more weight than mine possibly could, and notably Dr. Odery Symes,¹⁴ Dr. Maxwell Telling,¹⁵ and Dr. Hope Gosse,¹⁶ have gone into the matter carefully and arrived at much the same conclusion as myself. It therefore seems to me to be unnecessary to say more than this—that there are only three cases in my new series in which there is a history of previous rheumatic fever in the patient, and that in none of the three had any organic cardiac lesion persisted; that in four others there was a vague history of so-called rheumatism; and that in only five cases was there a family history of acute rheumatism. Again I wish to emphasize my conviction that the pseudo-rheumatism of nodal fever is an expression of arthritis or of teno-synovitis due directly to the "germ" which causes the skin eruption, or to the toxins to which it may give rise. Above all, I wish to reiterate the absolute uselessness of drugs of the salicylic acid group to ease these pains or to control the course of the disease.

Lastly, roughly speaking, there are no cardiac complications of nodal fever: a transient though distinct murmur may be noted during the illness, but it disappears; it is probably haemic or myocardial.

Tuberculosis.

When my book was published in 1905, in disputing the rheumatic theory which then held the field, I lightly said¹⁷ that it would be just as easy to prove, as far as mere statistics were concerned, that nodal fever was related to tuberculosis. I little dreamt then how large the tuberculous theory of its origin would loom in the next twenty years, though it was broached originally over half a century ago, or that I should read the dogmatic assertion in a retrospect of the year 1918¹⁸ that "the causative factor of erythema nodosum has now been determined to be tuberculosis." The subject, therefore, requires careful investigation. In this direction again I am forestalled by Dr. Symes, and I can only assert that the proportion of tuberculous manifestation preceding nodal fever is not greater in my experience than one would expect considering how widely spread tuberculosis is known to be, and that tuberculous sequelae are comparatively rare. In my whole series there are only two cases of nodal fever complicating tuberculosis—one a girl of 18 who had suffered since early childhood from morbus coxae, and a young married woman who was at the time suffering from, and who subsequently died of, phthisis. A mother, who had lost a son from tuberculous meningitis, died many years later from erythema papulatum, but without any evidence of being tuberculous herself.

OPINIONS OF OTHER WRITERS.

Some writers¹⁹⁻²⁰ have drawn attention to the fact that nodal fever occasionally follows shortly after measles, and I have notes of one such case. I can hardly think that there is any causal relationship, but the observation is one to be borne in mind.

There are many who still adhere to the rheumatic fever heresy (cf. references 21 to 27), but as a rule they only bring forward one or two isolated cases. Wiborg,¹¹ however, is an exception, as he recorded an epidemic of thirty cases which he considered to be of rheumatic rather than of tuberculous origin. Hallam²⁸ writes in opposition to the rheumatic theory.

Landouzy²⁹ excised a node and found in it Koch's bacillus; he inoculated a guinea-pig with a portion of this node and produced in the animal tuberculous lesions, but he does not himself contend that therefore all cases of erythema nodosum are tuberculous in origin. Ward³⁰ expresses similar views. Hildebrand²⁹ obtained with venous blood similar inoculation results. On the other hand, Otto Brian²⁹ induced tuberculosis in a guinea-pig in one experiment, but failed in all his others. His conclusion was that tuberculosis was the actual cause of erythema nodosum in only a few cases; Dufourt³¹ put it as high as 60 per cent. Deléarde and Haller³² also think that the greater number of cases arise from a tuberculous soil.

Intradermic injection of tuberculin is said²⁹ to have caused lesions exactly resembling erythema nodosum at the point of injection, but Dr. Darcy Cowan informs me that

he can recall no case following hypodermic injection. Stefano³³ obtained a positive reaction in all the 23 cases in which he tried von Pirquet's test. Vetlesen³⁴ plumps for tuberculosis. Several writers have recorded³⁵⁻³⁶ the fact of cases of erythema nodosum complicating tuberculosis and winding up with meningitis, and have verified their observations by necropsies. Haug³⁷ opines that the tubercle bacillus can provoke either erythema nodosum, or a form of arthritis which does not yield to sodium salicylate nor pass so quickly from joint to joint as usual. Meara and Goodridge²⁹ thought that erythema nodosum occurred under three conditions: (1) as a simple variety of erythema multiforme; (2) as a definite specific contagious disease; (3) as a lesion secondary to many things, such as infectious diseases, drug ingestion, alimentary disturbance, and nerve diseases.

