Selye (1949) reported a technique for the production of an acute arthritis and periarthritis by the injection of formaldehyde into the vicinity of joints. If large doses of formaldehyde were administered the acute stage was followed by a very prolonged chronic arthritis and periarthritis characterized by moderate oedema and pronounced connective-tissue proliferation. This chronic arthritic condition continued to proliferate for weeks after the initial injection of irritant. He also found that this arthritis was aggravated by a preliminary treatment with D.C.A. or crude anterior pituitary extract, and it could be almost completely inhibited by cortisone or adrenocorticotrophic hormone (A.C.T.H.), suggesting an antagonistic relationship between D.C.A. and crude anterior pituitary preparations on the one hand and cortisone and A.C.T.H. on the other hand.

In a recent paper Selye (1951) further reports that with electrophoretically pure somatotrophic hormone (S.T.H.) (growth hormone) he can increase the sensitivity of the rat to the production of experimental arthritis. He concludes that the S.T.H. appears to play a part equally as important as A.C.T.H. The former is responsible for the activity of the mineralo-corticoids which produce arthritic changes, whereas the latter regulates the secretion of the gluco-corticoids which protect against the formation of arthritis.

In discussing Selye's findings the *British Medical Journal* (1951) suggested that the effects obtained may be those of a non-specific allergic reaction to foreign substances. Selye (1950) has shown that naturally occurring desoxocortisone (Reichstein's compound "S") also causes the lesions, making this explanation very unlikely; and he finds the suggestion of allergy difficult to reconcile with the fact that among a group of adrenal steroids tested only those with mineralo-corticoid activity exert such an allergic action, while among a group of proteins tested only pituitary extracts with somatotrophic hormone activity elicit comparable changes under experimental conditions.

Furthermore, if considerations are limited to cattle pituitary proteins it is found that A.C.T.H. inhibits while S.T.H. enhances the development of these collagen lesions. Adrenalectomy prevents this detrimental effect of S.T.H.-containing pituitary extracts. This also argues against their allergic nature, since adrenalectomy generally sensitizes the rat to allergic responses. It is also known that salt supplements the unilateral nephrectomy in sensitizing the organism to the actions of the mineralo-corticoids and of S.T.H.-containing pituitary extracts. Neither of these factors influences the course of allergic reactions. In our patient it was notable that the administration of an antihistaminic (promethazine hydrochloride) with D.C.A. failed to prevent the development of the polyarthritis in the absence of cortisone. Also it seems unlikely that D.C.A., which is so closely allied to a naturally occurring substance that is not a protein, should act in this manner. Furthermore, if this response of the joints to D.C.A. and salt was an allergic reaction, it would be reasonable to expect it to occur promptly within 24 hours or less, whereas it has appeared three to five days after the D.C.A. and salt had been given.

Just as a rat treated with formaldehyde in the vicinity of a joint is predisposed to develop arthritis, it is apparent, from the long history of recurrent rheumatic joint lesions, that our patient was predisposed to develop arthritic lesions. The salt and D.C.A. acted as an aggravating factor and precipitated an attack of rheumatic joint disease. It has been stressed that the clinical association of Addison's disease and rheumatic joint lesions is notably infrequent, and this in spite of the free administration of D.C.A. and salt to many patients with Addison's disease.

On this account we cannot subscribe in detail to Selye's contention, but suggest that, provided there is a pre-existing tendency in an individual to develop rheumatic joint lesions, a significant aggravating factor in the pathogenesis of these lesions is an imbalance between the mineralo-corticoids and the gluco-corticoids of the adrenals.

Summary

A case of Addison's disease and recurrent polyarthritis is described.

Treatment with D.C.A. and salt appeared to precipitate an attack of polyarthritis with swelling and pain. Cortisone readily controlled this arthritis.

Also, an antihistaminic given with D.C.A. failed to protect the patient from the polyarthritis, which was again controlled with cortisone.

The pathogenesis of rheumatic joint lesions is discussed. It is concluded that, if there is a pre-existing tendency to develop rheumatic joint lesions, a significant aggravating factor in the pathogenesis of the joint lesions is an imbalance between the mineralo-corticoids and the gluco-corticoids.

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PENICILLIN TREATMENT OF ACUTE MASTOIDITIS IN CHILDREN

BY

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In July, 1949, I presented to the International Congress of Otolaryngology a report on 50 cases of acute mastoiditis in children treated with penicillin injections between July, 1946, and July, 1948. So far as is possible these cases have been followed up, and it would now seem appropriate to discuss them, note what was attempted, and assess progress up to the time of writing.

Diagnosis

In 1946 it was decided to attempt the treatment of obvious acute mastoiditis or abscess by penicillin injection alone. The selected cases were to be those admitted to hospital as emergencies under the diagnosis of acute mastoid abscess, because during the course of an acute suppurative otitis media a post-aural inflammatory swelling had appeared. It was most important that all cases should be true acute conditions and not post-aural abscess consequent upon exacerbation of chronic tympano-mastoiditis.

