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EFFECT OF CORTISONE IN EXPERIMENTAL SYPHILIS IN RABBITS*

BY

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During the treatment of collagen diseases with adrenocorticosteroids, it has been observed that biological false positive (non-treponemal) sero-reactions for syphilis become temporarily weakened or negative.

Turner and Hollander (1950, 1954) found that in some but not all syphilitic rabbits there was a fall in the reagins after 14 days' treatment with cortisone, accompanied by a pronounced change in the clinical manifestations of the disease.

DeLamater, Saurino, and Urbach (1952) found that cortisone-treated syphilitic rabbits had lower titres in Kahn and Kline reactions than control animals. Their explanation of this finding was that cortisone treatment hindered the formation or demonstration of reagin.

To prevent Herxheimer reactions, De Graciansky and Grupper (1955) gave cortisone to syphilitics before penicillin treatment, and in some cases they found a fall in the titres.

In the present study, we have examined the influence of cortisone treatment on sero-reactions in syphilitic rabbits. Both the *T. pallidum* immobilizins and the so-called reagins were investigated. While the immobilizins demonstrated by the *Treponema pallidum* immobilization test (TPI) are antibacterial antibodies, the nature of the reagins is not finally clarified, but their behaviour suggests that they are antibodies of anti-lipoidal nature. For example, electrophoretic investigations of the position of the reagin in serum (Neurath, Volkin, Erickson, Craig, Putnam, and Cooper, 1947; Laurell, 1955; Schmidt and Birch-Andersen, 1956; Vannier, 1956) support the concept of the reagin as an antibody, as it was shown that the localization in the serum corresponds to that demonstrated in other antibodies investigated.

Concurrently with the serological investigations, the influence of cortisone on the course of the disease was followed clinically.

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Material and Methods

Altogether 26 male albino rabbits, weighing approximately 3,000 g., were inoculated intratesticularly with the Nichols' strain of *T. pallidum*: 22 of the rabbits received 150×10^6 treponemes, two received 75×10^6 treponemes and two received 38×10^6 treponemes. As the serological results showed no differences which might be attributed to the difference in the inoculum, all the infected rabbits were considered as being uniformly infected.

Cortisone treatment (Cortone, Merck, containing 25 mg. cortisone acetate per ml.) was given as intramuscular injections of 25 mg. cortisone daily for 14 days, with subsequent tapering off for 6 days, during which 20 mg. cortisone was given for 2 days, 10 mg. for 2 days, and finally 5 mg. for 2 days.

A pilot experiment had shown that the course of the titre curve varied strongly with the time of beginning the cortisone treatment, and that the most pronounced effect took place when the hormone treatment was begun about 3 weeks after the inoculation.

In four rabbits, the cortisone treatment was begun simultaneously with the inoculation (Group 1), in eight rabbits it was begun 3 weeks after the inoculation (Group 2), and in four rabbits it was begun 5 weeks after the inoculation (Group 3). The remaining ten rabbits were left untreated as controls.

All the animals were examined clinically, daily at the start of the experiment and later every second or third day. All animals were weighed once a week.

Approximately 4 ml. blood was taken from an ear vein of all the rabbits twice weekly during the whole period of the experiment. All blood samples were examined by means of four sero-reactions with lipoid antigens, using both "crude" and cardiolipin antigens. Two complement-fixation reactions—Mørch's modification of the Wassermann reaction with cardiolipin antigen (C–WR–M) and the same reaction with an "incomplete" lecithin-free cardiolipin antigen (CardChol) (Schmidt, 1951, 1955a)—and two flocculation reactions—Kahn standard (KR) (Kahn, 1928) and VDRL slide flocculation test (Harris, Rosenberg, and Riedel, 1946)—were carried out. A selection of the sera (see below) was investigated by means of the quantitative TPI test (Nelson and Mayer, 1949; Nielsen, 1957).

The period of the experiment extended over 100 days, and 25 blood samples were examined from each animal.

