quantities so small as 0.000001 gram of a pure albumin, like egg albumin or serum albumin, are known to be sufficient to constitute a sensitizing dose for the guinea-pig (d'Herelle, 1923).

Comment.

This case is illustrative of a type of sensitization which, as concerns immunization by diphtheria anatoxin preparations, has hitherto scarcely been noted—namely, sensitization of patients to the albumin of the preparation—that is, to all intents, to the albumin of the nutrient medium employed for the culture of the diphtheria bacillus giving the toxin. In this way the case is instructive, and gives occasion for certain reflections.

Immunization against diphtheria, whether with toxin-antitoxin mixture or with anatoxin, gives apparently good initial immunity; this is deemed of such importance as to overshadow any ultimate inconveniences. Both methods, however, give rise to remote risks, and both to initial risks. The remote risks of toxin-antitoxin injections are so well known as to need only passing mention. The patient becomes sensitized to the horse serum of the antitoxin, and thereby risks anaphylactic manifestations whenever for any reason later in life therapeutic serums may have to be administered. Many clear-cut instances have been described in the literature, notably by Stewart (1926, 1927), Gatewood and Baldrige (1927), and Lathorp (1927). The initial risks of toxin-antitoxin immunization are practically negligible. Hundreds of thousands of children and adults have undergone this immunization during the past four or five years without any definite reaction. In fact, in this respect no particular note of alarm—so far as the literature goes—has been sounded. The case recorded by Wahl, referred to at the beginning of this paper, is one of the very few exceptions and observations of its kind.

This was the case of a 10 months' baby which, after supporting perfectly two injections at a fortnight's interval, on the occasion of the third injection, a fortnight later, developed respiratory discomfort, and within a few minutes a giant urticaria on the face and neck, spreading rapidly over the chest, abdomen, and lower extremities. All this occurred about ten minutes after the injection. Administration of 7 minims of adrenaline hydrochloride intramuscularly promptly gave relief.

As concerns anatoxin, the remote risks of the order encountered with toxin-antitoxin are believed to be non-existent, and this for two reasons: (1) because the preparation contains no horse serum antigen; and (2) because sensitization reactions are strikingly specific, and only follow reinjections of the same foreign protein antigen. These reasons of themselves are sufficient to justify the present tendency to adopt anatoxin, instead of toxin-antitoxin mixture, as the instrument of immunization in diphtheria. But the present study suggests a possible remote risk of another order.

We have seen that sensitization may occur to the albumin of the anatoxin, or perhaps it would be more correct to say to the nutrient broth entering into its composition. Persons immunized by anatoxin, therefore, should they later in life become subjects for vaccine therapy (and there is no reason to anticipate the popularity of vaccines waning), will require vaccines rigorously free from the albumins of nutrient broth; otherwise accidents may occur during vaccine treatment. Fortunately allowance is already made for this point of view in most "makes" of vaccine, although perhaps not in all. Confirmation, moreover, of this outlook may be found in some recent work of Nicolas and Katrandjieff (1928). These authors have established that the proteins of meat, after heat coagulation, redissolving in weak alkali, and neutralization, constitute excellent antigens, giving rise to antisera particularly rich in specific precipitins.

Concerning the initial risks of anatoxin immunization, the case here reported speaks for itself. The symptoms were fortunately mild, and gave no more need for alarm than would have done those of any simple case of serum sickness, which this case closely simulated. Its interest, however, mainly lies in indicating that if allergic accidents during the initial period of immunization are to be avoided, there is need to perfect both the preparation of anatoxin and the technique of its administration. It is well known that the birth of the allergic state ("altered reactivity" of cells) is a function of the sensitizing dose

of offending substance and of the time elapsing between its injection and reinjection. The possibility of allergic accidents should, therefore, largely disappear with the advent of anatoxin preparations of lower protein content—if that can be attained—affording protection by fewer injections (for example, two instead of three, as at present recommended) at shorter time intervals between the injections. Hopeful advances along such lines have already been signalled. Sdrodowski and Chalapina (1927), working with different diphtheria anatoxins of equal antigenic strength (Ramon), but unequal flocculating power, have found that the immunizing action is proportional to the rapidity of flocculation of the initial toxin. Working with such a preparation, they report immunization (Schick-negative results) with a single injection in 88.8 and 93.6 per cent. of cases, after three weeks and two and a half months respectively; and with two injections in 93.3 and 96 per cent. of cases. These figures are based on a sufficiently large clinical material to be impressive: 27,000 children Schick-tested, of which 4,600 were vaccinated by anatoxin, and in 1,861 the immunity produced was controlled by the Schick test.

SUMMARY.

A case is reported—the first of its kind known to the writer—of allergic symptoms arising in connexion with the use of anatoxin in diphtheria prophylaxis: with general remarks on the risks attending our present-day methods of diphtheria immunization.

