two nurses whom I induced to take their temperatures for a month. It would be interesting to get corroboration of this view. In a considerable number of females the tem-

CHART 3.

perature shows no alteration at all. Of course, in addition, there are the definite manifestations of tuberculosis given in the textbooks. There may be a definite febrile relapse before the menses (Chart 3), or the relapse may take

CHART 4.

the form of a menstrual or post-menstrual rise of temperature (Chart 4). One girl with a positive sputum had three rises of temperature at intervals of three weeks, but then her menstrual period and her temperature remained normal (Chart 5). Most of the relapses in females occur

about the time of the menstrual flow, and therefore at this time special care should be taken. Between the menses a temperature of 98.8° to 99° F. is probably febrile,

CHART 5.

whereas just before menstruation up to 99.4° F. may be considered normal. If a female patient is admitted to the sanatorium with a temperature of about 100° F. and a few days later the monthly period commences, the outlook for this patient is not as serious as if this temperature occurred midway between periods.*

3. In very few men is there any marked irregularity in the course of a normal temperature, but in women there are quite frequently fluctuations and irregularities. These women are usually of the nervous fidgety type. In febrile cases also there are often great variations in the course of the temperature.

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* A menstrual cycle of about three weeks seems to be fairly common for females in a sanatorium.

CUTANEOUS ALLERGY FOLLOWING DIPHTHERIA ANATOXIN ADMINISTRATION.

BY

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URTICARIAL eruptions are a frequent sequel of injections of therapeutic serums and constitute the most prominent symptom of serum fever. On the other hand, they are rarely seen following injections of toxin-antitoxin (serum) mixture, even with three injections at fortnightly intervals, as in diphtheria prophylaxis. For instance, Wahl (1927), with a personal experience extending over four years of several thousand children immunized by injections of toxin-antitoxin, has recorded only one such observation.

It is not, I think, so well known that urticarial symptoms—evidence of an allergic state—may arise in connexion with diphtheria immunization with anatoxin. The following case lends itself to interpretation in this way.

A children's nurse, aged 17, received three prophylactic injections of diphtheria anatoxin (Institut Pasteur) subcutaneously on July 4th, July 17th, and August 2nd, 1928. A thirteen-day interval separated the first and second injections, a sixteen-day interval the second and third. The doses given were 0.4, 0.8, and 0.8 c.cm. respectively. Apart from the usual local redness at the site of inoculation no reaction accompanied the first two injections. On the evening of the third day after the last injection (that is, thirty-two days from the beginning) she felt slightly out-of-sorts and retired early to bed. The next morning she woke up with a swollen puffy face, and while attempting to dress she noticed that suddenly "everything went dark" (? vertigo).

She was put back to bed, and when seen shortly afterwards the eyelids were found to be markedly oedematous, and there was a widespread urticarial eruption present over the body, especially noticeable on the legs, thighs, and chest, attended by itching. This, she stated, had been present from the night before on her legs and chest. The temperature was 99° F., the pulse 80. The urine, of specific gravity 1024, was acid, and slightly cloudy; albumin and sugar were absent; marked excess of indican and excess of creatinine were present. The bowels were regular.

After two days in bed, with mild purgation and low diet, the attack completely passed; the eruption lasted from thirty-six to forty-eight hours; during two months since there has been no return.

The patient's past history included measles, chicken-pox, and whooping-cough—all before the age of 7—no history of diphtheria, or of any injections. She had a tonsillectomy at 7, and thereafter a healthy childhood. A personal history was elicited of a

dietary idiosyncrasy towards eggs, especially the yolk, which she said always made her feel sick. This idiosyncrasy appears to have been indirectly familial; an aunt on the father's side possessed it. It has, however, to be viewed in a mild and rather relative light in both, for the patient has been known to take eggs without inconvenience when served in dressings, custards, and other dishes, where she was unaware of their presence; the aunt late in life developed diabetes, and then eggs formed an important part of her diet.

The foregoing clinical picture is indicative of an anaphylactoid state. The question arises, Was it of alimentary origin or due to the anatoxin injections? The excess of indican and the personal intolerance towards eggs suggested that the condition might be alimentary. Inquiry in this direction revealed that at lunch the day before the eruption the patient had partaken of clotted milk (*lait caillé*), an article of diet to which she was unaccustomed; there was no history of eggs. It was concluded, however, that there was little to incriminate in this; a view which has been confirmed since, for she has frequently partaken of the same and other brands of clotted milk without inconvenience of any sort.

By elimination, therefore, a diagnosis of anatoxin allergy was arrived at, the responsible factor being clearly the albumin content of the anatoxin.

Albumin Content of Anatoxin.

Anatoxin being a formalized filtrate, from a bacterial culture in nutrient broth, its albumin content naturally depends upon the nature of the broth, and, according to Ramon (1924), also upon the luxuriance of the bacterial culture.

Tested from the point of view of albumin and albumin derivatives, the diphtheria anatoxin employed gave a well-marked positive Heller's test, indicating the presence of albumin. This was confirmed by precipitation with trichloroacetic and hydroferrocyanic acids. The biuret and xanthoproteic tests were positive. Millon's and Adamkiewicz's tests gave negative or indefinite results. Evaluation of the albumin present, with trichloroacetic acid in a Sicard and Cantaloube rachialbuminometer, revealed a content of approximately 0.01 per cent.

This represents a content of 0.0001 gram albumin per c.cm. The figure is significant; it is practically identical with the recognized albumin content of toxin-antitoxin mixture. Now, from the point of view of anaphylaxis,

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.