(quoted by Oswald, 1958) that autogenous vaccines did not influence the titres in a small series of cases. Of the 21 men from whom blood was taken on both occasions only one did not report any benefit. He had received injections and his agglutination titre had fallen from 1/160 to <1/10.

Alteration in Skin-sensitivity Reaction.—There was no significant change in either group.

If volunteers are considered according to their degree of bronchitis it is found that the proportion of non-bronchitics with a positive response to *H. influenzae* at the first test is 48 out of 56 (85.7%) compared with 79.6% in volunteers as a whole. This confirms the findings of May and Faunce (1958, personal communication) who, using a phenol-killed suspension of *H. influenzae*, found many positive reactors among non-bronchitics.

Discussion

The late start to this trial was unfortunate in that not only were a large number of genuine cases unacceptable because of antibiotics administered during the epidemic of Asian influenza, but some others had begun their annual prophylactic course of antibiotics. Obviously any attempts to desensitize patients to *H. influenzae* should be completed by September, before the autumn and winter recrudescences occur.

When subjected to closer study the trial groups were found to contain many with mild symptoms. It was not possible to undertake a comprehensive investigation on account of the numbers involved. A more intensive study of a small group of severe cases, including complete clinical sputum and electrocardiographic examinations, might have been more profitable, and the bacteriological and immunological data obtained might have helped to elucidate the role of *H. influenzae* in chronic bronchitis.

The amazing co-operation and perseverance shown by the volunteers, in spite of a high percentage of minor ill effects, was the most outstanding feature of the trial, and demonstrates very clearly the working-man's fear of bronchitis and his willingness to undergo any attempt at prophylaxis—with the notable exception of attempts to convince him of the evils of cigarette smoking.

The dosage of vaccine used was arbitrarily chosen because of lack of previous experience, but the frequency of minor ill effects indicates that this dosage is about the upper limit of this particular preparation that could be tolerated.

Assessment of results was rendered difficult by the lack of any satisfactory criterion of improvement. Subjective assessments were unreliable, as shown by the improvement claimed by the control group. Absenteeism might have been more helpful under more favourable circumstances. The only yardstick available was the indirect M.B.C., which not surprisingly showed no advantage for the vaccine.

Even when all the unsatisfactory features of the trial are taken into account it would appear that, in a sample of this size, some advantage should have been demonstrated if the vaccine had been able to give any useful degree of protection against exacerbations of chronic bronchitis.

Summary

A trial is reported of injections of a specially prepared *H. influenzae* vaccine in a group of male factory workers, with a view to reducing the incidence of relapses of chronic bronchitis during the first three months of 1958. No evidence was gained to suggest

that the injections conferred any benefit as compared with a corresponding number of control patients.

It is suggested that, for the present, trials should be confined to small groups of carefully investigated subjects, so that the effect of such vaccines may be related more closely to changes in pathological findings and clinical condition.

We thank the managing director of the Stanton Ironworks Company Ltd. for permission to carry out the trial and publish the paper, the employees of the company for volunteering, the Medical Department staff for the additional work involved, and the Medical Department of Messrs. Glaxo Laboratories Ltd. for supplying materials, providing guidance, and carrying out pathological investigations. We would also thank the local general practitioners for their whole-hearted co-operation.

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SARCOIDOSIS OF THE NERVOUS SYSTEM

BY

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Involvement of the nervous system by sarcoidosis is now recognized with increasing frequency. Despite great variation in the symptoms and signs many cases present a recognizable clinical syndrome. It is the purpose of this paper to describe three further cases, to stress the features they showed in common, and to attempt an assessment of the results of steroid therapy.

Case 1

A married woman of 35 was admitted to hospital on June 1, 1954, under the care of Dr. D. V. Hubble. Her illness had begun four months earlier with pain in the lumbar region, soon spreading to the dorsal spine and neck. The pain appeared to be relieved after massage, but she then developed sensations of numbness in the left thigh, the whole of the right lower limb, and both upper limbs. The left upper limb felt weak and she experienced tingling in the right side of the face, later spreading to the left. These symptoms were severe for about two weeks and then improved. Six weeks before admission she developed swellings of both cheeks that subsided in a week. The right side of the face became weak and a few days later she lost her sense of taste and of smell. As these symptoms also improved she developed difficulty in swallowing and for two weeks could take no solid food. She remarked that her tongue felt like wood and was difficult to move. Two weeks before admission she was swallowing normally but

was having difficulty in chewing her food, and she began to stagger when walking.

