute interval. In three cases the drug was discontinued temporarily when the baby's condition was unsatisfactory, and treatment was restarted without causing any further ill effects. When the ophthalmologist considered the disease to be quiescent the dose was usually halved for two or three days before discontinuing treatment. The infant was then kept in hospital for a further period of at least eight days under the closest supervision, and subsequently followed up in the out-patient department. In no case has there been any relapse after discharge from the ward.

In our first case we were afraid of the possibility of relapse with rapid development of blindness on stopping the drug, and continued it very much longer than we would now consider necessary, giving a total of 1,025 mg. over 76 days. In the other five cases the duration of treatment varied from 22 to 39 days and the total dosage of A.C.T.H. was 300 to 620 mg.

Complications Arising During Treatment

Intercurrent Illness.—Hospitalization of these small premature infants is a serious responsibility, and strict barrier nursing in isolation cubicles is essential if they are to be treated in a children's ward. Three babies remained well throughout treatment, and the other three were ill at some time.

Immediate Reactions.—Transitory blanching of the infant may occur within one or two minutes of the injection, the condition passing off in less than 10 minutes.

Hypertension.—There has been moderate or severe hypertension in five of the six cases treated, and the systolic pressure has been extremely labile. The degree of hypertension has not followed the dose of A.C.T.H. closely, and in cases in which the drug has been stopped temporarily the hypertension has not necessarily returned on resuming the original dose. In three cases the pressure has reached 180–200 mm. Hg, and in two it has risen to 280–300 mm. Hg, on one or two occasions without any apparent change in the infant's condition. Hypertension is presumably due to impurities in the A.C.T.H., but we have not found it vary with the batch of drug in use. Our colleagues in New York had not mentioned it as a complication. We found some consolation in the fact that the infant's vessels are elastic and in the well-recognized observation that the small infant with pink disease can support a moderate degree of hypertension for several months with no apparent after-effects. Since treatment was stopped the blood pressure in all cases has returned to normal.

FIG. 1.—Records of A.C.T.H. dosage, eosinophil count, blood pressure, and weight in Case 4.

Electrolyte Balance.—As Dr. Day led us to expect, we have had remarkably little trouble and have not been able to ascribe any symptoms to changes in the electrolyte balance. In our first case blood was taken at frequent intervals for sodium and potassium estimation, but this was abandoned as causing unnecessary trauma. In subsequent cases we have relied upon electrocardiograms taken at weekly intervals. When the E.C.G. suggested a potassium deficiency we have given potassium in the form of potassium chloride, 0.5 g. daily in four divided doses by mouth.

Weight.—A rapid gain in weight may indicate water retention, but in only one of our cases did a transitory retention seem likely. Several infants gained little during treatment and rapidly improved immediately the drug was discontinued. The only infant who made a very satisfactory gain throughout was the one in whom hypertension never developed. In no case have we as yet encountered any complication which has persisted after treatment has been discontinued. Fig. 1 shows A.C.T.H. dosage in detail and its effect on the eosinophil count, blood pressure, and weight in one of our cases.

Case Histories

Case 1.—A boy, weighing 3 lb. 2½ oz. (1.4 kg.) at birth, was the first child of a 38-year-old mother who had severe toxæmia of pregnancy superimposed on chronic renal disease. Delivery was by caesarean section at 37 weeks. When the child was 2 months old many small retinal haemorrhages were seen. At 3 months there were retinal detachments in both nasal and temporal quadrants of the right eye, with new-vessel formation on the surface of the retina, and a vitreous opacity in front of this. The left eye seemed normal. During the next few days the condition of the right eye worsened rapidly and the baby was admitted to hospital for treatment with A.C.T.H. Next day the left eye showed an early detachment of the retina, and this progressed despite treatment. The right eye developed bands, or folds, in front of the detached retina, somewhat similar to the appearance of retinitis proliferans. Eventually the right retina became completely detached and a dense retrolental membrane developed. The left eye showed a grey mass of retina in the temporal quadrant, with a vitreous veil in front of it. There was nystagmus and the child did not follow a light. As the condition in the left eye seemed stationary, treatment was stopped after 76 days. We now consider this period too long, and it has been reduced in later cases. Six months after treatment ended the condition was unchanged, though the anterior chamber in the right eye was shallow. Nystagmus was less marked and the child picked up small objects, had a useful visual field, and was developing normally.

