goitre may acquire enormous dimensions which may produce marked congestion of the veins of the face, chest and upper extremities, and which may lead to actual thrombosis. If a goitre is producing respiratory embarrassment, the sooner operation is undertaken the better.

Graves's Disease.—The cardinal signs of exophthalmos, tachycardia, and tremor make the diagnosis of this condition easy. The ocular signs are well known. The etiology of the disease is obscure. The main issues are (a) that it is a neurosis, (b) that it is the result of perverted secretion or hypersecretion, (c) that it is due to sepsis. Pathologists have described haemorrhages in the fourth ventricle. If these haemorrhages were a constant feature we may be justified in assuming that the glycosuria of Graves resulted from a medullary lesion analogous to Claude Bernard's puncture of the fourth ventricle. Amongst the noteworthy features of this condition we have the cutaneous manifestations, which may take the form of pruritus, leucoderma, or of a pigmentation akin to that of Addison's disease; the unsusceptibility of these patients to cold, the occurrence of oedema, both simple and angioneurotic, and of intractable vomiting and diarrhoea. Singularly enough, in the glycosuria of Graves, as in diabetes, the patellar reflexes are lost.

The relation of hyperthyroid states to tuberculosis has been studied by Professor G. R. Murray, who holds the view that there is some sort of antagonism between the two conditions, as these patients rarely die from tuberculosis, and even if a focus be present it remains quiescent as long as the hyperthyroidism continues. The case which he mentioned in his presidential address at Brighton was operated on by me. There can be no doubt that, after the removal of the major portion of the gland, the patient, who had had the disease for over twelve years, succumbed to acute phthisis.

The treatment of Graves's disease still remains on an unsatisfactory basis. The bulk of the cases are still being treated with bromides and iodides. Kocher thinks well of phosphorus, and the Mayos and Thurstan Holland of *x* rays. The late A. Gibson claimed to have cured most of his cases by suprarenal gland extract, but the experience of others is very disappointing. Moebius's serum has not been a success. Pechlau recently reported a case which was cured by the administration of the milk of a thyroidectomized woman. Sir Thomas Fraser used to speak of marriage as having a curative influence on adolescent female exophthalmics. Good results have been obtained by antiseptic medication of the bowel and the elimination of all sources of sepsis. The excision or short-circuiting of the colon is not a measure likely to meet with general acceptance.

Surgery can claim the most brilliant and the most lasting results, but in this connexion we must bear in mind that institutional life, *x*-ray exposures, and tonic medication contribute to no small extent to the recovery of these patients. Crile's anoci-association method has a useful field in this condition in which "psychic strain" is a pronounced characteristic. Kocher favours the plan of ligating the vessels at successive sittings. Most surgeons prefer the removal of one lobe with the isthmus. One or both vessels of the remaining lobe may be ligatured later if the improvement after hemithyroidectomy is not satisfactory. Halsted has recommended the excision of practically the whole gland, leaving merely a strip on each side to maintain the blood supply to the parathyroids.

I have noticed that exophthalmic subjects, thin or even emaciated as they are as a rule, put on fat to an extraordinary extent after operation (Fig. 3). I have never seen complete recession of the eyes after operation or other treatment. Drs. Bythell and Barclay of Manchester assure me that they have obtained complete disappearance of exophthalmos by *x*-ray treatment alone.

THE *Journal of the American Medical Association* lately called attention to a two year graduate course offered by the University of Minnesota for the training of doctors who desire to specialize in ophthalmology. This course is analogous to the graduate courses offered by several medical schools for the training of health officers. It is thought probable that similar courses will be established for the training of those who wish to limit their practice to other special provinces of medicine.

NICOLLE AND BLAIZOT'S VACCINE IN THE TREATMENT OF GONORRHOEA.

BY

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THIS vaccine, which goes by the name of "Dimegon," was prepared by MM. Ch. Nicolle and L. Blaizot, of the Pasteur Institute, Tunis, and placed on the market as a stable, non-toxic vaccine for use in all cases of gonorrhoea. In October, 1913, they maintained its superiority over the vaccines in ordinary use.