I saw the patient in consultation on June 3. At that time her main complaint was of difficulty in walking, but she also complained of slight deafness and of a poor sense of smell. On examination there was bilateral anosmia. Both optic disks were swollen, but the swelling was of slight degree, and the retinae were normal. The right pupil was widely dilated and did not react to light or on convergence. There was no conjunctival injection or other evidence of iritis, no external ophthalmoplegia, and no sensory loss on the face or weakness of jaw muscles. There was bilateral facial weakness, more pronounced on the right, and bilateral moderate nerve deafness. Sense of taste was intact and there was no weakness of the tongue or palate. Flexion of the neck was very weak, with little contraction of the sternomastoid muscles.

No abnormality was found in the upper limbs, but there was marked proximal weakness of the lower limbs. The knee-jerks were absent, the ankle-jerks normal, and the plantar reflexes flexor. Scattered and ill-defined areas of hypaesthesia were present on the trunk and lower limbs, but deep sensation was normal.

A rash was present on the buttocks. This consisted of dark red, slightly tender raised areas approximately 2 cm. in diameter, resembling the lesions of erythema nodosum except for their location.

The patient was afebrile and the E.S.R. was 8 mm., rising to 37 mm. three weeks later. The C.S.F. was under normal pressure and contained 3 polymorphonuclear leucocytes and 3 lymphocytes per c.mm., and 55 mg. of protein per 100 ml. The Mantoux reaction was negative to a dilution of 1:100. The W.R. was negative. The serum calcium and proteins were normal. A radiograph of the chest showed bilateral hilar lymph-node enlargement. Biopsy of one of the skin lesions was reported by Dr. G. R. Osborn as showing the changes of sarcoidosis, with an inflammatory reaction containing giant cells extending into the subcutaneous fat.

She was treated with cortisone, beginning with 300 mg. a day and reducing to a maintenance dose of 75 mg. a day. Her improvement was slow. The rash fluctuated in extent and appeared on the shins and the left forearm, persisting until August. In October it was noted that her pupils did not react to light but reacted on convergence. She continued to complain of weakness of the legs until July, 1955. I examined her again in September, 1957, at which time she was still on cortisone. Both pupils were irregular, but of normal size, the right being larger than the left. They did not react to bright light, but contracted briskly on convergence. There was bilateral anosmia. The left facial palsy had recovered, but on the right side associated movements between the muscles around the eye and mouth were obvious. In the limbs there was slight weakness of hip flexion on the right.

Case 2

A married woman of 50 was admitted to hospital on August 14, 1955, as an emergency case, thought to be suffering from pneumonia. She had been operated on for a prolapsed lumbar intervertebral disk eight years earlier and had had a number of attacks of bronchitis. Her present illness began six weeks before her admission, with pain in the lumbar region passing round to the abdomen in a band and lasting for about two weeks. Ten days before admission she became acutely ill with fever, vomiting, cough, and pain in both shoulders on inspiration. She had been treated with sulphonamides and antibiotics without benefit.

On admission she was running a remittent fever up to 102° F. (38.9° C.). Crepitations were heard over both lung bases, but there were no signs of localized pneumonia, and a radiograph of the chest showed bilateral hilar lymph-node enlargement. On August 20 she developed a rash resembling erythema nodosum on both legs which persisted for two weeks. The Mantoux reaction was negative to a dilution of 1:100.

In the succeeding few days she complained bitterly of pain in the mastoid region bilaterally and also of abdominal pain. At this time there was some mental confusion, particularly at night. On September 4 the right side of her face became paralysed and three days later the left side also. There was some conjunctival injection. Sense of taste was absent on the anterior portion of the tongue. A lumbar puncture showed that the C.S.F. was under normal pressure and contained 33 lymphocytes per c.mm. and 140 mg. of protein per 100 ml. The W.R. was negative. The blood count was normal, the E.S.R. was 9 mm., and the serum proteins were normal.

The fever subsided as the skin lesions cleared, but she continued to have severe abdominal pain and developed a circular area of anaesthesia involving the whole of the skin of the abdomen. The superficial abdominal reflexes were absent. No other cranial-nerve palsies developed and there was no weakness or sensory loss in the limbs or any change in reflexes. She was not ataxic on testing in bed, but her gait was unsteady and was thought to indicate cerebellar disease.

