

While previous experiments on ovariectomized animals<sup>7</sup> showed that the simultaneous administration of œstrin plus corpus luteum hormone causes mucification of the vagina and progestational proliferation of the endometrium, the present experiments indicate that progesterone alone has no effect on the vagina itself. The diœstrous condition of the vagina observed after progesterone is more likely to be the sequence of the ovarian atrophy caused by this hormone.

*Summary.* Daily administration of 4 mg. of synthetic progesterone to normally cyclic female rats causes immediate cessation of cycles, without vaginal mucification. There was ovarian atrophy, hypertrophy of the pituitary, and slight atrophy of the thymus. It has no effect whatsoever upon the condition of the mammary gland. Since œstrin is also without any direct effect upon the mammary gland (as shown in hypophysectomized animals) the effect of ovarian hormones on the mamma must be largely dependent upon the presence of pituitary secretions.

### 8665 C

#### A New Approach to the Therapeusis of Hemolytic Streptococcal Infections.

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The approach to this problem has had as its objective the *in vivo* transformation of virulent organisms into their avirulent phases as indicated previously.<sup>1</sup> Such objective became a possibility following our demonstration in 1915-17<sup>2</sup> (and later) that streptococci may have pleomorphic granular bacilli as at least one of their avirulent dissociants. The isolation of such strains from blood-cultures of untreated patients convalescent from streptococcal infections lent support to the above working-hypothesis.<sup>3</sup> It suggests, perhaps, a natural tendency on the part of the host to combat the parasite by dissociating it into a less virulent, or perhaps into an innocuous form.

<sup>1</sup> Mellon, R. R., and Cooper, F. B., *PROC. SOC. EXP. BIOL. AND MED.*, 1935, **33**, 451.

<sup>2</sup> Mellon, R. R., *J. Bact.*, 1917, **2**, Nos. 2, 3, 4.

<sup>3</sup> Koch, K. R., and Mellon, R. R., *J. Bact.*, 1930, **19**, 25.

Attempting to reinforce such tendency we have employed immune horse-sera prepared from 2 anomalous dissociants of an hemolytic streptococcus from a human case of cellulitis. Patients responding to this treatment often show hemolytic streptococci in a definite transition from their mucoid or matt to intermediate smooth, or to rough colony-forms. In several cases of marked severity this colonial change was correlated with a clinical crisis following the treatment; and sometimes the transformation appeared in all colonies isolated from several foci. At other times the *in vivo* dissociation may be initiated in large smooth colonies of hemolytic streptococci which in later sub-culture may dissociate into avirulent, non-hemolytic diphtheroids.<sup>1</sup> Definite antigenic community between the latter and their antecedent hemolytic streptococci may be present and will be reported by Hadley. It will be necessary, of course, that a sufficient number of cases show this dissociative phenomenon before relating it finally to the mechanism of recovery.

*Summary of therapeutic results:* Over a period of nearly 10 years we have treated and carefully studied 118 cases of general hemolytic streptococcal infection. They comprise 63 cases of cellulitis (including 9 of abscess) with 85.7% recovery; 28 cases of erysipelas and erysipeloid with 100% recovery; 3 of septic sore throat, with 100% recovery; 14 of acute sepsis (some complicating a cellulitis) with 71.5% recovery; 5 cases of mastoid infection taking clinically a septic course with 100% recovery; also, 2 cases of acute infectious thrombophlebitis, and 3 of lymphangitis, all of which recovered. No meningitic or puerperal infections have been treated. Of the total, 104 cases recovered and 14 died, a mortality of nearly 12%. The highest mortality occurred in the fulminating cases; that is those having the organism in the blood-stream within 48 to 72 hours.

Of special interest was the age-grouping of the erysipelatous cases, all of whom recovered; 6 were from 6 months to one year; 4 from one to 6 years; none from 6 to 12 years; 8 from 12 to 50 years. Ten were over 50, the oldest being 76. The mortality at the extremes of life is very high, particularly in infants, where it is scarcely less than 75 to 80%. Only 7 of our cases fell in the age group between 15 and 50 years, where the mortality is normally sufficiently low to bring the average down to 8 or 10%.