Case 2.—A girl, one of non-identical twins, the other child being normal, was born by spontaneous labour at the 33rd week and weighed 3 lb. 10 oz. (1.6 kg.). The neonatal period was complicated by bronchopneumonia, which responded to penicillin and streptomycin. At 6 weeks of age retrolental fibroplasia was diagnosed. Both eyes showed gross arterial and venous dilatation spreading out to the periphery, with many visible capillaries and a few small haemorrhages, and there was a retinal detachment on the left. Treatment by subconjunctival and oral administration of cortisone was tried. After a week of this treatment, when the child had received 1.5 mg. cortisone by injection and 150 mg. by mouth, the retinal condition showed no sign of diminishing activity and the right eye developed a peripheral detachment. A.C.T.H. was then substituted for cortisone. At this time there was gross vascular engorgement in each eye, with a few small retinal haemorrhages and peripheral detachments of the retinae. These vascular changes were more marked in the left eye. Vitreous opacities appeared in the right eye. When the stage of active vascular dilatation was over, a retinal fold developed, running from the retinal detachment to the optic disk and obliterating the right macular region. The retina in the left eye became completely detached. When the child was seen

at 9 months of age the left eye showed a complete retrolental membrane, and the right eye a retinal fold, but the child takes an interest in her surroundings and can see small objects.

Case 3.—A girl, birth weight 4 lb. 6½ oz. (2 kg.), 33 weeks' gestation. The mother had severe toxæmia a week before the child was born after induction of labour. At 3 weeks of age the child was found to have engorged retinal vessels, but the peripheral grey areas were within normal limits. At 5 weeks a small detachment had appeared in the right eye and treatment with A.C.T.H. was begun. Within the next 10 days, despite treatment, the detachment had become more definite in the right eye and there were signs of activity in the left. The vascular engorgement lessened and the detachment did not increase after the child was 8 weeks old. Treatment was stopped, and the ocular condition has remained unchanged. When the child was 8 months old the central fundi of both eyes were normal; in the left eye there was marked greyiness in the temporal periphery. She has good vision.

Case 4.—A boy, birth weight 3 lb. 15 oz. (1.8 kg.), gestation 36 weeks, labour spontaneous. A diagnosis of retrolental fibroplasia was made when the child was 6 weeks old because of a typical vitreous opacity and dilated vessels, with an apparent retinal detachment, in the temporal half of the right eye. Treatment was begun and for the next few days no change occurred. At 8 weeks of age a tongue of vitreous haze was seen on the extreme nasal side of the right eye and there was vascular dilatation behind this. In the left eye there was increased tortuosity of vessels and new-vessel formation on the edge of the temporal grey zone. At 9 weeks there seemed to be a definite detachment behind the vitreous haze in the right eye, whilst the left eye had a suspicious area in the inferior quadrant of the globe. There was no nystagmus, and the child seemed to follow a light. At 11 weeks all that could be seen to be abnormal was a small tongue of detached retina in the extreme nasal periphery in the right eye, whilst in the left there was no detachment or dilated vessels. Treatment was stopped when the child was 13 weeks old, as there had been no further changes in the retinae for the previous few days. The vitreous opacity in the right eye has remained much as it was, but the retinal detachment seemed to have become less. The changes in the periphery of the left eye consisted of the presence of a large grey zone in the retina. When 9 months old the child could obviously see well; in the right eye the detachment was still present but flat, and no gross abnormality was seen in the left eye.