Treatment with cortisone was begun on September 14, starting with 300 mg. a day and reducing gradually to 75 mg. a day, which was continued until June, 1957. The facial palsies recovered slowly and incompletely, and associated movements were well marked bilaterally. Unsteadiness in walking and frequent falls persisted until May, 1956; and in November, 1957, she had a further attack of erythema nodosum. The hilar lymph-node enlargement had subsided, and, apart from the residual facial palsies, there were no neurological symptoms or signs.

Case 3

A married woman of 25 was admitted to hospital on March 1, 1957. Her illness began in January, 1957, with pain behind the left ear, followed within a few hours by a left facial palsy. Five weeks later, when the palsy was rapidly resolving, she became unsteady when walking and her vision became blurred. Two weeks later she developed pain behind the right ear and a right facial palsy. She was unable to taste her food properly and had a sensation of numbness in the ulnar two fingers of the left hand and in a band around the lower ribs. She felt giddy on turning her head quickly. The day before admission she had difficulty in swallowing food.

On admission she had a fever up to 101° F. (38.3° C.). She was distressed and frightened. Her gait was ataxic. Bilateral anosmia and marked bilateral oedema of the optic disks were present. The conjunctivae were injected and the right pupil was irregular. Mr. J. E. Coates reported bilateral cyclitis. The right side of the face was paralysed and the left side weak. The palate moved in the midline, but fluids came down her nose on drinking. The right sternomastoid muscle was paralysed. There was no weakness or change in reflexes in the limbs and no ataxia on testing in bed. Slight cutaneous sensory changes were present in the left hand and in a band around the lower ribs.

The next day she was completely unable to swallow; she was nursed in the semi-prone position with the foot of the bed raised, and was fed by gastric tube. A radiograph of the chest showed bilateral hilar lymph-node enlargement. The blood count was normal, the E.S.R. 5 mm., rising to 39 mm. a few days later. The serum calcium and proteins were normal, and the Mantoux reaction was negative to a dilution of 1:1,000. The C.S.F. was under normal pressure and contained 4 lymphocytes per c.mm. and 35 mg. of protein per 100 ml.

Prednisolone, 40 mg. a day, was begun on March 4, the dose being reduced to 20 mg. a day over five days. The eyes were treated with atropine and hydrocortisone drops. By March 13 the bulbar palsy had completely recovered and the cyclitis and papillitis resolved a few days later. She continued to experience attacks of pain in scattered areas on the thorax and abdomen, but no fresh signs appeared. By

the time she was discharged from hospital a month later all symptoms and signs had disappeared, apart from the right facial palsy, which was still complete. The hilar lymph nodes were still enlarged.

The facial palsy began to improve in June, but never resolved completely. Associated movements developed and also the syndrome of "crocodile tears" on eating. The chest x-ray examination was normal in August and all treatment was stopped in November. No fresh symptoms have appeared, but the residual facial palsy and the effects of faulty reinnervation remain obvious on any facial movement.

Discussion

The diagnosis may be established by examination of biopsy material, on clinical grounds, or, as in many reported cases, at necropsy. Isolated sarcoidosis of the nervous system may present a formidable problem which is greatly simplified by the recognition of characteristic lesions elsewhere. In the present series biopsy was carried out in one case. Hilar-node enlargement was present in all three cases, skin lesions resembling erythema nodosum in two, parotitis in one, and cyclitis in one. The combination of one or more of these common features of sarcoidosis with a neurological disorder should at once suggest the diagnosis. It is partly the purpose of this paper to emphasize that the neurological features also often follow a recognizable pattern.

Other aids to diagnosis are merely subsidiary. The cerebrospinal fluid was abnormal in two cases, with a slight increase in cells and protein, but the changes were not, of course, specific. The Mantoux reaction was negative in all three cases, as is frequently observed in sarcoidosis. The Kveim test was not employed. It is worth noting that the E.S.R. was normal in all patients when first seen.