After reading the haemolysis percentage, or alternatively the size of the floccules in each serum dilution, the logarithmic titre value (log. val.)* was calculated by Kärber's method (see, for example, Finney, 1947).

Results

In the dosage employed, cortisone showed a pronounced toxic effect on the rabbits. Thus, almost all the cortisone-treated animals showed loss of weight and poor condition (reduced appetite, dull fur, apathy). However, there were no deaths as an immediate consequence of the treatment. The sera from those cortisone-treated animals which were most severely affected showed pronounced lipaemia, but in spite of this, it was still possible to read the sero-reactions in all cases, though the reading of the TPI test in particular caused difficulty.

Some of the animals turned out to be poor reagin producers, and the results from them have been omitted from the final analysis of the material.† Table I shows the final number of animals in each group.

TABLE I

DIFFERENCES BETWEEN MEAN TITRES ON 20TH DAY AND 34TH DAY

Group		Controls		Group 1		Group 2	
No. of Rabbits		7		4		6	
		d	SE	d	SE	d	SE
Test	C–WR–M	−0·55	0·06	0·45	0·08	−0·78	0·07
	CardChol	−0·51	0·06	0·52	0·08	−0·61	0·07
	KR	−0·46	0·07	0·36	0·09	−0·70	0·08
	VDRL	−0·69	0·10	0·15	0·13	−0·75	0·10

d = difference between mean titres. SE = standard error.

In each group of animals, a mean titre was calculated for each experimental day and each method, and curves of these mean titres were drawn. For reasons of space, only the C–WR–M mean curves are given for the three groups: the Control Group, Group 1 (cortisone-treated from day zero), and Group 2 (cortisone-treated from the 21st day). Although the curves for the different sero-reactions do not show an identical course, the tendency is uniform.

The control curve (Fig. 1) shows that the maximum titre (C–WR–M = 1·76 log val.) is reached on the 17th day after the inoculation. CardChol, KR, and VDRL showed maximum titres of respectively 1·56, 1·8, and 2·23 log val. After the maximum is reached, a spontaneous fall takes place throughout the whole experimental period. Around the 90th day, the C–WR–M titre is about 0·6 log val., KR and VDRL about 0·7 log val., and CardChol about 0·4 log val.

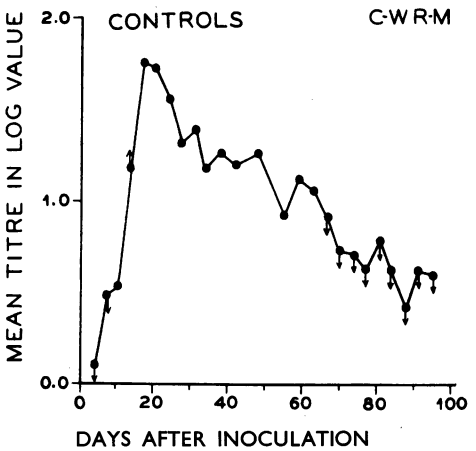

FIG. 1.—Mean titre for C-WR-M in Controls (seven untreated animals).

The mean curves for the cortisone-treated animals show a different course from those of the control group (Figs 2 and 3, opposite).

Group 1.—The animals reach their maximum titre on the 31st day, *i.e.* 10 to 14 days later than the controls. The maxima in the various reactions are approximately 0·2 log val. lower than those of the controls, with the exception of VDRL, but the differences are not significant, as the variation is great. The fall in titre after the peak is reached does not differ essentially from that found for the controls.

Group 2.—The course of the curve during the first phase of the infection is not essentially different from that of the controls, apart from the fact that their maximum titre is slightly but not significantly lower. Immediately after the start of the cortisone treatment (3 weeks after *T. pallidum* inoculation), a quite considerable fall in titre is seen, which is repeated in all four sero-reactions. The lowest titre during cortisone treatment occurs on the 37th day, *i.e.* at a time when the tapering off of the cortisone dose had already commenced. Thereafter, a second

* 1·0 log. val. means that 50 per cent. haemolysis or floccules of Size 2 are obtained in a serum dilution of 1 in 10. In both the KR and VDRL tests, the size of the floccules are evaluated as 4, 3, 2, and 1. The initial dilution has not been taken into account.