Dependence was placed for this upon careful history taken from a parent or other responsible source. All 50 cases eventually collected appeared as the typical post-aural inflammatory swelling accepted as mastoiditis or mastoid abscess, and in 25 of them fluctuation was detectable on first examination or became evident later under treatment as the surrounding swelling settled.

The general condition of the children varied from normal to high fever. As a rule there was little pain, this having eased as the swelling appeared behind the ear. All cases had active otitis media, with otorrhoea present in 31 and absent in 19 at the time of the first examination. The duration of this otitis media, judged so far as was possible by the onset of pain, varied from one day to two months. Most cases had had some treatment, often by sulphonamides, previous to being admitted to hospital, but this was ignored.

These cases were considered suitable for a clinical trial of penicillin injections because they presented a good clinical picture easy for day-to-day assessment. They were not, as commonly thought, surgical emergencies, but could quite safely be kept under trial treatment for a few days.

Treatment

At the beginning it was decided to give penicillin by intramuscular injection of 25,000 units or 50,000 units six-hourly, the dosage being decided roughly by the size of the patient. Sulphonamides were not used, partly because they were thought to be unnecessary and partly because possible side-effects could mimic most of the complications of the treated disease. No local treatment of the ear was given apart from wiping away pus as necessary when it ran outside of the organ. Incision of the tympanic membrane was not considered. Bacteriological examinations were not made, the possibility that penicillin-resistant organisms were present being left to declare itself by failure of the treatment provided.

The results were assessed by simple clinical examination, general and local. So long as the signs and symptoms were improving, the treatment was persisted with until the patients' return to normal. No prescribed course or duration of treatment was attempted, results being the determining factor.

Results of Treatment

In all the 25 cases in which no fluctuation could be detected in the post-aural swelling there was a complete return to visible normality in from four to fourteen days. It was found that where the tympanic membrane was not ruptured the return to normal was quicker than when otorrhoea was present. Treatment was stopped when the aural region had regained anatomical normality, and not maintained until hearing had been regained. This occurred a little later.

At first it was expected that when fluctuation was present incision of the subperiosteal abscess would be required, but in some cases it decreased rapidly in size and was absorbed without any surgical intervention. Eventually resolution without surgical help occurred in 9 cases, but not in the remaining 16. In these 16 cases, if the size of the abscess was unchanged after a few days a trial was given to aspiration of the pus, but the rigidity of the walls prevented collapse and the cavity refilled with blood-stained fluid. Very soon it was decided that simple incision and drainage was preferable. After incision of the fluctuant abscess when necessary, the penicillin injections were continued, and rapid resolution usually occurred. Three cases retained a post-aural fistula for up to four weeks, and one case persisted for three months, eventually requiring a limited conservative mastoidectomy. One other case had mastoidectomy earlier. Ultimately, in all 50 cases a dry ear was produced, and in only one case was there a residual unhealed perforation.

Hearing.—With the younger children it was very difficult to decide about any residual deafness. The return of hearing was often delayed for a few days or weeks after the tympanic membrane had regained a normal appearance, but no permanent deafness was detectable at follow-up examinations up to about three months.

Failures.—It must be accepted that any recourse to surgical intervention is an acknowledgment that treatment by chemotherapy and antibiotics has failed. This occurred in 16 out of the 50 cases, and two of these eventually required limited conservative mastoidectomy. More important is the possible danger of failure owing to mistaken diagnosis. While this series was being collected one case was accepted for treatment, but the post-aural abscess increased in size, and when incised was found to contain foul pus. A review of the history revealed that otorrhoea had been present for a long time and the otitis was really a chronic lesion. Mastoidectomy revealed cholesteatoma. No harm had occurred from the few days' delay before operation; rather was the operation done with greater knowledge and under better circumstances than as an emergency. One other case, although suspected as tuberculous tympano-mastoiditis with a large fluctuant post-aural abscess and facial palsy, was given penicillin injections for two days before operation, and, far from coming to any harm, the facial palsy recovered. Subsequent tympano-mastoidectomy and streptomycin injections healed the lesion.

Original Opinion

On the evidence of this series it was accepted that acute mastoiditis in children could be cured in most cases by penicillin injections alone, with perhaps incision of the post-aural abscess when present; and, further, that there was no harm in trying this form of treatment even if mastoidectomy did eventually become necessary. The next step was to simplify the treatment by using the newly available preparations of penicillin which require injection only once daily. It was also hoped that by education and encouragement of the general practitioner in the need for early treatment of acute otitis media by antibiotics, and offering admission to hospital for this if requested, the incidence of mastoiditis would be lowered.

Follow-up of Cases

Of the original 50 cases it has been possible to follow up only 39, of which six were found to have slight but clinically detectable deafness. Of these six, three had either enlarged adenoids or sinusitis, and were referred for the appropriate treatment. Of the remaining three, one had had mastoidectomy originally as mentioned, and another had required this operation during a subsequent attack of tympano-mastoiditis. Among the 39 patients seen, seven had had further suppurative otitis media, which had settled under treatment.