The drawbacks to the use of the latter, and of gonococcal vaccines in particular, where results have been far from uniform or encouraging, had led them to seek a means of overcoming these defects. In their opinion the two chief obstacles to the success of vaccine-therapy are the present crude methods of sterilizing the living cultures, and the more or less constant toxicity of all vaccines, but more especially of gonococcal vaccines. Even Besredka's method of sensitizing has failed, according to them, to abolish this toxicity.

They stated that, as the result of a year and a half's work, they had succeeded in entirely suppressing the toxicity of gonococcal vaccines, and claimed by their new method of sterilizing to have prepared a vaccine in which the organismal elements are conserved practically in the same condition as obtains in the living culture—in other words, that their vaccine was non-toxic and stable. How this was attained was not at first divulged; the authors merely stated that the toxicity had been abolished by growing the organisms on a special medium, while stability had been achieved by the use of a special solution as lethal vehicle.

Their personal statistics up to that time covered some 200 cases, including 24 cases of ophthalmia, 3 of rheumatism, 25 of orchitis, and 127 cases of acute and chronic urethritis. They stated that ophthalmia was cured after a few injections, sometimes after one, an injection being given each day; that in acute orchitis the pain disappeared in a few hours, or at most within a day or two after the first injection, fever declined, and the patient was able almost at once to resume his daily occupation; and that gonorrhoeal rheumatism rapidly cleared up under two to eight injections. The most striking case was one where a woman, bed-ridden for eight months, was able to come for the eighth injection. In acute urethritis the symptoms, they stated, cleared up with equal rapidity. The discharge ceased later, but in many cases it had disappeared after the third injection. They recommended that the injections, which were repeated every two days, should be continued till seven or eight had been given. Simultaneous local treatment had a favourable effect. None of the acute cases under prompt treatment developed any extra-urethral complications. Old-standing gleet (a year and a half) had been cured by this vaccine, the injections being given every three or four days.

Truly these are wonderful results and all obtained without provoking any untoward or disagreeable reaction! Beyond these facts, however, nothing was known about this vaccine till in November, 1913, Nicolle and Blaizot² revealed their secret.

Vaccines prepared in the usual way are damaged by the coagulating effect of heat, and are unstable because they undergo later a process of autolysis. To obviate these disadvantages the authors make use of a fluoride solution since fluorides have been shown by other workers not to possess the property of coagulating albumin.

Method of Preparation.

The organisms are suspended in a 0.7 per cent. solution of sodium fluoride in which they die after a variable time depending on the temperature and species. For instance, gonococci die after forty-eight hours' exposure in an ice-chest to the action of the fluoride. The authors claim that the organisms remain practically unaltered and, since the solution retards autolysis, long preserve their morphological and staining characters. The fluoride is also said to aid in diminishing the toxicity. The latter, however, is mainly brought about by growing the gonococci on special culture media which at first consisted of: Broth 100, urea 0.4, glucose 2, phosphate of ammonia 0.5, agar 1.5.

To this in tubes of 5 c.cm. each are added 0.5 c.cm. rabbit serum. The gonococcus is first grown on this and, by sub-

culture on successive media less and less rich in serum, it is trained to grow on the above medium minus the serum.

A twenty-four hours' growth is then scraped off, suspended in the fluoride solution and repeatedly washed and centrifuged in order to obtain well isolated organisms.

Since gonococcal vaccines, as ordinarily prepared, yield very inconstant and disappointing results, the authors sought for and claim to have found another organism frequently found along with the gonococcus. To this organism they give the name "Synococcus." The latter closely resembles the gonococcus, but grows easily on serum-free media, produces an orange pigment, and is Gram-positive. It provokes no reaction, but possesses the same curative effect as the gonococcus. They suggest that it is related in some way to the gonococcus, and that ordinary gonococcal vaccines owe their lack of success to a failure to recognize the important part played by this new organism.

Their vaccine, then, consists of one part of gonococcus to 9 parts of the synococcus, and, since it is given in doses of 0.5 c.cm. containing 250 million of cocci, it follows that only 25 million consist of gonococci proper, while the other 225 million are "synococci."

