If m is prime, we have $M = m - 1$ and the determinant representing $F_m(x)$ by adding to the first column all the other ones is immediately reduced to the polynomial $1 + x + x^2 + \ldots + x^{m-1}$. In the general case the coefficients of $F_m(x)$ are not of so simple a character as perhaps might be presumed. Only two of them, the coefficients A_1 and A_{M-1}, take the simple value $-\mu(m)$ and therefore I may end with the proposition

IX. If m is the product of unequal odd prime factors, then

$$\mu(m) \times \begin{vmatrix} 0 & \left(\frac{1}{m}\right) & \left(\frac{2}{m}\right) & \ldots & \left(\frac{M-1}{m}\right) \\ \left(\frac{-1}{m}\right) & 0 & \left(\frac{1}{m}\right) & \ldots & \left(\frac{M-2}{m}\right) \\ \left(\frac{-2}{m}\right) & \left(\frac{-1}{m}\right) & 0 & \ldots & \left(\frac{M-3}{m}\right) \\ \ldots & \ldots & \ldots & \ldots & \ldots \\ \left(\frac{-M+1}{m}\right) & \left(\frac{-M+2}{m}\right) & \left(\frac{-M+3}{m}\right) & \ldots & 0 \end{vmatrix} =$$

$$= \begin{vmatrix} 0 & \left(\frac{1}{m}\right) & \left(\frac{2}{m}\right) & \ldots & \left(\frac{M-2}{m}\right) & \left(\frac{M}{m}\right) \\ \left(\frac{-1}{m}\right) & 0 & \left(\frac{1}{m}\right) & \ldots & \left(\frac{M-3}{m}\right) & \left(\frac{M-1}{m}\right) \\ \left(\frac{-2}{m}\right) & \left(\frac{-1}{m}\right) & 0 & \ldots & \left(\frac{M-4}{m}\right) & \left(\frac{M-2}{m}\right) \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ \left(\frac{-M+1}{m}\right) & \left(\frac{-M+2}{m}\right) & \left(\frac{-M+3}{m}\right) & \ldots & \left(\frac{-1}{m}\right) & \left(\frac{1}{m}\right) \end{vmatrix}.$$

Thus it is shewn that the symbol $\mu(m)$ is expressible by LEGENDRE symbols only.

Pathology. — "*On passive immunisation against tetanus.*" By Prof. Dr. C. H. H. SPRONCK and WILHELMINA HAMBURGER, Arts.

(Communicated in the meeting of November 25, 1916).

As known, the injection of a heterologous serum not seldom causes symptoms of disease, and experience teaches us, that the injection of a large quantity of serum oftener causes the so-called serum disease than the injection of a smaller quantity. Hence the endeavours of the serum institutes to produce an immune serum with high titre, so that the injection of a small quantity of serum

will be sufficient. For the same reason in some countries a minimum titre has been prescribed by law for a few sera. In Germany e.g. it has been fixed by law that antitetanus serum has to contain at least 4, diphtheria serum at least 500 antitoxic units (A.U.) in one c.c. serum.

As, regarding the possibility that also our country might be drawn into the war, great quantities of antitetanus serum had to be produced, to immunize the wounded against tetanus, the question rose, whether indeed there are sufficient reasons to refuse an antitetanus serum that contains less than 4 A.U. in 1 c.c. for this purpose.

The research we have made to answer this question, has given a surprising result. For it has become clear to us, that the cheaper anti-tetanus serum with a titre of 2 A.U. is not only fit to immunize the wounded, but that it is even to be preferred for this purpose to the much more expensive product with a titre of 4 A.U.

Whilst in the beginning of the European war many died of tetanus, this dreaded wound-disease has now, so to say, entirely disappeared, thanks to the prophylactic injection of 20 antitoxic units into each wounded man. At present little is known about the titre of the antitetanus serum, which is used in the warfaring countries for prophylactic inoculations. Referring to Germany however, we have been told, that they inject serum of 4 A.U. as well as serum of 2 A.U. When there came a shortness of tetanusantitoxine of 4 A.U., the German Gouvernment also allowed the injection of a serum with a titre of 2 A.U.

According to theoretical considerations we had come to the supposition, that the passive immunity caused by the injection of 20 A.U. in 10 c.c., is not quite identic to the injection of 20 A.U. in 5 c.c., as in the latter case the inoculated antitoxine might disappear sooner out of the organism than in the former case.

It is not to be doubted, that the injection of horse serum causes the development of antibodies, which attack the horse serum and destroy it. Hence that from the 5th till 7th day after the injection, when in the mean time a certain quantity of antibodies has been produced, the horse serum and also the antitoxine for an important part disappear out of the blood, as DEHNE and HAMBURGER [1]) demonstrated. That the tetanus antitoxine and the horse albumen disappear out of the blood at the same time, is referred by these researchers to the fact, that the antitoxine is chemically united to the horse albumen.