† Those animals which did not reach a primary reagin maximum of at least 1·0 log. val. were omitted from the material. It is well known that the animals vary greatly in their ability to form reagin, but the reason for this has not yet been discovered.

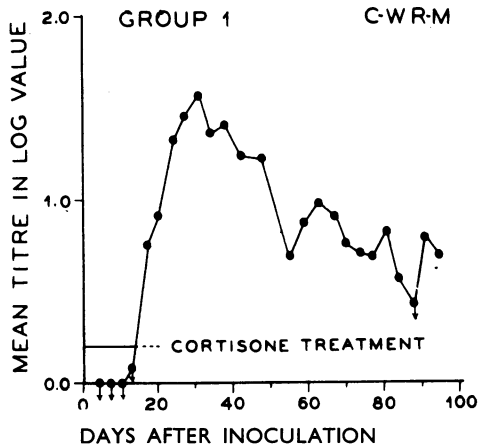

FIG. 2.—Mean titre for C-WR-M in Group 1 (four animals cortisone-treated from day of inoculation).

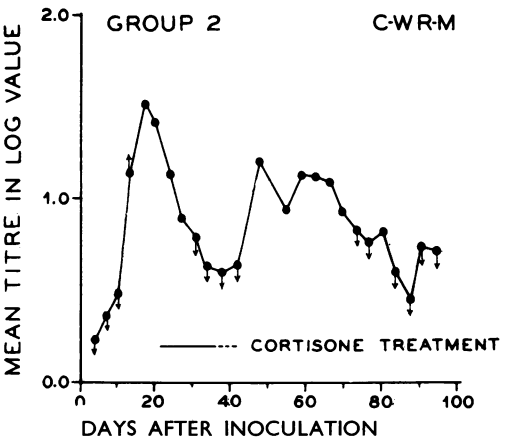

FIG. 3.—Mean titre for C-WR-M in Group 2 (six animals cortisone-treated from 21st day after inoculation).

rise occurs, so that the titre curve shows a double-peaked course.

Group 3.—In those animals which received cortisone from the 35th day, a considerable variation in the titre course is observed. Only two of the animals in this group reached significant titres, so that the group is not suited for the evaluation of the effect of cortisone on the sero-reactions. However, all four animals in this group are included in the TPI mean titre curve.

Fig. 4 shows that the maximum titre has its onset more or less simultaneously for all animals within each group. The delay in the appearance of the maximum titre observed in the case of those animals treated with cortisone from day zero is thus not due to an excessive delay in the titre of a single animal.

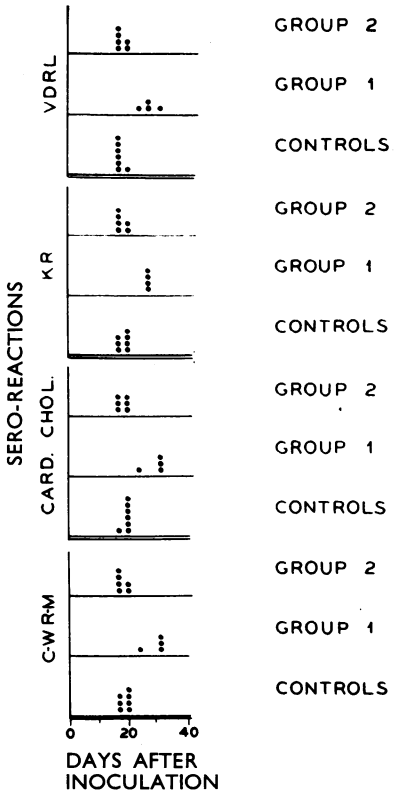

FIG. 4.—Distribution of maximum titres on different days. Each dot represents one animal.