In the directions for the employment of the vaccine it is recommended that the 0.50 should be diluted with 1.50 c.cm. physiological saline, supplied in a separate ampoule, and the 2 c.cm. injected deeply into the muscles. This is preferable to subcutaneous injection owing to the slightly caustic action of the fluoride. In the instructions, however, no reaction is said to follow either method, while intravenous injection is decried, as it is likely to determine a febrile reaction. The above summarizes the main facts known about the vaccine, together with the claims advanced by the authors. The next question that arises is, How far have these claims been justified? In order to answer it I have collected as many published references as I could find, and to these I add a very brief account of 4 cases which have been treated with this vaccine in the out-patient department of the Royal Berkshire Hospital, Reading.

I omit reference to the few cases chosen from among the 200 mentioned by Nicolle and Blaizot in their communication, as well as those published by their colleague, Remlinger³ of Tunis.

Bar and Lequex⁴ give their experience with the vaccine whose nature at that time was unknown to them. Their series includes:

A case of purulent ophthalmia in a child 4 days old cured by one injection of 2½ drops.

Four cases of salpingitis in non-puerperal women:

1. Cured in fifteen days by four doses of 10 drops each.
2. Cured in seventeen days by three injections; both of these cases were of moderate severity.
3. Cured after seven injections, although previously she could not be examined owing to pain.
4. Double salpingitis; right tube cleared up after three injections. Operation, performed later, showed that the left tube was still affected, and gonococci were demonstrated in it.

The same authors state that slight anuria of a few hours' duration was occasionally observed, and once they noticed an urticarial rash. Some of the patients complained of a fairly acute pain at the site of injection, which might last some four or five hours, and even recur after some days.

Masson⁵ reported a case of salpingitis cured by the injection of antimeningococcal serum. Sauvage⁶ tried this new vaccine on a little girl, the subject of acute vulvovaginitis, who four days after infection developed peritonitis; 1.0 c.cm. of the vaccine was given on the third day after the onset of peritoneal symptoms, and the same dose was repeated on each of the two subsequent days without any effect. Laparotomy was performed, and gonococci were subsequently shown to be present in the tube.

Troisfontaines⁷ mentions 5 cases. In 3, men with acute epididymitis occurring in the course of chronic gonorrhoea, the most striking effect of the vaccine administered subcutaneously was the disappearance of the pain and swelling either immediately or after two injections. The vaccine did not influence the discharge, and gonococci were found at the end of the so-called cure as at the beginning. Two cases of gonorrhoeal arthritis in women were cured by three injections.

Broussegoutte⁸ employed the intravenous method of administering the vaccine, without any untoward results, in 3 cases:

1. Cystitis and prostatitis cured after injections of the vaccine combined with rigorous local treatment.
2. Urethritis cured in the same way.

3. Case of acute orchitis, which rapidly lost all pain after receiving the vaccine, but an abundant discharge returned, which contained numerous gonococci. In this case only two injections were given.

C. and H. Fromaget⁹ record a case of purulent ophthalmia treated with this vaccine for four days. After the second injection there was a recrudescence of the trouble, and recourse was then had to silver nitrate in addition to the vaccine. Cure was effected at the end of eight days after three injections had been given. Leuret¹⁰ reports 3 cases:

1. Gonorrhoea, contracted about two months before, which had not cleared up under the usual classic remedies, was cured after three injections, with complete disappearance of the discharge.

2. Gonorrhoeal arthritis of four months' duration, cured after four injections. The first injection was followed by slight febrile reaction and headache, thought to be influenzal in character.

3. Gonorrhoea and arthritis of nearly three months' standing, almost cured in nine days after four injections.

Mauriac¹¹ mentions 4 cases: 2 had urethritis, 1 suppurating arthritis of the knee, and 1 epididymitis. The arthritis rapidly cleared up, and after 3 injections the patient was able to walk. Mauriac has noted pain the day following the injection, and sometimes a slight general reaction with temperature. He goes on to say that the effect of the vaccine on the discharge appears to be nil, though the gonococcus appears to be more sensitive to the action of antiseptics. Fienx¹² has treated two patients suffering from an acute exacerbation during the course of a chronic affection (salpingitis) with good results. He records one failure, a case of ophthalmia neonatorum treated on the fourth day.

Dr. Wansey Bayly,¹³ in a recent article in this JOURNAL, states that in his limited experience some cases benefited, but he was not much impressed with its merits.