After the 5th till 7th day a certain quantity of antitoxine and

[1]) Wiener klin. Wochenschrift 1904 and 1905.

horse albumen may remain circulating in the blood for a longer or shorter time.

According to LEMAIRE,[1]) who investigated how long the horse albumen can be shown in the blood of children that received an injection of diphtheria serum, also produced by horses, this albumen remains present for at least 10, and at most 50 days.

That horse albumen remains circulating longer in one individual than in another, is referred until now to the fact that the production of antibodies individually differs a great deal. The more antibodies the organism produces, the sooner the horse albumen will disappear out of the body.

According to our supposition a second factor is of influence upon this, namely the *quantity* of horse serum.

We have experimentally proved the rightness of this supposition in the following way:

Two goats of about the same age and size, got each one subcutaneous injection of antitetanus serum, which we had obtained from horses and accurately tested. One goat (**A**) got 80 A.U. (BEHRING-EHRLICH) in 20 c.c. serum, the other (**B**) 80 A.U. in 40 c.c. serum. Afterwards both goats have been bled four times, namely on the 10th, 17th, 24th and 31st day after the inoculation. With the serum with which these bleedings supplied us, a great number of experiments have been taken on white mice, to determine, if the antitoxine disappeared sooner out of the blood of goat **A** than of goat **B**.

Every time increasing doses of goat serum were administered subcutaneously into series of mice under the skin of the back. Exactly after 24 hours these mice and also a control-mouse got a lethal dosis of tetanustoxine under the skin of the left hind-leg, which killed the control-mouse regularly in 3 days. This constant toxic action has been reached by using a tetanustoxine, filtered through a CHAMBERLAND filter, precipitated by means of sulfas ammoniae and dried in vacuo; from this toxine every time 50 m.g. was taken for each experiment, dissolved in 10 c.c. physiological salt solution; from this, a hundred times diluted solution, 0.3 c.c. has been injected into each mouse.

The sera we got from the first bleeding, proved to act equally immunizing. Those from the second bleeding (17 days after the inoculation) on the contrary, did not show any more an equal immunizing action (see experiment n° 1).

Also 24 days after the injection the serum of both goats still

[1]) Thèse de doctorat. Paris 1907.

EXPERIMENT N°. 1

Goat A.				Goat B.			
Mouse	Date	Subcut	Result	Mouse	Date	Subcut.	Result
N°. 411	11 Sept. '16	0.2 c c. serum		N°. 414	11 Sept.	0.2 c.c. serum	
	12 „	0.3 c c. toxine			12 „	0 3 c.c. toxine	
	13 „		no symptoms		13 „		no symptoms
	14 „		local tetanus		14 „		local tetanus
	15 „		local tetanus		15 „		local tetanus
	16 „		dead		16 „		lives
N°. 412	11 Sept.	0.3 c.c. serum		N°. 415	11 Sept.	0.3 c.c. serum	
	12 „	0.3 c c. toxine			12 „	0.3 c.c toxine	
	13 „		local tetanus		13 „		no symptoms
	14 „		local tetanus		14 „		no symptoms
	15 „		local tetanus		15 „		no symptoms
	16 „		lives		16 „		no symptoms
N°. 413	11 Sept.	0.4 c.c. serum		N°. 416	11 Sept.	0.4 c.c. serum	
	12 „	0.3 c.c. toxine			12 „	0 3 c.c. toxine	
	13 „		no symptoms		13 „		no symptoms
	14 „		local tetanus		14 „		no symptoms
	15 „		local tetanus		15 „		no symptoms
	16 „		lives		16 „		no symptoms

CONTROL.			
Mouse	Date	Subcut.	Result
N°. 417	12 Sept.	0.3 c c. toxine	
	13 „		local tetanus
	14 „		dying
	15 „		dead

EXPERIMENT N°. 2.