It would seem reasonable to assume that the contrast between the control animals and those of Group 1 would be greatest early in the course of the infection, while the contrast between the control animals and those of Group 2 would be most pronounced at a later stage of the infection. It was therefore decided to compare the differences between the mean titres on the 20th and 34th days with the differences between the mean titres on the 34th and 59th days. The differences of means and their standard errors* are shown in Table I (above) and in Table II (overleaf).

The Tables serve to confirm the observed differences in the course of the mean curves. Thus, the control animals show a fall around 0·5 log val. from the 20th to the 34th day, while the Group 1 animals show a rise of around 0·4 log val. The differences between the two groups are significant for all reactions. On the whole, Group 2 shows a greater

* A standard deviation corresponding to the variation in titre within each animal group was calculated for each serological reaction from the differences between the titres on the first and last day in the two periods (20th–34th day, 34th–59th day) as observed for the individual animals.

TABLE II

DIFFERENCES BETWEEN MEAN TITRES ON 34TH DAY AND 59TH DAY

Group		Controls		Group 1		Group 2	
No. of Rabbits		7		4		6	
		d	SE	d	SE	d	SE
Test	C-WR-M	−0·06	0·09	−0·49	0·12	0·49	0·10
	CardChol	−0·17	0·09	−0·45	0·12	0·39	0·09
	KR	−0·17	0·08	−0·51	0·11	0·24	0·09
	VDRL	−0·26	0·10	−0·45	0·14	0·30	0·11

fall from the 20th to the 34th day than the control group, but the difference is only significant for the C–WR–M and KR tests. From the 34th to the 59th day, however, the differences between Group 2 and the control group are significant for all reactions.

Thus, cortisone has had an influence on the reagins, as registered on the titre curves, both when administered simultaneously with the inoculation and at a later date when the reagin titres have reached their maximum values.

In the case of the TPI titres, it has been impossible to demonstrate a corresponding influence. For technical reasons, it was necessary to make a selection of sera for the TPI test. Sera were examined for selected days from the same animals which finally constituted Groups 1, 2, and the control group in the other sero-reactions, together with the whole of Group 3* (Table I).

The mean curves (Fig. 5) show that the TPI titres for all four groups increase more or less uniformly throughout the period of observation. None of the minor deviations was significant (standard error of the mean = approximately 0·1 log val.).

It has been demonstrated in previous experiments (Schmidt 1955b, 1956) that the relation between the various sero-reactions changed during the course of the infection. In the present work, therefore, it was considered desirable to investigate the influence of cortisone on the relations between the various sero-reactions. The sero-reactions are compared in pairs, and the variation of the titre differences during the course of the infection has been investigated for each pair (Table III)†

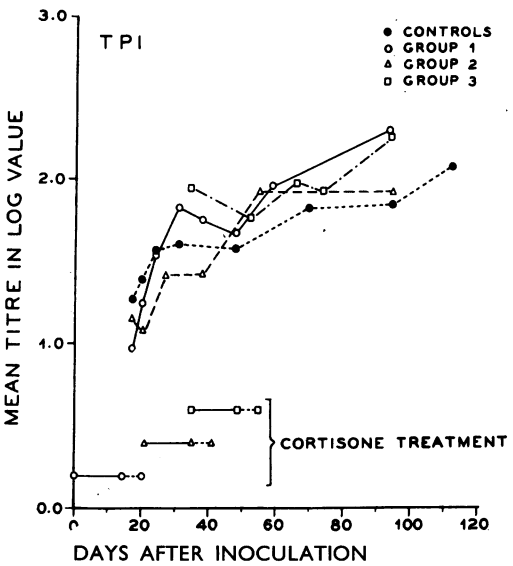

FIG. 5.—Mean titre for TPI for all groups investigated, including Group 3 (four animals cortisone-treated from 35th day after inoculation).

* This selection can be considered as "random", as in the pilot experiment no agreement could be demonstrated between the reagin titres and the TPI titres.