Case 5.—A boy, birth weight 3 lb. 4 oz. (1.5 kg.). His mother was a primipara aged 17; she had toxæmia of pregnancy, and surgical induction was performed for this; normal labour followed. An upper respiratory infection in the child was treated by chemotherapy. At 5 weeks the upper temporal vessels were dilated and tortuous in the left eye and many vessels were dilated at the edge of the grey zone; at least one haemorrhage was seen. The right eye showed similar but less obvious changes. Three days later a detachment in the left temporal periphery could be seen and the grey zones of the right eye had become more extensive. Because of these changes a diagnosis of retrolental fibroplasia was made and treatment with A.C.T.H. begun. The condition remained active in both eyes and a vitreous haze appeared, partly hiding the detachment in the right eye; the detachment in the left eye became more extensive and the vessels very dilated; there was a fresh haemorrhage in the right eye. Two weeks later the disease appeared stationary. A curious feature observed at this stage was a red patch in the middle of the detached area; this appeared to be a hole through which one could see the choroid. In another week the vasodilatation had disappeared and treatment was stopped. When last seen (at 13 weeks old) no further change had taken place, but the retinal detachments were flatter. The central areas appeared to be normal. At 7 months scarring was present in the

peripheral retinae of both eyes, and the left eye was probably becoming myopic. The child takes an interest in his surroundings and picks up objects.

Case 6.—A girl, birth weight 2 lb. 6 oz. (1.1 kg.); born by caesarean section. Apart from a scalp laceration during the operation and an attack of vomiting and abdominal distension which responded to chemotherapy, the neonatal period was uneventful. At 10 weeks, on routine ophthalmological examination it was noticed that there was vasodilatation, more marked on the following day, and that a shallow retinal detachment was present in the periphery of both eyes. The infant was given A.C.T.H. for 10 days. The disease made no further progress and the detachments became flatter. She has been examined several times since, and, apart from a shallow retinal detachment or thickening in the periphery of the upper temporal quadrant of the right eye, the eyes appeared normal; there was a large grey zone in the left eye, but no detachment. When 10 months old this child proved difficult to examine, but both fundi appeared to be within normal limits, and the child could see well.

Comment on Untreated and Treated Cases

Untreated Cases.—The early cases were all in a late stage of the disease when first seen. In one of them the process had apparently been confined to one eye, but in 15 it was bilateral. The degree of visual defect varied. In those children in whom there was a complete retrolental membrane with total detachment of the retina, gross nystagmus was present and there was no perception of light. In others, useful vision has been retained, despite the presence of peripheral retinal detachment. Such vision as has been retained is not commonly central, but is adequate to enable the child to avoid obstacles. On the other hand, central visual acuity may be good. This frequent preservation of useful vision makes it essential that these eyes should not be removed simply in order to confirm the diagnosis. The clinical picture, taken in conjunction with the history, is characteristic.

A further six cases were seen early enough to permit A.C.T.H. treatment, and they are described in some detail below.

Cases 1 and 2 had a florid active type of the disease, which we should have expected to proceed to the full development of retrolental membrane and complete retinal detachments in both eyes. Our impression was that after treatment the disease was arrested at an earlier stage than would have been expected without treatment. We are aware, however, that this is often a self-limiting disease, and have seen two untreated cases in which one eye did not develop the disease to the full extent.

Cases 3, 4, 5, and 6 were diagnosed earlier than the first two, and treatment started immediately. The disease settled fairly quickly, and after the eyes became quiet no further deterioration occurred. It may be that we were dealing with a milder form of the disease, as variation in the severity is known to occur, but it is a fact that these cases showed fairly steady improvement after the use of A.C.T.H.

Though no definite conclusion can be drawn from this small series, the following comparison can be made between the results of the disease in babies born during the year preceding the use of A.C.T.H. and the results of treatment with A.C.T.H. In the former group three children were totally blind; three were partially blind, retaining sufficient vision to avoid large objects; and another child, who has now left this area, is expected to have good vision in one eye. In the latter group only two complete retrolental membranes developed, and no child was totally blind.

Pathology

We agree with those (Reese, 1948; Kinsey and Zacharias, 1949) who believe that the increased incidence of retrolental fibroplasia cannot be completely explained by the recent improvement in survival rate among infants of low

birth weight. Confusion has been caused by the suggestion that we may be dealing, not with one disease, but with several, the final result of each of which is the formation of opaque tissue behind the lens. Another possibility is that the disease itself is changing in character, for the description by Terry (1948) differs widely from more recent ones (Owens and Owens, 1949; Hepner, Krause, and Davis, 1949; Reese and Blodi, 1951a).