Lastly, several writers have been impressed with the possible infectious and contagious nature of nodal fever. These include: Anderson and Cooper,³⁸ Clarke,³⁹ Craig,⁴⁰ Durante⁴¹ (who excludes tuberculosis and rheumatism), Wendler,⁴² Settgastr⁴³ (who considers rheumatism a complication, not a cause, and excludes tuberculosis from consideration), Dorth,⁴⁴ and Moses.¹⁰ Guéissaz⁴⁵ finds it to be an acute exanthem, and that marvellous observer Sir Jonathan Hutchinson⁴⁶ almost said the same thing more than half a century ago. Amongst English writers Odery Symes⁸ bears me out in almost every respect, whilst Maxwell Telling¹⁵ also considers it to be an acute specific disease, but does not agree with me, I fancy, as to its relationship to erythema multiforme.

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THE CHEMOTHERAPEUTIC TREATMENT OF GONORRHOEA AND ITS COMPLICATIONS.*

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Introduction.

THOUGH gonorrhoea, when first contracted, is a local infection, nevertheless changes do occur in the blood of the host, particularly in the protein particles of the plasma in which resides the host's main protective substance. Treatment with chemical substances and protein extracts (vaccines) acts by increasing the patient's resistance and not by killing the invading micro-organisms directly. Considering that vaccine treatment alone leaves much to be desired, it has been my endeavour for some years past to find a chemical compound which would have much the same effect in gonorrhoea as has arsenobenzene in syphilis.

The last milestone in this work was marked by the introduction of manganese butyrate, a drug which has proved

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of value, particularly in the acute complications of gonorrhoea. These are due, perhaps, more to the invasion of staphylococci than actually to the gonococci. In short, manganese butyrate has a better chemotherapeutic effect in pure staphylococcal than in pure gonococcal infections. As the gonococcus is higher in the scale of bacterial evolution than the staphylococcus, a drug more powerful than manganese butyrate is required to combat its invasion.

Metallic preparations appear to act by increasing the number of the protein particles constituting the defence, thereby augmenting the area exposed to the bacteria. Hydrogen and sodium atoms may effect this change even more effectually than manganese, provided they are liberated from a sufficiently large molecule. Moreover, such atoms are less liable to destroy the host's protective substance and to produce metallic intoxication. Therefore, the ground last covered has been in this direction, and the present paper marks the introduction of two further drugs: (1) the symmetrical urea of meta-benzoyl-meta-amino-benzoyl-amino-naphthol-3-6-sodium sulphionate, or "sum 36" for short; (2) the symmetrical urea of para-benzoyl-para-amino-benzoyl-amino-naphthol-3-6-sodium sulphionate, or "sup 36." The former is to be preferred in pure gonococcal infections, and the latter in the complications arising from the supervention of Gram-positive cocci. Both drugs were kindly made at my instigation by Mr. T. H. Fairbrother of the British Dyestuffs Corporation, Ltd. They have been in use since the latter part of 1923, and the following practical conclusions are derived from the treatment of several hundred cases.

Gonococcal Urethritis and Vulvitis.

In the male two intramuscular injections of "sum 36," each of 0.002 gram, should be made at five days' interval. In the female it is better to inject 0.01 gram intravenously. The two injections should be followed by a course of vaccines. In most cases of fresh infection this treatment suffices. Any recurrence of an acute discharge can be stopped by two further injections of the urea compound. Provided the patient is not on the point of developing an acute posterior urethritis or an acute cervicitis when the first injection is made, no complication need be expected. The immediate effect of this drug in acute gonorrhoea is disappearance of the subjective symptoms and lessening of the discharge.

Pure Gonococcal Complications.

Under this heading are included acute ophthalmia and acute primary, as opposed to recurrent, arthritis associated with a copious urethral, vulval, or cervical discharge. In these cases "sum 36" is the drug of choice. In gonorrhoeal ophthalmia in infants one or two intramuscular injections, each of 0.004 gram, will clear up the acutest case. In a boy of 6, who had a prolapsed iris, a single injection of 0.005 gram of "sum 36" caused an enormous improvement of the lesion within forty-eight hours, by which time the iris had regained its normal position. In adults the dose should be 0.01 gram, and the injections may be made either into the muscles or into the veins. In acute primary arthritis a single injection of 0.01 gram will cause the pain and swelling of the joint to disappear the following day.

