- 13 Mayer, *Ueber die Prognose der Syphilis*, 1904, p. 12.
 14 Private Case-book, D., fol. 452.
 15 Daniel Turner, *De Morbis Cutaneis*, A Treatise of Diseases Incident to the Skin. Fifth Ed., 1756, p. 60.
 16 Audry, *Ann. de Derm. et de Syph.*, 1906; also loc. cit. 1905, p. 793.
 17 Soffiantini, *Trans. Int. Derm. Congress*, London, p. 375.
 18 Emery, *Traitément de la Syphilis*, 2nd Ed., 1906, p. 41.
 19 Neisser, *Allgem. med. Central. Zeitung*, 1904.
 20 Lafay, *Pharmacologie de l'huile grise*, 1906 (with many details of great interest), *Ann. de Derm. et de Syph.*, 1906.
 21 Lambkin, *The Treatment of Syphilis in the Public Services*, 1899.
 22 *The Treatment of Venereal Disease and Scabies in the Army*, Final Report (no date, but issued in 1906).
 23 Duhot, *Int. Med. Congress*, Lisbon, 1906.
 24 Claude et Dobrovici, *Ann. des Mal. Vén.*, No. 2, 1906.
 25 Kretzing, *Berl. klin. Woch.*, No. 38, 1905 (reprint); also Nicolas, *Lyon Méd.*, July, 1906.
 26 Jullien, *Journ. des Mal. Cut. et Syph.*, August, 1902 (reprint); Kobert, *Lehrbuch der Intoxicationen*, vol. ii, 1904-6, 2nd Ed., for a general review with very full bibliography of mercurialism in all its forms.
 27 Emery et Druelle, *Presse Méd.*, No. 12, 1905.
 28 Chatin, *Les Syphilitiques aux eaux minérales, Traitement intensif de la Syphilis à Urriage*, 1904, p. 18.
 29 Discussion on Intravenous Injections in Syphilis, *Trans. Int. Derm. Congress*, London, 1896.
 30 Abadie, vide Emery, *Traitément de la Syphilis*, p. 48.
 31 Martin, Paul, *Le Lépideol*, Lyons, 1905.
 32 Nicolas, Joseph, *Assoc. française pour l'Avancement des Sciences*, Lyons, 1906. See also Nagelschmidt, *Ueber Immunität bei Syphilis*, Berlin, 1904.
 33 Nicolas, loc. cit. supra, p. 14 (reprint); Metchnikoff, *The New Hygiene, Harben Lectures*, 1906, p. 84.
 34 *Trans. of the Life Assurance Medical Officers' Association*, London, 1904-5 (1906), pp. 266, et seq.
 35 Chatin, op. cit. supra (28).
 36 Bertier, *Paris Thesis*, 1905.
 37 Ferras, *Paris Thesis*, 1901.
 38 Cooper, op. cit. supra (4), p. 132.
 39 Neisser (with Baermann and Halberstädter), *Deut. med. Woch.*, 1906, Nos. 1-3.
 40 Maisonneuve, Paul, *Paris Thesis*, 1906.
 41 Lévy-Bing, *Ann. des Mal. Vén.*, No. 2, 1906, p. 115.
 42 Gaucher, *Ann. des Mal. Vén.*, No. 3, 1906, p. 219.
 43 Lévy-Bing, loc. cit. supra (41), p. 120.
 44 Queyrat, *Soc. de Derm. et de Paris*, March, 1905.
 45 Sabareanu, *Paris Thesis*, 1905.
 46 Duhot, loc. cit. supra (23).
 47 Trousseau, *Clinique Médicale de l'Hôtel-Dieu*, 1865, vol. i, p. 64. Jenner was acquainted with this. See Pernet, *Vaccination Rashes and Complications*, *Lancet*.
 48 Abbé, Marcel, *Le Cytodiagnostic*, etc., Paris, 1903.
 49 Ravaut, *Ann. de Derm. et de Syph.*, 1904; Ross, *Trans. Path. Soc.*, Ivii, 1906, p. 361.
 50 Trousseau (the ophthalmologist), *Ann. d'Oculistique*, May, 1900, p. 458; also Pernet, abstract in *Brit. Journ. Derm.*, xiii, 1901, p. 70.
 51 Pernet, *Berl. med. Woch.*, No. 37, 1904.
 52 Jullien, *Journ. des Mal. Cut. et Syph.*, July, 1904. Also see *Injections Mercurielles* (26), December, 1904.
 53 Nonne, *Syphilis und Nerven System*, 1902, many references.
 54 Pernet, *Diseases of the Nails*, *Encyclopaedia Medica*, vol. viii.
 55 Stockmann, Wilh., *Ueber Gummisknoten im Herzfleisch bei Erwachsenen*, 1904.
 56 Franceschini, *Ann. des Mal. Vén.*, No. 4, 1906, p. 241.
 57 Gastou, *Rev. d'Hygiène et de Méd. Inf.*, vol. iii, No. 3, 1904.
 58 Matzenauer, *Arch. f. Derm. u. Syph.*, 1903. Also Matzenauer, *Wien. klin. Woch.*, 1903.
 59 Jullien, *Int. Cong. of Derm.*, Paris, 1900. Also Pernet, *Brit. Journ. of Derm.*, 1899, p. 459.
 60 Pernet, *BRITISH MEDICAL JOURNAL*, vol. ii, 1904, p. 1423; Gregory, *Report of Medical Officer of Health for the Colony of the Cape of Good Hope* for 1903; also for 1904 (especially pp. xcv and following).
 Also Fournier, *Le Traitement de la Syphilis*; Gaucher, *Le Traitement de la Syphilis* (a concise review), etc.
 In preparation, a very full treatment of the subject, Emery and Chatin's *Traitément de la Syphilis*.