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A CASE OF GENERALIZED MENINGOCOCCUS INFECTION.

BY

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THE following type of case of meningococcal pyaemia is of rare occurrence, and in one of its features—a double metastatic irido-choroiditis—would appear to be unique. The clinical facts are as follows.

On September 29th, 1927, a female child, aged 2½ years, was admitted to Booth Hall Infirmary. The glands of the right side of the neck had been swollen for seven days, and the mother had been massaging these with olive oil. She appeared to be quite well in general health, and had been playing until two hours before admission, when she vomited, and became very ill.

On examination she was found to be in good general condition, but very pale; her temperature was 102° F., and the right cervical glands were moderately swollen, tender, and firm. Her throat appeared to be quite normal, but a routine swab was taken, and was found to show Klebs-Loeffler bacilli. By evening the temperature fell, and the child became comfortable and slept. On the next day the cervical glands had subsided a little, but the temperature began to rise, and at night the child was restless and noisy. No further signs or symptoms were discovered until October 2nd, when both conjunctivae became injected; the corneae were hazy, and the next day there was pus in both anterior chambers. At the same time the small joints of the hands and feet became swollen, and several petechial spots appeared on the hands, the lower part of the body, and the legs and feet. By evening the elbows and knees had begun to swell, and the temperature was high, the patient being extremely ill and restless. On October 4th the eyes had improved slightly, but the joints were still swollen, and did not begin to subside until October 6th. Iritis was present in both eyes. At no time was there any demonstrable splenic enlargement, nor were there positive signs of meningeal involvement.

By the second week the patient was generally much better, but there was still inflammation of both eyes, and it was soon evident that she did not distinguish light from dark, although mentally she was quite bright and intelligent again. The temperature remained above normal for nearly a month.

On October 3rd a sample of spinal fluid was collected, but neither this sample nor subsequent ones showed any excess of cells or protein. On the two subsequent days pus was aspirated from the knee-joints and found to contain, in large numbers, a Gram-negative organism having the microscopical characters of the meningococcus. On culture this organism fermented glucose and maltose, but not sucrose; it grew freely on serum media at 37° C., but not at room temperature.

On December 8th she was examined by Dr. T. M. Bride, consulting ophthalmologist to the infirmary, who reported that the right eye was quiet and the cornea clear; there was no keratitis punctata. The anterior chamber was shallow, and the pupil irregular with posterior synechiae. The lens was clear, but the vitreous was full of a yellowish-white exudate. The condition in the left eye was similar to that of the right; metastatic uveitis was present.

Subsequently the child developed broncho-pneumonia and recovered. She is now—one year from the start of her illness—quite well, and is gaining weight. She is exceptionally intelligent for 3 years of age, but is liable to sudden bursts of temper, which quickly pass off. This, like her mental state generally, is no different from what it was previously. She is, unfortunately, completely blind. There is no glandular swelling.

Cases of meningococcal septicaemia without meningitis have occurred not infrequently in adults, but apparently very rarely in children. I have noticed references only to two children. Pybus records the case of a girl, aged 3 years, who was taken ill with general septicaemia and died in thirteen hours. Blood cultures yielded a pure growth of the meningococcus, but there was no meningitis. The second case, reported by Flack, is that of a child, a contact of a carrier and also of a clinical case, who developed arthritis of the knee, which proved to be meningococcal. The cerebro-spinal fluid and the blood, in this instance, were both negative.

There are other instances in which these lesions complicate frank cerebro-spinal meningitis, and there is also an intermediate case in which meningitis developed secondarily, in point of view of time at least, to other meningococcal lesions. In this case a female patient exhibited multiple joint lesions, meningococci being found in the blood; she developed meningitis two months later, but ultimately recovered. It has been suggested in textbooks that septicaemia patients would develop meningitis if they lived, and while this is strongly supported by the case quoted above, it is equally tenable that they need not. It is twelve months since the acute stage of the case reported here; during this time the child has been under constant hospital observation, without showing any signs of meningitis. Careful questioning of the parents fails to reveal any meningitis prior to admission.

The adenitis is interesting in view of the fact that it is an unusual complication in the early stage of meningitis when the organism is presumably in the throat. In a series of cases of meningitis studied by Worster-Drought and Mills Kennedy only one patient developed adenitis, and this was late in the disease. Fairley and Stewart state that with them a few of the convalescent patients developed adenitis. To account for its occurrence in the present case we must presume that it was due to some other infection of the tonsils, on which, later, the meningococcal infection was superimposed. From a consideration of the rash and the temperature chart in this case it would appear that the meningococcal infection occurred just before admission to hospital—that is, when the child suddenly became ill, possibly with a rigor. The rash was purely petechial and several of the spots suppurated. The face in this particular case escaped. The joint lesions were more widespread than is usual, and were of the nature of a synovitis. There was, after the acuteness diminished, a rapid complete recovery in all of them.