† As a start, the mean of the titre differences for each animal group was plotted against the number of days from the time of the inoculation, but as the curves showed a great variation from day to day, the experimental period was divided into three sections: namely, from the 20th to the 40th day, from the 41st to the 68th day, and from the 69th to the 95th day. Thereafter, both the mean differences per period and the standard deviations corresponding to the variation of the differences within the periods were calculated, and from this again was calculated the standard error of the mean differences.

TABLE III

MEAN DIFFERENCES BETWEEN THE SERO-REACTIONS CALCULATED FOR THE THREE PERIODS 20TH TO 40TH DAY, 41ST TO 68TH DAY, AND 69TH TO 95TH DAY

Sero-reaction	Period (days)	Controls		Group 1		Group 2	
		d	SE	d	SE	d	SE
C-WR-M − CardChol	20th–40th	0·20	0·03	0·10	0·03	0·10	0·03
	41st–68th	0·16	0·02	0·04	0·02	0·08	0·02
	69th–95th	0·17	0·05	0·02	0·05	0·07	0·05
C-WR-M − KR	20th–40th	−0·12	0·04	−0·12	0·04	−0·22	0·04
	41st–68th	−0·13	0·05	−0·21	0·05	−0·15	0·05
	69th–95th	−0·21	0·04	−0·28	0·04	−0·21	0·04
C-WR-M − VDRL	20th–40th	−0·47	0·06	−0·53	0·06	−0·56	0·06
	41st–68th	−0·10	0·08	−0·44	0·08	−0·39	0·08
	69th–95th	−0·19	0·04	−0·47	0·04	−0·29	0·04
KR − VDRL	20th–40th	−0·34	0·06	−0·42	0·06	−0·34	0·06
	41st–68th	−0·01	0·05	−0·23	0·04	−0·24	0·04
	69th–95th	0·01	0·02	−0·19	0·02	−0·08	0·02

In the control animals the differences C–WR–M/CardChol and C–WR–M/KR are more or less identical for the three periods, while the differences C–WR–M/VDRL and KR/VDRL are significantly greater for the period 20th to 40th day than for the other two periods. The same is largely the case for the two cortisone-treated groups. Deviations from the results in the control group are, however, noted in the animals treated with cortisone from day zero (Group 1), as the difference C–WR–M/KR is significantly less for the period 20th to 40th day than for the period 69th to 95th day, and the difference C–WR–M/VDRL is about the same in all the three periods.

Thus, the relation between the sero-reactions does not appear to be affected to any noteworthy extent by the cortisone treatment.

Clinical Observations

Control Group.—The clinical course was rather uniform. All animals developed early orchitis, beginning about the 5th day. The orchitis was moderate in three animals, well developed in five, and very severe in two. Shortly after the subsidence of the orchitis, the majority of the animals developed small epididymal nodules and, in a few cases, superficial ulcerations. These changes disappeared quickly.

Group 1.—One animal presented a well-developed orchitis beginning on the 4th day, while the others developed slight orchitis on the 6th, 8th and 15th days, respectively. The later course in this group cannot be distinguished from that of the controls.

Group 2.—The early development of the orchitis here did not differ from that seen in the controls. With the introduction of cortisone treatment (3 weeks after TP inoculation) at a time when the orchitis had subsided, the lesions developed quite another character. Two of the eight animals had insignificant or no changes. In the others, very large masses, large and deep necroses, and "cartilaginous" infiltrations in the cutaneous and subcutaneous tissue were seen. These changes, which could arise individually or collectively, were seen approximately one week after the beginning of the cortisone treatment and culminated around the time of its discontinuation.

Group 3.—Two animals cortisone-treated from the 35th day showed no changes apart from the orchitis. The other two animals had severe lesions similar to those of the six animals in Group 2. The lesions occurred in the same time relation to the treatment, but culminated in both cases after its discontinuation.

As previously mentioned, all the animals were weighed once a week throughout the period of the experiment. Mean weights were calculated for each group. The weight curve of the controls showed a steady increase, but the weights in the other three groups decreased during the period in which the cortisone was given. The animals of Group 1 reached the lowest weight on the 27th day of the experiment, those of Group 2 on the 42nd day, and those of Group 3 on the 62nd day.