Vascular Basis

Terry (1948) described the first evidence of the disease as a dot-like opacity occurring behind the lens and spreading outwards towards the periphery. This spread, in Terry's view, is associated with a reopening of the hyaloid vessels and consequent vascularization of the retrolental membrane.

The hyaloid vessels were also thought to be involved in the disease by Reese and Payne (1946), who described cases

FIG. 2.—Fibrovascular connective tissue membrane behind lens. Complete retinal detachment extending beyond ora serrata. Subretinal exudate.

of "hyperplasia of the primary vitreous with persistence of the tunica vasculosa lentis." These authors considered the condition to occur antenatally in either premature or full-term babies. They also state that the retina in these eyes may or may not be in position. This does not agree with our experience and that of many others, in which the condition of retrolental fibroplasia as it now occurs is of post-natal development and associated, in the fully developed case, with a totally detached retina; these eyes are ophthalmoscopically normal at birth and for a variable period afterwards. Unsworth (1948) also concluded that the disease was post-natal and suggested that the anaemia of prematurity was the cause. Reese (1949) and Klien (1949) reported further cases, reiterating their belief that the matrix of the disease was present at birth and angiomatic in nature.

Lately the part the retinal vessels themselves play in the development of the disease has been increasingly stressed, and our experience supports this change of emphasis. Owens and Owens (1949) and Reese and Blodi (1951a) have described the early stages of the disease as characterized by vascular dilatation on the retina, exudation into the vitreous, and the development of a peripheral detachment of the retina. Others (Laopus and Bousquet, 1951) regard the

occurrence of retinal haemorrhages as an essential part of the picture, but these have occurred in only a few of our cases. Reese and Blodi (1951a) have convincingly shown the early involvement of the retinal vessels in the disease process.

It is possible that an exudative choroido-retinitis causes a retinal detachment, which sets up a cyclitis with the formation of a retrolental membrane (Fig. 2). The retinal detachment may be due to a developmental defect (Wolff, 1950; Dixon and Paul, 1951). These authors have put forward evidence that a retinal separation has occurred in the pars ciliaris retinae of eyes in which the disease develops.

Associated Abnormalities.—Whether or not retrolental fibroplasia represents a generalized abnormality of neuro-ectodermal structures is a question which still remains to be answered. Krause (1946) was convinced that this was so and that the ocular changes were merely a part of what he called "encephalo-ophthalmic dysplasia" which led to mental retardation as well as gross visual defect.

It is difficult to assess the mental development of a very young child handicapped by blindness, but mental abnormality in these children has not been stressed by most writers. In some of our cases mental development has been slow, but we feel it is too early yet to assess the ultimate intellectual capacity of the children.

Sex Incidence and Multiple Births.—Speert, Blodi, and Reese (1950) analysed a series of 104 cases and found the sex incidence approximately equal. In Oxford 9 out of 22 cases were twins, but Kinsey and Zacharias (1949), in their larger series, could find no correlation between multiple births and the incidence of retrolental fibroplasia.

Antenatal and Post-natal Factors

American workers have concluded that the mother's age, race, parity, and rhesus group are not related to the development of the disease. There is no evidence that toxæmia of pregnancy, antenatal bleeding, drugs used in pregnancy or labour, or the cause of the premature labour are significant. It has not been possible to correlate the incidence of any chronic disease in the mother with the development of retrolental fibroplasia. Speert, Blodi, and Reese (1950) report two cases in which the disease had followed maternal rubella in the first three months of pregnancy, but no other known bacteria or virus has been implicated.

One of the first post-natal factors to be investigated was the effect of light on the immature retina. Hepner, Krause, and David (1949) covered the eyes of five babies weighing 3 lb. (1.4 kg.) or under at birth, for up to 60 days of life. Four babies developed retrolental fibroplasia, while the fifth remained normal.