Neurological Features

Sarcoidosis of the nervous system has been classified into meningeal, encephalitic, and polyneuritic forms, but, as pointed out by Höök (1954), such a classification has little real value. At the extremes there are certainly many cases presenting with symptoms and signs of an isolated intracranial mass, indistinguishable on clinical grounds from a cerebral tumour, and many others where the symptoms may be wholly attributed to peripheral lesions. In many cases, however, there is evidence of involvement of the spinal cord, brain stem, and other areas of the central nervous system, combined with peripheral and meningeal lesions. Accounts of such cases may be found in the comprehensive reviews of Colover (1948), Höök (1954), and Jefferson (1957). In the present series, in addition to the prominent evidence of the peripheral lesions, mental confusion was present in one case and ataxia on walking, not obviously attributable to weakness, in two.

The characteristic feature in the present cases was one often noted before—fluctuating and asymmetrical cranial polyneuritis. In Case 1 there was objective or subjective evidence of involvement of all the cranial nerves, except those supplying the external ocular muscles, in the course of six weeks. In Case 2 there was bilateral but asynchronous facial palsy, and in Case 3 bilateral anosmia, optic neuritis, and facial palsy with bulbar palsy and paralysis of one sternomastoid muscle. In all cases there was evidence of involvement of spinal nerves; this was most severe in Case 1, in which marked proximal weakness of the lower limbs developed. In the other two patients scattered areas of pain and

sensory loss of unusual distribution were present, producing anaesthesia of the skin of the abdomen in Case 2 and symptoms suggestive of pleurisy in Case 3. Perhaps more remarkable than the distribution of the lesions was their evanescence, most clearly shown in Case 1. Among other symptoms this patient had suffered from bulbar palsy, which had remitted completely within two weeks. This distribution and the temporal behaviour are not likely to be encountered in any other condition with the exception of the unexplained remittent cranial-nerve palsies described by Symonds (1958), one of whose patients appeared to be a case of sarcoidosis.

The pathological findings in cases fully examined at necropsy have been reviewed by Meyer, Foley, and Campagna-Pinto (1953). These fatal cases do not afford a satisfactory explanation of the fluctuating cranial-nerve palsies. The cases were naturally of the type with either massive cerebral involvement or extensive granulomatous meningitis. The polyneuritis of sarcoidosis is clinically very different from the symmetrical lesions of "allergic" polyneuritis, and, in spite of the frequent very rapid recovery, the individual lesions seem likely to be due to direct involvement of the nerves or meninges by sarcoid tissue.

Treatment

The response to steroid therapy is difficult to assess. In the case reported by Fitzpatrick and Ewart (1957) there was clear evidence of remission followed by relapse on stopping treatment and a further remission. Jefferson (1957) mentions steroid therapy in some of his cases but does not assess its value. The rapid improvement in the bulbar palsy in Case 3 was attributed at the time to the treatment, but can be exactly paralleled by Case 1 before treatment and by cases reported before steroids were available (Ramsay, 1921). Although Cases 1 and 2 did not improve rapidly and it seemed at the time that cortisone was producing little benefit, on viewing the three cases in retrospect it is clear that no fresh neurological symptoms or signs developed after treatment was begun. It is not of course possible to exclude with certainty the chance of this being due to the natural course of the disease, but it certainly suggests that cortisone is an effective treatment.

Sequelae

Of the six facial palsies in these three patients only two resolved completely. The remaining four showed evidence of denervation and faulty reinnervation as in the delayed type of recovery from Bell's palsy. As all these patients were females, and one a strikingly handsome young woman, this result was disappointing.

More remarkable, and probably even more unfortunate, were the residual pupillary abnormalities in Case 1. The pupils were irregular and unequal, and did not react to light but reacted on convergence. Although they were not greatly contracted, the resemblance to the Argyll Robertson pupil was striking. This curious sequel has twice been reported before (Mackay, 1921; Höök, 1954) and cannot be attributed to iritis, which was not present in any of the reported cases and which could not account for the different pupillary response to the two stimuli. As the condition appears likely to be permanent the possibility of sarcoidosis in the past should be considered in patients with unexplained Argyll Robertson pupils.

Summary

Three cases of sarcoidosis of the nervous system of the predominantly peripheral type are described.

The response to steroid therapy appeared to be good, as no fresh nervous lesions developed after treatment had begun.

Attention is drawn to the frequency of incomplete recovery of the facial palsies. In one patient a further sequel was a condition closely resembling the Argyll Robertson pupil.