Goat A.				Goat B			
Mouse	Date	Subcut.	Result	Mouse	Date	Subcut.	Result
N°. 431	22 Sept.	1.6 c.c. serum		N°. 434	22 Sept	0 8 c.c. serum	
	23 „	0.3 c.c. toxine			23 „	0.3 c.c. toxine	
	24 „		local tetanus		24 „		local tetanus
	25 „		dead		25 „		local tetanus
	26 „				26 „		local tetanus
	27 „				27 „		lives
N°. 432	22 Sept.	1 8 c.c. serum		N°. 435	22 Sept	0.9 c.c. serum	
	23 „	0.3 c.c. toxine			23 „	0.3 c.c. toxine	
	24 „		no symptoms		24 „		local tetanus
	25 „		local tetanus		25 „		local tetanus
	26 „		local tetanus		26 „		local tetanus
	27 „		dead		27 „		lives
N°. 433	22 Sept.	2.0 c.c. serum		N°. 436	22 Sept.	1.0 c.c. serum	
	23 „	0 3 c.c. toxine			23 „	0.3 c.c. toxine	
	24 „		no symptoms		24 „		no symptoms
	25 „		local tetanus		25 „		no symptoms
	26 „		local tetanus		26 „		no symptoms
	27 „		dead		27 „		no symptoms

CONTROL.			
Mouse	Date	Subcut.	Result
N°. 437	23 Sept	0.3 c.c. toxine	
	24 „		local tetanus
	25 „		dead

showed a distinctly immunizing action, but the serum of goat **B** a twice as great action as the serum of goat **A** (see experiment n° 2).

Comparing the sera got 31 days after the injection, the immunizing action of the serum of goat **B** still proved to surpass that of goat **A** distinctly.

It would have been clearer, if we had been able to inject twice as much serum of goat **A** as of goat **B**. But in the mean time the immunizing action of the serum of goat **A** had declined in such a way, that the quantity to be inoculated became too large to be injected into mice (see experim. N°. 3).

EXPERIMENT N°. 3.

Goat **A.**				Goat **B.**			
Mouse	Date	Subcut.	Result	Mouse	Date	Subcut.	Result
N°. 438	25 Sept.	2.0 c.c. serum		N°. 439	25 Sept.	2.0 c.c. serum	
	26 „	0.3 c.c. toxine			26 „	0.3 c.c. toxine	
	27 „		local tetanus		27 „		no symptoms
	28 „		general „		28 „		no symptoms
	29 „		dead		29 „		no symptoms
	30 „				30 „		no symptoms

CONTROL			
Mouse	Date	Subcut.	Result
N°. 440	26 Sept.	0.3 c.c. toxine	
	27 „		local tetanus
	28 „		dying
	29 „		dead

As we had to consider the possibility that the immunity of goat **B** did last longer because this animal was less fit to produce antibodies against horse albumen than goat A, we have repeated the experiment on two other goats.

We chose again two goats of about the same age and size, and injected subcutaneously into goat **C** 80 A.U. in 20 c.c. serum, into goat **D** 80 A.U. in 40 c.c. serum. At the 10th, 17th, 24th and 31st

EXPERIMENT N°. 4.

Goat **C.**				Goat **D.**			
Mouse	Date	Subcut.	Result	Mouse	Date	Subcut.	Result
N°. 448	20 Oct.	0.2 c.c. serum		N° 451	20 Oct.	0.2 c.c. serum	
	21 „	0.3 c.c. toxine			21 „	0.3 c.c. toxine	
	22 „		local tetanus		22 „		no symptoms
	23 „		local tetanus		23 „		no symptoms
	24 „		local tetanus		24 „		slight loc. tetan.
	30 „		dying		25 „		slight loc. tetan.
N°. 449	20 Oct.	0.3 c.c. serum		N° 452	20 Oct.	0.3 c.c. serum	
	21 „	0 3 c.c. toxine			21 „	0.3 c c. toxine	
	22 „		local tetanus		22 „		no symptoms
	23 „		local tetanus		23 „		no symptoms
	24 „		local tetanus		24 „		no symptoms
	30 „		dying		25 „		no symptoms
N°. 450	20 Oct.	0.4 c.c. serum		N°. 453	20 Oct.	0.4 c.c. serum	
	21 „	0.3 c.c. toxine			21 „	0.3 c.c. toxine	
	22 „		local tetanus		22 „		no symptoms
	23 „		local tetanus		23 „		no symptoms
	24 „		local tetanus		24 „		no symptoms
	30 „		lives		25 „		no symptoms

CONTROL.

Mouse	Date	Subcut.	Result
N°. 454	21 Oct.	0.3 c.c. toxine	
	22 „		local tetanus
	23 „		dead

EXPERIMENT N°. 5.