Discussion

Although treatment with ACTH and cortisone is of relatively recent date, the literature contains numerous references to the effect of these hormones on the defence mechanisms of the organism. Dougherty, White, and Chase (1944) found that administration of steroid hormones resulted in an increase of circulating antibodies, but these results have not been confirmed. On the contrary, a large number of authors have found that the administration of steroid hormones produces a fall in the antibody content. Fischel, LeMay, and Kabat (1949) found the antibody content unchanged or reduced in twelve rabbits which received ACTH or *x*-rays after having been immunized with crystalline egg albumin. Bjørneboe, Fischel, and Stoerck (1951), who immunized rabbits with pneumococci, found a fall in the concentration of circulating antibodies on the administration of ACTH or cortisone. This fall occurred whether the hormone treatment was given at the start or at a later stage of the immunization period. In contrast to these results, Berglund (1956) found that the cortisone effect on *S.typhi H*-antibodies and haemolysin in rats depended on the time relations between the administration of the hormone and the immunization. He found further that the effect of the cortisone varied for different antigen-antibody systems. It also appears that the secondary antibody rise (the booster effect) can be suppressed by the administration of cortisone (Fischel, Vaughan, and Photopoulos, 1952). After immunization with egg albumin or gamma globulin, Dews and Code (1953) found a high antibody concentration in rabbits after 3 weeks, while at this time none of the cortisone-treated animals had measurable antibody. In guinea-pigs, however, these authors could not demonstrate any effect of cortisone on the haemolysin concentration. Nicol, Snell, and Bilbey (1956), investigating in animal experiments the method whereby cortisone

affects the defence mechanisms of the body, found among other things a reduced concentration of serum gamma globulin.

Only a few studies of the cortisone treatment of experimental syphilis in rabbits are available. Turner and Hollander (1950, 1954) found that the lesions in intradermally inoculated rabbits changed their appearance after cortisone treatment with varying doses, starting from one day before inoculation to approximately 30 days after. The lesions in the cortisone-treated animals grew to large proportions, became pale in colour, soft, and globoid, and were found to contain enormous numbers of *T. pallidum*. After withdrawal of cortisone, the lesions became very much enlarged, whereupon they reverted to the pattern of the controls. When the healing stage was well advanced, however, cortisone treatment was not followed by any modification of the lesions. In a number of rabbits cortisone-treated with different doses from 13 days after inoculation, serological observations at 14-day intervals indicated a fall in reagin titres in the groups receiving the largest doses; the fall was not remarkable, and the individual variations were great. Quantitative TPI tests could only be performed in a few instances, because of technical difficulties, and no demonstrable effect of cortisone was found. These authors suggest that the change in the lesions is not brought about so much by an inhibition of the antibody formation, as by a direct action on the tissues at the point of contact between host and treponemes, whereby the removal of the treponemal hyaluronic acid is hindered wholly or partly. DeLamater, Saurino, and Urbach (1952) found that, in rabbits treated with cortisone from the day of intratesticular inoculation, the number of treponemes was tremendously increased in the lesions. The reagin titres were lower in the cortisone-treated animals than in the controls.

Cortisone in the dosage used here (approximately 8 mg./kg. body weight) was toxic for the rabbits. The dosage was relatively great, approximately six times the dose used therapeutically in humans, but it must be remembered at the same time that the tolerance to cortisone of the different species, let alone the single individual, is little known. The administration of cortisone had an obvious effect on the reagins, as a change in titre in relation to that of the controls could be demonstrated in the four sero-reactions employed. The assumption that the poor general condition of the animals during cortisone treatment could cause a fall in antibody titres cannot be ignored. It is, however, a fact that administration of cortisone in what are apparently non-toxic doses does cause a fall in the gamma globulin concentration. Overman and Hanan (1953), investigating the effect of cortisone on immunization of rabbits with mumps virus and bovine serum albumin, found suppression of the development of antibodies although the animals remained in good health and without any appreciable weight loss.