Irido-choroiditis occurs early in meningococcal meningitis and is usually unilateral. I have not been able to find any record of bilateral irido-choroiditis occurring in any case similar to this. Throughout the illness there was a varying amount of enteritis. The Klebs-Loeffler infection of the throat did not appear to give any special symptoms and persisted for many weeks. As soon as the nature of the infection was established specific treatment was commenced in the form of anti-meningococcal serum, given intrathecally and intramuscularly.

In view of the recovery, it is interesting to contrast this with the same disease in adults. According to Herringham the disease commences with "malaise not severe enough altogether to prevent duty, lasting from three to seven days, followed by a severe illness which is fatal in four days."

My thanks are due to Dr. G. D. Dawson for permission to use the bacteriological reports; to Dr. T. M. Bride for the report on the final condition of the eyes; and to the medical superintendent, Dr. D'Ewart, for his assistance in connexion with this case.

Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

STATUS LYMPHATICUS.

I CONSIDER the two following cases of status lymphaticus, which occurred in the same family, so unusual as to merit being recorded.

On the evening of October 6th, in response to an urgent summons, I visited a young woman, aged 30 years, and on arrival found life had been extinct some fifteen minutes. Though I had attended other members of her family I had never before seen her—in fact, was unaware of her existence. Owing to her nervous temperament and liability to epileptic attacks she was shielded by her family from all undue excitement. Her parents' description of her epileptic fits of some years' duration, and for which she had at one time received hospital treatment, lead me to conclude that they were of the nature of petit mal. She was of medium height, fat, and flabby.

In communicating with the coroner I explained that her epileptic attacks were too trifling to be an adequate cause of death, so he ordered a *post-mortem* examination, which revealed the following abnormal features: The persistence of a thymus gland over 1 oz. in weight. An enlarged heart—13½ oz. in weight—showing no sign of disease, but an unusual amount of fatty infiltration. An enlarged spleen—8½ oz. in weight—soft and hyperaemic. The brain and other organs were quite healthy and there did not appear to be any hyperplasia of lymphatic structures. Death was obviously due to status lymphaticus and accelerated by unusual excitement—a wedding that day in the family.

Sixteen months previously a sister, aged 25 years, a quondam patient, suddenly expired in a dancing hall in London. A necropsy at the Middlesex Hospital revealed status lymphaticus as the cause of death.

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RAT-BITE FEVER IN HONG-KONG.

SINCE this case of rat-bite fever is the first of its kind to be reported in Hong-Kong, it may be worthy of publication.

On September 25th a Chinese man, aged 32, was bitten by a rat (*Rattus decumanus*) about the middle of the upper border of the left trapezius muscle; the bite was a small puncture. There were no symptoms till October 7th, twelve days after the bite, when the temperature rose, and a raised violet-coloured circle appeared round the bite. On October 17th, ten days after the rise of temperature, a rash developed. The patient was seen on the eleventh day of fever, when his condition was as follows. The bite was represented by a callous ulcer, 1 inch in diameter; around it was a purple indurated ring 1½ inches wide. From the ulcer to the middle of the anterior fold of the axilla ran a purple streak 1½ inches broad. Under the anterior axillary fold were a few hard glands. Spread over the face, body, arms, and thighs was a rash, which began as a faint pink raised macule, about 1/4 inch in diameter; in the course of a few hours it assumed a bluish tinge. It was most marked on the face, along each side of the spine, where the spots coalesced in places, and over the shoulder-blades, and was very similar to that of typhus fever. The fever was of the continuous type between 100° to 103° F. each day; at its height there was usually vomiting and some sweating. Mental symptoms were marked; there was some delirium at night, and delusions that cockroaches were running over him. Pain was intense in the region of the bite; there were also articular and muscular pains so severe that the patient expressed a wish to commit suicide.

A search was made in the blood for the spirochaete, both in stained slides and with the dark ground, but none was identified; 10 c.cm. of blood was cultured, but no growth of organisms was obtained. There was no leucocytosis, and the differential count was: polymorphonuclears, 69 per cent.; large mononuclears, 18 per cent.; small mononuclears, 7 per cent.; large hyalines, 6 per cent.; eosinophils, nil. He was too ill to postpone treatment, and on the twelfth day of fever 0.45 gram of novarsenobenzol was given. Six hours later he was vomiting and the temperature was 103°; twenty-four hours after the injection he sweated profusely, the temperature fell to normal, and all pain ceased; thirty-six hours after the injection the purple areola round the wound had gone, and the lymphangitis over the pectoral muscle had nearly faded. The rash was still faintly visible, and in many places had become a brown stain. He expressed himself as being perfectly well. This dramatic effect of arsenical injections is apparently diagnostic of the disease.

Hong-Kong.

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