When it is considered that the 2 antisera employed contain no neutralizing antibodies for the toxins, either of erysipelatous or scarlatinal streptococci, some other *modus operandi* must be postu-

lated in explanation of the clinical results. Nor can we as yet assign an exclusively important rôle to bacteriotropins (opsonins), even though one of the sera appears to contain them in appreciable amounts. These are applicable to a rather wide range of strains, not being in any sense type specific. However, most of the tested cultures were not freshly isolated.

In connection with the question as to the extent to which such sera are specific, it should be realized that this is not an indispensable requisite of our approach to the problem. That is to say, bacterial dissociation may be induced quite as readily by certain environments that do not contain specific factors as by those that do. Moreover, when one considers that in streptococcal infections the mouse-protection test has not proved a reliable index of therapeutic potency—even in the mice themselves—the precise rôle of such so-called protective antibodies in the patient still awaits convincing demonstration. The purely experimental approach then, has not given us definite information on the mechanism of recovery, once infection is under way.

Yet, if the effects of this mechanism prove to be faithfully reflected in dissociation of the parasite, such effects may ultimately direct us to their causes. It is for this reason that our primary concern has been to establish a clinical phenomenon sufficiently successful to justify following its leads—whether they be in the direction of antibodies *per se*, or other tissue-functions associated with them.

That certain of these tissue-functions of the host may conceivably condition antibody-action is suggested by a rather constant fluctuation in the calcium-phosphorus product in the blood. Summarized, it appears that this product is commonly lowered during the active stages of the infection, returning to normal limits during convalescence, or thereabouts. And this, regardless of whether a complete therapeutic calcium regime is given in addition to the serum. In contrast to a normal product of 40 (Ca 10 x P 4), a value of 30 or below is common and 20 has occasionally been observed. This diminution is usually decidedly more at the expense of the phosphorus than the calcium; the latter rarely falling as low as 8, while the phosphorus often reaches 2. Nothing approaching tetany-values for the calcium has ever been observed. Paradoxically, an occasional fulminating—or at least a very severe case—may have rather slight change.

The evidence as to the significance of these findings is as yet inconclusive; in fact, the approach as a whole is still regarded as

being in the experimental stage. An added uncertainty concerns itself with the instability of the strains employed in the development of the sera. And we agree with the recent conclusions of Colebrook,<sup>4</sup> whose experience has made him averse to the conventional practise of submitting such sera to clinical trial generally—and as so often has proved, prematurely. But regardless of the ultimate validity of these working hypotheses we believe the clinical results to be sufficiently decisive to justify thorough inquiry into that most fundamental problem of all serious infections, namely, the tendency to invade distant tissues, instead of remaining localized.

Although diversification of duty has of necessity given a sporadic cast to these observations, the appreciable span of years covered by them makes it desirable to record them to this extent. Control-observations with the conventional streptococcal antisera, as well as frankly nonspecific ones, have been, and are being, employed as opportunity offers.

*Conclusions:* 1. In a series of 118 cases of general hemolytic streptococcal infections a mortality of but 12% has attended the administration of antisera prepared from 2 anomalous dissociants of a cellulitic strain of hemolytic streptococcus. 2. The objective of the treatment has been the *in vivo* transformation of the virulent types to dissociants whose virulence is diminished or absent. Clinical bacteriological evidence of this effect is submitted. 3. Associated with recovery of the patient is a return of the calcium-phosphorus product of the blood to normal. This product is usually lowered during the active stages of the disease.

### 8666 C

#### Serologic Studies with Streptococci Isolated in Cases of Myasthenia Gravis.

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Green-producing streptococci from the muscles, foci of infection, and nasopharynges of patients with myasthenia gravis were isolated by methods already described.<sup>2</sup> A carbohydrate was ex-

<sup>4</sup> Colebrook, L., *Lancet*, 1935, 1, 1083.

<sup>2</sup> Rosenow, E. C., *Internat. Clin.*, 1930, 2, 29.