Owens and Owens (1949) state that vitamin E is deficient in the newborn rat, and that the deficiency might be enhanced by a reduced fat diet and by the administration of vitamin A and iron. They gave 150 mg. of α -tocopherol acetate orally each day, and reduced amounts of vitamin A and iron, to 23 infants of 3 lb. (1.4 kg.) or less at birth. Of these, only one baby developed retrolental fibroplasia. In a control series of 78 infants of 3 lb. (1.4 kg.) or less, 17 babies developed the disease. In nine early cases vitamin E was given and the lesion was arrested in five of them. Unfortunately this work has not been confirmed. In Oxford during 1950–1 five infants developed retrolental fibroplasia while having vitamin E in the form and dosage suggested by Owens and Owens.

No known post-natal infections play a part in the aetiology of retrolental fibroplasia, but it is possible that some unknown infective agent may be responsible.

In looking for a recent change in treatment which might be held responsible, oxygen was considered, for modern oxygen cots and tents permit a very high concentration of the gas. Kinsey and Zacharias (1949) found that babies developing retrolental fibroplasia had been treated for a

significantly longer period in oxygen than those who remained normal. Campbell (1951) found a significantly higher number of cases in a hospital where oxygen was freely used than in a second hospital where the use of oxygen was limited. It is doubtful, however, whether the two series are comparable. One baby in our series who had received no oxygen developed the disease, and in other centres where oxygen is used freely no cases have occurred. The importance, if any, of delayed feeding in the handling of small babies is obscure.

Incidence

Retrolental fibroplasia was reported in the United States 10 years ago, but so far as can be assessed it has appeared in England more recently. Reese and Blodi (1951b) report 272 cases studied at the Institute of Ophthalmology in New York; 236 of these were diagnosed during and after 1944. In Boston also the increase has been considerable. The disease is unevenly distributed amongst the various American centres. Exline and Harrington (1951), from New Orleans, report 80 infants under 3 lb. 5 oz. (1.5 kg.) at birth over a two-year period ending December, 1948, amongst whom no case of retrolental fibroplasia was found: 80% of these children were negroes.

From Paris, Lelong (1951) reported 44 cases during the period 1948–50. Campbell (1951) reported 27 cases from Melbourne. In England the first cases were reported by Martin and Franklin (1949), Moffatt (1950), Crosse (1950), and Minton and Cole (1951). It is known that cases are being diagnosed in other centres in England and that the number of cases is increasing.

In Oxford eight cases were diagnosed in 1949, representing 3.8% of surviving premature babies. In 1950 there were five new cases, and up to the end of June, 1951, four babies had developed the disease.

During 1950, Dr. Alison Webb, of the Children's Department, investigated the causes of blindness among pre-school-children in Oxfordshire, Berkshire, and Buckinghamshire. Although the numbers are very small, in 1950 retrolental fibroplasia was the largest single cause of blindness among these children.

An attempt was made to examine all babies weighing 4 lb. (1.8 kg.) or under at birth born or treated in the Oxford hospitals over the period from 1946–50. Of these children, 88% were traced and no signs of the disease were found in these.

Summary

Retrolental fibroplasia is a disease of recent appearance in Great Britain. It is confined to premature infants of low birth weight, is of post-natal appearance, and may lead to gross visual defect or blindness of both eyes.

Since 1947, 22 cases have appeared in Oxford. Their diagnosis is discussed.

The method, results, and side-effects of treatment of six cases with A.C.T.H. are given. It is considered that the disease was restrained by this treatment.

Despite gross intraocular damage, many of the eyes retain sufficient vision to enable the child to avoid obstacles and to walk about unaided. Excision of the eye is unnecessary, and is to be avoided in view of this possibility.

The aetiology and pathology of the disease are briefly discussed. Its cause remains unknown.

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DEPRESSION OF TUBERCULIN SENSITIVITY IN GUINEA-PIGS BY CERTAIN ANTITUBERCULOUS SURFACE-ACTIVE AGENTS

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Substances known to depress skin sensitivity to tuberculin are few in number (Long and Miles, 1950; Fisher, Harrington, and Long, 1951; Long, Miles, and Perry, 1951c), and when such depression is associated with anti-tuberculous action the question arises whether the chemotherapeutic mechanism is the same as, or is allied to, the anti-allergic.