Goat C.				Goat D.			
Mouse	Date	Subcut.	Result	Mouse	Date	Subcut.	Result
N°. 455	27 Oct.	1.6 c.c. serum		N°. 458	27 Oct.	0.8 c.c. serum	
	28 „	0.3 c.c. toxine			28 „	0.3 c.c. toxine	
	29 „		local tetanus		29 „		local tetanus
	30 „		dying		30 „		local tetanus
	31 „		dead		31 „		local tetanus
	1 Nov.				1 Nov.		lives
N°. 456	27 Oct.	1.8 c.c. serum		N°. 459	27 Oct.	0.9 c.c. serum	
	28 „	0.3 c.c. toxine			28 „	0.3 c.c. toxine	
	29 „		local tetanus		29 „		local tetanus
	30 „		dying		30 „		local tetanus
	31 „		dead		31 „		local tetanus
	1 Nov.				1 Nov.		lives
N°. 457	27 Oct.	2.0 c.c. serum		N°. 460	27 Oct.	1.0 c.c. serum	
	28 „	0.3 c.c. toxine			28 „	0.3 c.c. toxine	
	29 „		local tetanus		29 „		no symptoms
	30 „		local tetanus		30 „		no symptoms
	31 „		dead		31 „		no symptoms
	1 Nov.				1 Nov.		no symptoms

CONTROL.			
Mouse	Date	Subcut.	Result
N°. 461	28 Oct.	0.3 c.c. toxine	
	29 „		local tetanus
	30 „		dying
	31 „		dead

EXPERIMENT N°. 6.

Goat C.				Goat D.			
Mouse	Date	Subcut.	Result	Mouse	Date	Subcut.	Result
N°. 462	3 Nov.	2.0 c.c. serum		N°. 464	3 Nov.	2.0 c.c. serum	
	4 „	0.3 c c. toxine			4 „	0.3 c.c. toxine	
	5 „		local tetanus		5 „		no symptoms
	6 „		dead		6 „		no symptoms
	7 „				7 „		no symptoms
	8 „				8 „		no symptoms
N°. 463	3 Nov.	2.0 c.c. serum		N°. 465	3 Nov.	2.0 c.c. serum	
	4 „	0.3 c.c. toxine			4 „	0.3 c.c. toxine	
	5 „		local tetanus		5 „		no symptoms
	6 „		dying		6 „		no symptoms
	7 „		dead		7 „		no symptoms
	8 „				8 „		no symptoms

CONTROL.			
Mouse	Date	Subcut.	Result
N°. 466	4 Nov.	0.3 c.c. toxine	
	5 „		local tetanus
	6 „		dead

day after the immunization both goats were bled and the antitoxic potency of their serum was compared.

As it appears from the experiments 4, 5, and 6, the results were quite conformable to those we got for goats A and B.

The result of the experiments mentioned above, shows clearly that, to fix the dosis of an immune serum which has to be injected to acquire an immunity of a certain degree and duration, *not only attention has to be paid to the titre* of the serum, as now generally happens, *but also to the quantity*. The quantity may not be chosen too small, because the organism defends itself against the heterolo-

gous serum and is easily able to destroy a small quantity in a few days, even if the titre is very high.

To obtain an immunity for a longer time, a quantity of serum has to be injected, which the organism, even if it defends itself vigorously against the foreign serum, cannot destroy too soon. The disadvantage that is attached to the injection of a large quantity of serum, namely the developing of symptoms of serum disease, which are always temporary, is not of great importance when a perilous illness is to be prevented.

Relating to the passivei mmunization of the wounded against tetanus, which gave rise to our research, we came therefore to the conclusion that there is absolutely no cause to use for this purpose, as now commonly happens in our country, an antitetanus serum that contains in one c.c. 4 A.U.

The injection of 10 c.c. antitetanus serum with a titre of 2 A.U. deserves to be preferred, because in this way, an equal degree of immunity is produced as by injection of 5 c.c. antitetanus serum of 4 A.U., and the immunity lasts longer.

Moreover, the results of our experiments give an important indication concerning the immunization against diphtheria. Years ago, when in all countries diphtheria serum was used with a titre of about 100 A.U., it has been fixed empirically that the injection of 5 c.c. serum (= 500 A.U.) was sufficient to protect a child against diphtheria for about 3—4 weeks. Afterwards in some countries the titre of the diphtheria serum has been raised more and more. If now, — relying on the false supposition, that the duration of the immunity has nothing to do with the quantity of serum that is inoculated —, to prevent diphtheria, 1 c.c. diphtheria serum with a titre of 500 A.U. is injected into a child, expecting to get in this way the same result as formerly with the injection of 5 c.c. with a titre of 100 A.U., there is a great chance that the immunity, instead of 3 or 4 weeks, only lasts 1 week.

Chemistry. — "*On the Allotropy of the Ammonium Halides*". III [1]). By Dr. F. E. C. SCHEFFER. (Communicated by Prof. P. ZEEMAN.)

(Communicated in the meeting of Nov. 25, 1916).

§ 14. In § 1 I said that in the older literature statements occur which point to the occurrence of two different modifications of ammonium bromide and ammonium chloride, and that it has been demonstrated in a paper by WALLACE that ammonium bromide is

[1]) First paper. These Proc. XVIII p. 446. Second paper. These Proc. XVIII p. 1498.