Researches

ON THE

BACTERIOLOGICAL DIAGNOSIS OF CHOLERA,

CARRIED OUT BY MEDICAL OFFICERS OF THE SANITARY,
MARITIME AND QUARANTINE COUNCIL OF EGYPT,
UNDER THE DIRECTION OF
MARC ARMAND RUFFER, M.D.,
PRESIDENT OF THE COUNCIL.

IN 1897, during the return of the pilgrimage from Mecca, Dr. Galvani showed me microscopical preparations from the intestinal contents of a pilgrim, who had been found dead on a ship returning from Jeddah. No history of the man's illness could be obtained.

I was greatly astonished to find in these preparations a large number of micro-organisms, not to be distinguished microscopically from cholera vibrios. At the autopsy of this pilgrim, dysenteric lesions were found, together with fibroid kidneys and heart. Cultures from the intestinal contents, made first in peptone water and then in gelatine, showed the presence of comma-shaped, monociliated,

motile, non-phosphorescent vibrios, which were extremely virulent for guinea-pigs, did not coagulate milk, and gave a marked indol reaction. In fact, the cultures could not be distinguished from those of cholera.

The agglutination test with the serum of a horse repeatedly injected with cultures of cholera obtained from Professor Pfeiffer, showed that the vibrios agglutinated and gave Pfeiffer's reaction, exactly like those isolated from cholera cases. No quantitative or qualitative differences were noticed.

My first idea was that the patient had either suffered from, or had been in contact with, cholera. After careful inquiries, this theory had to be abandoned, for it was found that no cases of cholera had occurred among the pilgrims in the Hedjaz, nor on the return journey. A sharp look-out was kept at El Tor for cases of sudden diarrhoea, vomiting and cramps, but in vain. No disease resembling cholera was observed.

On the days following this discovery, the intestinal contents of every pilgrim who died in the camp were examined bacteriologically. I superintended the autopsies and examined all the patients in hospital, together with Dr. Zachariadis Bey; who, having seen several epidemics, was well acquainted with the clinical signs and lesions of cholera. Nevertheless no case of cholera was discovered, though in no less than five typical cases of colitis and dysentery we isolated cultures not to be distinguished from those of cholera, even by the agglutination test and Pfeiffer's reaction. The pilgrims finally left El Tor, five days after the finding of the vibrio, and no cases of cholera occurred either on the ships or after the pilgrims reached home.

During the four following years, the work of reorganization and the lack of skilled assistance prevented the systematic prosecution of these researches; though I frequently observed vibrios in the stools of pilgrims free from all symptoms of cholera.

In 1902, the pilgrims brought back typical cholera from Jeddah and Yambo to El Tor. The observations performed at the time showed three facts quite clearly:

1. The stools of almost every pilgrim suffering from diseases other than cholera—namely, pneumonia, rheumatism, dysentery, constipation, diarrhoea, etc.—contained vibrios numerous enough to be recognized microscopically.

2. Vibrios agglutinating with cholera serum were isolated from patients showing no symptoms of cholera. On the other hand, some vibrios isolated from typical cases of cholera did not agglutinate with cholera serum.

3. Although it was unavoidable that pilgrims carrying vibrios should mix with other pilgrims, yet only one fresh case of cholera occurred in the camp; all the others were imported. In the general hospital, where the majority of patients were excreting vibrios in every stool, not a single case of infection occurred among the patients, the European or native attendants. Further, not a single case of cholera occurred on the ships leaving El Tor after the period of quarantine was over.

BACTERIOLOGICAL INVESTIGATIONS.

In 1905, after the Hedjaz and El Tor had been free from cholera for nearly two years, Dr. F. Gotschlich examined systematically for vibrios the stools of every patient who died at El Tor. The autopsies were made by myself, and it may be stated once for all that no lesions resembling cholera were found in any case.

The results of these bacteriological examinations may be summed up as follows: Vibrios were found in 38 patients out of 107 cases examined. Thirty-two of these vibrios did not agglutinate, but six agglutinated readily with cholera serum. The characteristics of those which agglutinated with cholera serum were as follows: they were monociliated, non-phosphorescent, very virulent (with one exception) for guinea-pigs, and not virulent for pigeons, did not coagulate milk, liquefied 10 per cent. gelatin and gave a well-marked indol reaction. The morphological characteristics were not the same in all, but the differences were not greater than those existing between cholera vibrios isolated from different cases.