Like many antibodies, *e.g.*, pneumococcal antibodies, reagins can be influenced by cortisone. We believe that this, together with the facts of their position in serum, their appearance in direct association with the syphilitic infection, and their disappearance during treatment, can be cited in support of the concept of reagins as true antibodies. The immobilizing antibodies demonstrated by the quantitative TPI test were unaffected by cortisone given for a 14-day period. Although the reproducibility in this test is poor (Nielsen, 1957), large variations in titre can be demonstrated. A satisfactory explanation why the immobilizins are unaffected is not available, but it might be imagined that this is due to the fact that the immobilizins are formed and eliminated much later and more slowly than the reagins. Thus, if the immobilizins were to be demonstrably affected by cortisone, the treatment might have to extend over a longer period of time, or begin at a later stage.

Investigations are in progress on the effect of cortisone on immobilizins, at a time when these antibodies have reached their maximum.

Cortisone had no appreciable influence on the mutual relations between the different sero-reactions.

Clinically, those animals which received cortisone at a time when the syphilitic infection, judged serologically, was at its maximum, showed aggravation of the symptoms.

Summary

The effect of large doses of cortisone for 14 days, with 6 days tapering off, was studied in rabbits inoculated intratesticularly with virulent *T. pallidum* (Nichols' strain). Four animals were treated from the day of inoculation (Group 1), eight from 3 weeks after inoculation (Group 2), and four from 5 weeks after inoculation (Group 3). Ten untreated rabbits served as controls.

Four sero-reactions with lipoid antigens were carried out on blood samples from all the rabbits twice a week for 100 days. The quantitative TPI test was performed on selected sera.

In Group 1, the rise in reagin titre was delayed, and the maximum titre was reached 10–14 days later than in the controls. In Group 2, there was a

decline in titre from the onset of cortisone treatment, but only in two of the sero-reactions was it significantly greater than in the control group. After the fall, a second rise in titre occurred in Group 2, in contradistinction to the continued fall in the controls. No conclusions could be drawn from Group 3, as only two of the animals reached significant reagin titres.

The relations between the different sero-reactions did not alter materially as a result of cortisone treatment. No demonstrable effect on the TPI titres was found.

Clinically, the orchitis was delayed in onset and remained slight in three of the four animals in Group 1. Six of the eight animals in Group 2 and two of the four animals in Group 3 showed very pronounced aggravation of the lesions during cortisone treatment. Loss of weight and poor general condition were found in most of the cortisone-treated animals, and those most severely affected developed marked lipaemia.

The fact that "reagins" are affected by cortisone in the same manner as a number of known antibodies is quoted as compatible with the concept of reagins as true antibodies.

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CORRESPONDENCE

TO THE EDITOR OF THE *British Journal of Venereal Diseases.*

Dear Sir,

I was particularly interested in the article by Dr. R. S. Morton on "Side-Effects of Penicillin Treatment" (*Brit. J. vener. Dis.*, 1957, **33**, 176), and should like to confirm his findings more particularly in relation to the anaphylactoid reactions which have followed the intramuscular injection of penicillin-G and the procaine salt of penicillin aqueous suspension in the treatment of gonorrhoea and syphilis. The onset of the anaphylactoid reaction in some patients bore no relation to the dose of penicillin-G or procaine penicillin administered. For example, one clinician with whom I discussed this question advised me that patients with early syphilis treated with one mega unit penicillin-G experienced an anaphylactoid reaction.

There is also much more evidence of anaphylactoid reactions after the use of procaine penicillin in the treatment of venereal diseases than has been noted in the medical press.

It was, therefore, surprising to me that Dr. Morton gave no examples of the apparent freedom from anaphylactoid reactions in patients treated with P.A.M. I cannot recall any personally communicated or published examples of this type of reaction occuring after the use of P.A.M. In one clinic it was routine to treat old cases of syphilis with weekly injections of 8 mil. P.A.M. for a period of 4 weeks and no untoward reactions occurred.

Yours faithfully,

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