I am indebted to Professor D. V. Hubble for permission to describe Case 1.

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PERINEAL CARRIAGE OF STAPH. AUREUS

BY

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The possibility that the perineal region might be a carrier site on which *Staph. aureus* could multiply was suggested in a previous paper (Hare and Ridley, 1958), but no information was available on the proportion of the population who are perineal carriers, whether they can disperse the organisms into free air, or the relationship between nasal and perineal contamination or carriage. This investigation of 50 male medical students was designed to answer some of these questions.

Experimental Methods

Media and Isolation of *Staph. aureus*.—Nutrient agar containing phenolphthalein diphosphate, as used by Hare and Thomas (1956), was employed for the isolation of *Staph. aureus*. In general, only colonies giving a positive slide coagulase test (Cadness-Graves *et al.*, 1943) were counted as *Staph. aureus*, but the tube test was used for all strains which were phage-typed or which gave a doubtful positive in the slide test. It is possible, therefore, that a small number of staphylococci which lack bound coagulase (Duthie, 1954), but are nevertheless able to produce free coagulase, were missed by this method of identification.

Nasal and skin swabs were taken in the same way as described by Hare and Ridley (1958). The areas of skin covered by the perineal and adjacent swabs were each very small compared with other skin samples, measuring approximately 3 square cm., and were defined as follows: (a) The left and right perineal swabs covered the area bounded by the base of the penis in front, the upper part of the thighs on each side, and a line at least 1 in. (2.5 cm.) anterior to the anus behind. (b) The anal fold swab was drawn over the anal orifice in

an anterior-posterior direction, and this swab was invariably taken after the perineal swabs to avoid artificial contamination of the perineum from the anus. (c) The whole of the lateral surface of the scrotum on each side comprised the right and left scrotal areas. (d) The dorsal surface of the penis was also swabbed.

Faeces Culture.—A loopful of each specimen was inoculated directly on to one plate containing nutrient agar and phenolphthalein diphosphate and on to a second nutrient agar plate containing 8% sodium chloride. The remainder of the specimen was then emulsified in about 4 ml. of broth, and 0.1-ml. and 0.5-ml. amounts were immediately spread on nutrient agar and 8% salt plates respectively. The plates were incubated at 37° C. and examined daily for five days; any colonies resembling *Staph. aureus* were subcultured on nutrient agar without the addition of salt before coagulase-testing. Culture in fluid media was avoided in order to get some idea of the amount of faecal contamination.

Results

Two groups comprising 15 final-year clinical students and 35 preclinical students, who rarely entered the hospital itself, were studied during the period October, 1957, to February, 1958. Cultures were made of each nostril and 16 skin sites, and press plates were taken from the front and back of the drawers. The latter cultures were made by impressing an area of the inside of the drawers directly on the surface of the medium in a Petri dish with a circular wooden block, with a diameter of 3 in. (7.5 cm.), held on the outside of the material. The results of this initial investigation are given in Table I under the heading Survey I.

It will be seen that, of the 50 students, 26 had no *Staph. aureus* in the nose or on any of the perineal areas; ten had *Staph. aureus* in the nose but not on the perineum; while no fewer than 14 had this organism on the perineal area, some of them with *Staph. aureus* in the nose as well. It is therefore apparent that *Staph. aureus* can be isolated from the perineal area of a comparatively large proportion of the male population.

In several instances, however, very few *Staph. aureus* were isolated from the perineum and adjacent structures—no more, in fact, than were found on other areas of the skin, such as the abdomen and thighs. It would therefore be inadvisable to regard such individuals as perineal carriers. Many were much more heavily contaminated, and, if a total of 30 colonies from the six perineal sites be taken as the dividing line, it is evident that on the results of the initial survey 10 of the subjects can on this basis be regarded as perineal carriers.

It is of some importance, however, to determine whether the presence of *Staph. aureus* on the perineum is due to contamination of the area by the organism coming from the faeces or to its ability to multiply in or on the skin of this region.

To obtain an answer to the first of these questions, samples of faeces were obtained from 14 subjects at the time the original survey was made, while another 10 were reinvestigated, nasal and perineal examinations being carried out at the same time as the faeces were obtained. The results of these investigations are given in Table II.

It is at once evident that faecal contamination alone cannot be responsible for the presence of *Staph. aureus*

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