The following are brief notes of the cases at the Royal Berkshire Hospital:

1. Female, infected two months before, received eight injections, one every two days, into the muscles. Result: Severe local pain after each inoculation, together with headache and malaise; vaginal discharge considerably diminished, but still present.

2. Female; vaginal discharge of three to four months' duration, untreated; now received nine injections, as in Case 1, and was instructed to wash external genitals with weak antiseptic. Result: Discharge rapidly diminished and apparently disappeared; following the ninth injection, however, her temperature rose, a pustular eruption appeared on the body and subcutaneous nodules on the shins. On recovery she was examined again, and a copious discharge, containing gonococci, was found.

3. Male, infected eleven months before, treated in the classical way till only a "morning drop" remained. Treatment: Four injections, one every third day; after a week's rest seven further injections were given with the same spacing, sometimes intramuscularly, sometimes subcutaneously. Result: Headache and dizziness after the first four injections, coming on towards evening and lasting a few hours. The discharge remained uninfluenced and gonococci were still plentiful.

4. Male, infected twenty-two months before, treated in usual way, together with stock vaccines; slight morning discharge, however, remained obstinate. Hospital treatment: Four injections of the Nicolle and Blaizot vaccine on alternate days, followed by a week's rest. Another five injections were then given with same spacing. Result: Slight headache on one occasion, but at the end of the treatment the discharge had actually increased and gonococci were still present.

From a consideration of these cases it must be admitted that the vaccine has not completely fulfilled the claims of the authors and their colleagues.

It is true that the number of published observations made by independent workers is comparatively small. I do not, of course, include the cases referred to but not published in detail by Nicolle and Blaizot, nor do I include Remlinger's. These, we are told, were successful cases. The others which I have summarized number 29, and of these only 15 are reported as definite cures. Several of the patients showed signs of undoubted general disturbance such as is common after the use of ordinary vaccines. Judging from these reports the vaccine does not always cure and is not always atoxic. Of course it may be urged by the supporters of the vaccine that in some of these cases a sufficient number of doses was not given. In the 4 cases reported here for the first time the average number of doses said to be necessary for a cure was exceeded and in one case the only result was an increase in the discharge. Moreover, each dose costs

5 francs. The majority of the cases, however, according to the reports, seem to have benefited, and probably the most striking effect of the vaccine has been the rapid manner in which it appears to have relieved pain in cases of arthritis and orchitis. Whether it will always act in this way in the hands of other workers remains still to be seen. Several cases of a similar nature have cleared up as rapidly after the injection of antimeningococcal serum.

Another feature is the ease and rapidity with which ophthalmia cleared up, but a sufficient number of cases have not yet been recorded. If it proves to be a constant character of the vaccine, we have a very potent weapon with which to combat a disease which, as a nation, we are endeavouring to control.

An interesting question is how far the cases of urethritis as reported cured are actually infection-free or whether the disease has merely been rendered latent. This is a point not brought out in the cases recorded.

As regards the fluoride vehicle, I doubt if it can have much effect in reducing toxicity. Lately I have been preparing vaccines in this way, and have found that the focal and general reactions respectively have been as marked as those produced by the injection of autogenous vaccines prepared by one of the older methods. In any case there is one objection to the use of fluoride solutions where rapidity of preparation is an essential. Gonococci, according to the authors, are only killed after forty-eight hours' exposure to the solution in an ice chest, and the length of time necessary to sterilize a given organism depends on the temperature and the species, but it depends also on the concentration of organisms in the vaccine. I find that the greater the number of organisms present per cubic centimetre the longer is the exposure necessary to effect complete sterilization. For instance, a vaccine containing 1,600 million of staphylococci per cubic centimetre still gave a growth after six days' exposure at room temperature. In such cases, therefore, we must adopt one of the older methods for the sterilization of the preliminary doses at any rate. As regards the constituents of the vaccine, the toxicity of one of them, the gonococcus, is said to be reduced in the manner described. But this organism represents only one-tenth of the total number of organisms present, since there are only 25 million present in each dose.

Moreover, while the synococcus provokes no reaction on inoculation, according to Nicolle and Blaizot, it nevertheless possesses the same curative action as the gonococci themselves. If this be so it seems at first sight unnecessary to go through the elaborate process of reducing the toxicity of the gonococci proper when present in such small number or even to include them at all.