Gonococcal Complications due in part to Secondary Micro-organisms.

Belonging to this category are the following clinical conditions: (1) acute Cowperitis with abscess formation; (2) acute prostatitis with abscess formation; (3) acute cystitis; (4) acute epididymitis and salpingitis. In all these cases two injections of "sup 36," each of 0.01 gram, should be made intramuscularly or intravenously at three days' interval. The two injections should be followed by one or more courses of vaccines. But in cases of epididymitis and salpingitis the vaccines should be preceded by an intramuscular injection of contramine (0.25 gram). This injection of contramine, which is the carbon disulphide product of di-ethyl-amine, reduces the formation of fibrous tissue to the minimum and thereby lessens the liability of a local recurrence in the future. Bearing in mind the common

view that cases of salpingitis need operating upon, it is interesting to record that in twelve cases treated with "sup 36" all were up and about within a week of the first injection. The day following the initial injection the temperature became normal and the subjective symptoms vanished. In a case of gonococcal periostitis of the upper end of the tibia, which looked as if it needed incision, a single injection caused the redness, swelling, and pain to vanish the next day.

Chronic Complications of Gonorrhoea.

Under this heading are included stricture, chronic epididymitis, conjunctivitis, and iritis, and the various forms of muscular rheumatism—neuritis, fibrositis, teno-vaginitis, and arthritis. Contramine, probably by reason of its sulphur content, is a softener of fibrous tissue, and many strictures resisting dilatation may be rendered dilatable by injecting intramuscularly one dose of 0.25 gram and two doses of 0.5 gram at approximately weekly intervals. This treatment is advised in cases of chronic epididymitis, but it should be succeeded by a course of vaccines, because micro-organisms hidden by the fibrous tissue may be released as the latter is destroyed. Bilateral conjunctivitis is a common harbinger of polyarticular gonococcal arthritis. Since patients with this prodromal symptom are often much debilitated care must be used in stimulating their resistance, and it is wiser to make three injections of contramine, each of 0.125 gram, on alternate days. Six half-doses of vaccine (I use 1,250 million Lock Hospital vaccine, made by our pathologist, Major V. Corbett) should then be prescribed and injected every second or third day. Following this the injections of contramine should be repeated in half or full doses according to the patient's condition, and the treatment concluded with another course of vaccines. The same treatment should be adopted in severe cases of gonococcal iritis and in gonococcal arthritis when the patient is really ill. Where it is obvious that the host's resistance is at its lowest ebb, no injections should be made. In ordinary cases of gonococcal rheumatism, neuritis, fibrositis, teno-vaginitis, and arthritis 0.25 gram of contramine should be injected as soon as possible, followed by two further injections, each of 0.5 gram, at five to seven day intervals. Then a course of vaccines should be prescribed—four doses of 2,500 million and four doses of 5,000 million injected at weekly intervals. A second course of contramine and vaccine injections may or may not be necessary. In no circumstances should an infected joint be put up on a splint, and neither the prostate nor the urethra should be examined while the arthritis is active. An infected joint should be exercised at the earliest possible moment.

NOTE ON THE USE OF CHEMOTHERAPEUTIC PREPARATIONS.

The urea compounds are soluble in water. They should be dissolved in distilled water, and preferably just before use, particularly if they are to be injected intravenously. Intramuscular injections may be made anywhere, provided the bulk of the solution does not exceed 1 c.cm. The preparation "sup 36" is useful in many inflammatory conditions other than those met with in gonorrhoea. Owing to the large size of the nucleus or molecule of the urea compounds an injection may be followed by a mild degree of shock. The occurrence of shock is very rare and passes off in a few minutes.

Contramine must be injected into the gluteus medius; it should never be allowed to get into the subcutaneous tissue for fear of the formation of a sterile abscess. The recipients of contramine should avoid alcohol for two or three days after each injection, because in a few cases the taking of alcohol is followed immediately by flushing and giddiness. Contramine, provided it is not more than a year or so old, is soluble in distilled water; solutions should always be freshly prepared. It is equally valuable in cases of rheumatism of other than gonococcal origin, but in the type met with in women round about the menopause thiol-histamine, injected in 0.002 gram doses on three successive days, is better. Both these sulphur preparations were made for me by the British Drug Houses, Ltd.