Further Progress in Treatment

Up to the end of 1949 68 additional cases had been collected. These were treated in separate hospitals and there were variations in details of treatment, but 19 cases had penicillin injections of 300,000 units once daily, only two of them failing to return to normal. These two proved to be tuberculous tympano-mastoiditis, and required streptomycin and operation. It does seem, then, that the injection of 300,000 units of penicillin once daily, using the appropriate preparation, is adequate.

Among the 118 cases, there were 59 in which fluctuation was absent, and in all these resolution to normality was complete without any surgical intervention. In the remaining 59 fluctuation was present, and in 38 incision of the post-aural abscess was required; in the remaining 21 absorption of the abscess occurred naturally. Only three cases required mastoidectomy, and one of these was a tuberculous infection.

It is to be noted that the Hospital for Sick Children, Newcastle-upon-Tyne, admitted about 20 cases of acute mastoiditis in each of the years 1947, 1948, and 1949, and that there were only four cases during 1950. Probably this is to some extent due to the freer use of penicillin by the general practitioner now that it need be given only once daily.

Present Position

From the experience gained by study of over 100 of these cases I now make it a matter of routine to treat mastoiditis in children by penicillin injections, and at the moment 300,000 units once daily of the appropriate preparation is advocated. For reasons previously given, sulphonamides are not used, and incision of the tympanic membrane is deprecated.

When a case is first seen a careful history is taken to make sure, if possible, that one is dealing with a new acute infection; no immediate harm, however, will result from treating a chronic lesion, and the mistake will be revealed in the lack of progress later. Accurate recording of the local and general clinical picture is important as a basis for noting progress. The general state of the little patient may vary from very high fever to normality, and the first improvement under treatment should be reflected by a reduction of the former if present. Locally there will, of course, be evidence of otitis media with or without otorrhoea, and an evident post-aural inflammatory swelling, perhaps fluctuant. The presence of a facial palsy does not have any particular significance, but lymph-node enlargement usually indicates tuberculosis.

Once the penicillin treatment is begun the patient should be examined daily. Each sign or symptom, local or general, should begin to get better and disappear. A rapid improvement in the general condition and temperature is to be expected. In the course of a few days the post-aural swelling should show a reduction in size. When fluctuation is detected, if the abscess remains the same size for 24 hours it should be incised. If otorrhoea is present, and does not cease in about seven days, the pus should be examined bacteriologically for penicillin-resistant organisms, and appropriate action taken. No operations have been required for persistent otorrhoea in this series of cases. Should any new symptoms or signs develop during the course of treatment, all treatment should be stopped to allow of a free diagnosis. In some cases it has been found that external otitis has developed with pain and swelling, but has settled after cessation of the penicillin injections.

So long as all is going well the injections should be continued until the tympanic membrane regains a normal texture and the tympanum is air-containing. They can be stopped when a little deafness remains and a perforation is still unhealed. There is no prescribed period of treatment; it may vary from three days to three weeks, until the condition is cured. All cases should be followed up for about three months to be sure that hearing returns and that recovery is not retarded by other factors, such as enlarged tonsils and adenoids or sinusitis.

Summary

A survey is made of 118 cases of acute mastoiditis in children treated with penicillin.

In 59 cases in which fluctuation was absent resolution to normality occurred without surgical intervention.

In the remaining 59 cases fluctuation was present, and in 38 of them the post-aural abscess was incised. In the other 21 absorption occurred naturally.

Only three cases required mastoidectomy, one of them being a tuberculous infection.

The dosage of penicillin recommended is 300,000 units daily by intramuscular injection.

A CASE OF MYXOEDEMA DEVELOPING DURING *p*-AMINOSALICYLIC ACID THERAPY

BY

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As the result of the recent report of the Medical Research Council (*Lancet*, 1949) it is probable that the use of combined streptomycin and *p*-aminosalicylic acid (P.A.S.) therapy will be increasingly evident, and therefore it is of interest to report a complication that we have experienced during the past few months.

Case Report

The patient, a girl of 8½ years, was admitted to hospital on October 17, 1949, for the treatment of miliary tuberculosis and tuberculous arthritis of the right hip. At the onset she was given intramuscular streptomycin, but, as the second lumbar puncture revealed changes in the cerebrospinal fluid indicative of an early tuberculous meningitis, daily intrathecal streptomycin was begun. This treatment was continued without change until January 4, 1950, when P.A.S. was given in addition by mouth. At first the child had 9 g. daily, and subsequently (April 20) this was increased to 12 g. daily.

Under this regime her condition improved steadily, and she was discharged from hospital in July with a clear chest *x*-ray picture, a normal cerebrospinal fluid, and no evidence of disease of the hip. It was thought advisable at that time to continue the P.A.S. treatment, and the same dose was maintained. The child continued to attend at monthly intervals for *x*-ray examination of the chest and lumbar punctures, and she remained well until her visit on October 25, when her mother stated that she had been ill for a fortnight with fever, swelling of the face, loss of energy, and headache, and in addition she had vomited once or twice.