The development of experimental tuberculosis in mice was shown by Cornforth, Hart, Rees, and Stock (1951) to be markedly inhibited by the injection of non-ionic, water-soluble, surface-active polyoxyethylene ethers of

$n=0, 1, 2, 3$, and higher integers. $x=10, 20$, or 60 (average value).

low toxicity, having the general formula given here, and obtained by polymerization of ethylene oxide with condensation products of formaldehyde with *p*-tert-octyl phenol. The antituberculous effect of these detergents

has since been confirmed in the guinea-pig, in which a substantial curative action was shown in an established (three-weeks-old) infection. Routine quantitative tuberculin tests made at the end of a 60-day course of treatment showed a marked reduction in hypersensitivity in the detergent-treated animals as compared with their controls. The desensitization appeared to be specific rather than due merely to suppression of tuberculosis, since it was more evident than in a parallel group of streptomycin-treated animals with somewhat greater suppression of disease. This unexpected observation has led us to a more precise study of the depression of tuberculin sensitivity by these agents in B.C.G.-sensitized guinea-pigs, using the method of Long and Miles (1950). We hoped to see whether this action resembled that of other substances known to diminish tuberculin allergy, and whether it was related to antituberculous activity.

Materials and Methods

Surface-active Agents.—Representative members of the series (see formula) were used (average of 20 units of ethylene oxide per phenolic nucleus, unless otherwise stated). These were D2, a mixture of compounds having various values of n from 0 upwards; D2a, a similar mixture but with a smaller proportion of the lower members of the series; D9a, an isolate with $n=1$ ("triplet"); D14, a mixture like D2 but with 10 units of ethylene oxide per phenolic nucleus, and therefore less hydrophilic; D22, a mixture like D2 but with an average of 60 units of ethylene oxide per phenolic nucleus, and therefore more hydrophilic. Compounds D2, D2a, and D14 were chemotherapeutically active in the tuberculous mouse; D9a and D22 were inactive. The compounds were synthesized by our colleagues, Dr. J. W. Cornforth and Mr. J. A. Stock. They were given intravenously in 0.5 ml., or subcutaneously in 1 ml., saline.

Cortisone was given as the acetate (Merck), subcutaneously in 1 ml. normal saline.

Guinea-pigs.—The Hampstead strain of albinos was used, the animals weighing about 350 g. They were fed on a pelleted diet (Bruce and Parkes, 1947) supplemented, unless otherwise stated, with unlimited cabbage. B.C.G.-sensitization was carried out as described by Long and Miles (1950).

Tuberculin Sensitivity.—This was tested by intracutaneous injections of 32 and 320 international units of O.T. in 0.2 ml. saline.

Effect on Tuberculin Sensitivity

The intravenous route was considered most likely to reveal any differences between the surface-active agents, since variations in absorption would be excluded. Intravenous injection of the chemotherapeutically active preparations D2, D2a, and D14 in doses of 10 mg. in the B.C.G.-sensitized guinea-pigs, immediately before tuberculin injections, produced a significant though limited diminution of sensitivity as compared with untreated sensitized controls; the diminution was of the same order as that produced by cortisone 2 mg. given subcutaneously six hours before the tuberculin. On the other hand, the chemotherapeutically inactive D9a and D22 were without appreciable effect in these intravenous doses, and even at 25 mg. (this dose, in the case of D22, being chosen so as to contain the same weight of phenolic nuclei as 10 mg. of D2—see above).

The desensitizing properties of D2a were further examined, choosing the more convenient subcutaneous route, injections being given in groups of ten B.C.G.-sensitized guinea-pigs two hours before the tuberculin. Under these conditions D2a gave its maximal effect on tuberculin depression, in comparison with the controls, at doses of 100 to 10 mg., there being no significant difference from the effect of cortisone 2 mg.; D2a had no effect at 1 mg.

Cortisone has no direct effect on tuberculin allergy; its desensitizing action depends on dietary factors (Long, Miles,