What exactly the "synococcus" is, and what relation, if any, it bears to the gonococcus proper, is not clear, but the suggestion is that in gonorrhoea we are dealing not with a single strain but with a group of organisms all more or less related to one another—not at all an unlikely thing. On the other hand, the synococcus may be related in no way to the gonococcus proper except in so far as their symbiosis may modify the course of the disease. In other words, one must take account not merely of the main causal organism but also of other organisms in symbiosis which may considerably modify its effect and character. It would be interesting to know if the authors have used the gonococcus alone after modifying its toxicity in the method they advocate and in the same doses, and if the same effect could not be got in this way, leaving out altogether the synococcus.

These are some of the questions that arise in connexion with this preparation. Meanwhile, one must remain sceptical until a sufficient number of cases can be investigated and a little more of scientific value is known about the vaccine. This ought to be a matter of a short time only since there are no contraindications to its use, and the administration can easily be carried out by the general practitioner, no special bacteriological knowledge being necessary for its proper control. As for the route by which it is administered, it would appear from the cases recorded that it may be given either under the skin, into the muscles, or directly into a vein. Contrary to what the authors say, subcutaneous inoculation may be painless, intramuscular injections may be followed by severe pain, while no ill effects seem to attend intravenous inoculation.

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BLOOD PLATELETS IN THE TREATMENT
OF DISEASE.

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(Preliminary Note.)

THE employment of blood platelets together with the plasma in which they are suspended has given such very satisfactory results in the treatment of a large variety of morbid conditions that I think it well to publish this short preliminary note upon the methods of preparation, the technique, and results of administration.

I have employed blood platelets therapeutically in three definite ways. In the first the blood platelets are isolated from a person in perfect health, the absence of specific disease being determined by means of the Wassermann test, and of tuberculosis by means of von Pirquet's cuti-reaction; the platelets so obtained are used parenterally in varying amounts according to indication, in order to reinforce the powers of the body against the different local and general diseases due to bacteria.

In addition to satisfactory clinical results following the administration of blood platelets, determinations of the opsonic and phagocytic index, quantitative agglutinin tests, as well as complement deviation reactions, indicate that after each of such injections there is a very marked rise of the antibody content of the blood.

The different immunity reactions applied to the platelets and their containing plasma, more especially when applied thereto after recovery from microbic disease or after preliminary vaccine injection, indicate that they contain a very large part of the different antibodies produced in response to bacterial invasion of the organism. In addition to germ-caused diseases, the exhibition of blood platelets has been found satisfactory in cases of deep-seated hæmorrhage, such as hæmoptysis, hæmatemesis, and renal hæmorrhage.

A second way in which I have employed blood platelets therapeutically in the treatment of bacterial disease has been as follows:

The specific organism is isolated from a patient and with a vaccine made therefrom a healthy friend receives several injections until the various opsonic or agglutinin reactions indicate that this person's serum has a high antibacterial content to this particular organism. The blood platelets and their plasma are then obtained and used in the treatment of the original case. The employment of stock instead of autogenous vaccines has also given good results and effects a considerable saving of time. I have also used platelets isolated from patients who have passed through an attack of bacterial disease, such as those due to staphylococci, streptococci, and pneumococci. In such cases I have made the opsonic index my guide and have only used the platelets isolated from patients whose opsonic index is high.

A third method, used in cases in which the toxæmia is not extreme, such as chronic ulcers, furunculosis, acne, and tuberculosis, has been to sensitize vaccines obtained by isolating the organism from the patient's lesions by means of the platelets and their plasma. In addition to good clinical results obtained therewith, the completeness of the sensitization can be gathered from the very slight local reaction which follows their employment.

The usual technique I have used for the preparation of such sensitized vaccines has been to make an emulsion of the organism in as small a quantity of saline solution as possible, usually 5 c.cm. This emulsion I have generally exposed to a temperature of 60° C. for half an hour in order to kill the organisms; in certain cases that has been effected by adding 1 per cent. phenol after sensitization is complete.

The emulsion is added to the platelets, and their plasma under sterile paraffin, and exposed to a temperature of