The results of the agglutination test are shown in the accompanying tables.

Five of these vibrios therefore agglutinated with specific serums just like cholera vibrios, and did not agglutinate at all with ordinary serums. One of them agglutinated far less than the others, but similar differences occur among vibrios isolated from typical cholera cases.

TABLE I.

Number of Culture.	Name of Pilgrim from whom Vibrios were Isolated.	Nationality.	Post-mortem Diagnosis.	Horse Cholera Serum. Standard, 1 in 3,000.	Goat Cholera Serum. Dilution, 1 in 500.	Rabbit Cholera Serum.	
						Dilution, 1 in 200.	Dilution, 1 in 1,000.
1	Osman Hussein	Anatolian	Colitis	Limit, 1 in 1,000	+++	++	+ (limit)
2	Sanka Ushalinga	Russian	Dysentery	Limit, 1 in 2,000	+++	+++	+
3	(?)	Turk	Colitis gangrenosa	Limit, 1 in 1,000	+++	+++	+
4	Ahmed Salih	Rumelian	Colitis	Limit, 1 in 1,000	+++	+++	+
5	Bekir Mahomet	Anatolian	Colitis	Limit, 1 in 500	+	+ (slight)	0
6	Achmet Aly	Rumelian	Dysentery	Limit, 1 in 2,000	+++	+++	+

N.B.—The control tubes containing vibrios, normal serums, and physiological salt solution showed no agglutination.

TABLE II.—Showing Results of Pfeiffer's Reaction.

Number of Culture.	Specific Bacteriolytic Rabbit Serum.			Control: Normal Rabbit Serum; Serum, 0.05; Culture, 1 Loop.
	Serum, 0.005; Culture, 1 Loop.	Serum, 0.01; Culture, 1 Loop.	Serum, 0.02; Culture, 1 Loop.	
1	Complete bacteriolysis; death after 24 hours	Complete bacteriolysis; death after 60 hours	Complete bacteriolysis; animal survived	No bacteriolysis; death after 24 hours.
2	Complete bacteriolysis; animal survived	Complete bacteriolysis; animal survived	Ditto	Ditto
3	Complete bacteriolysis; animal died after 48 hours	Ditto	Ditto	Ditto
4	Ditto	Ditto	Ditto	Ditto
5	Avirulent	—	—	—
6	Complete bacteriolysis; animal survived	Complete bacteriolysis; animal survived.	Complete bacteriolysis; animal survived	No bacteriolysis; death after 24 hours.

The six vibrios all belonged to the same class, for on immunizing rabbits with each vibrio, the serums of all the rabbits diluted to 1 in 2,000, agglutinated not only all the six vibrios, but the cholera micro-organism also.

Pfeiffer's Reaction.

One culture, being avirulent, could not be tested on animals, but the rabbits inoculated with cholera serum and cultures either recovered, or lived much longer than the controls.

Further, the six serums of animals inoculated with any of these vibrios protected animals against every one of these micro-organisms.

These researches were continued during the pilgrimage season of 1906, when the intestinal contents of 127 dead pilgrims were examined. Vibrios were found in 18 cases of dysentery and colitis, which presented no lesions or symptoms of cholera. Two of these vibrios gave with cholera serum all the reactions of true cholera vibrios, and were agglutinated also by the serums of animals injected with one of the six vibrios isolated in 1905.

In order to establish the relations existing between the micro-organism isolated at El Tor from dysenteric and colitis cases (in future called "El Tor vibrios"), and the vibrio of cholera, all the monociliated comma-shaped micro-organisms isolated by us during the epidemic of 1902 and the El Tor vibrios, were studied by bacteriological methods by Dr. Milton Crendiropoulos. Some vibrios kindly sent by Professor Gaffky of Berlin, Dr. Rogers of Calcutta, Mr. E. H. Hankin of Agra, and Dr. Gotschlich of Alexandria, were examined also.

Agglutination Test.

Two serums were used: first, a highly agglutinating serum kindly provided by Dr. Gaffky; and secondly, an agglutinating and bacteriolytic serum prepared in these laboratories with a microbe having all the characteristics of the true cholera vibrio, and isolated from a cholera stool (vibrio CK). The Berlin serum had very highly agglutinating properties, and was tested in solutions not weaker than 1 in 3,000 (Berlin Institute standard), which agglutinated in half an hour at the temperature of the laboratory, all the vibrios reacting to this test. The serum prepared with vibrio CK was far weaker and did not act equally on all the vibrios. Nevertheless, the

action of both serums was identical, in so far that all the agglutinating micro-organisms were acted on by both serums. The method employed was the usual one. The agar cultures were always 18 hours old, and the serums were diluted in 9 per 1,000 NaCl solution.

Table III gives the main results of this examination, as far as the agglutination test is concerned.

Table IV gives the details not only of the agglutination but of all the other tests as well.

Saturation Test.

Bordet was the first to notice that an emulsion of a microbe, added to the agglutinating serum of an animal previously injected with the same microbe, absorbed most if not all, of the specific agglutinins of the serum. The specific agglutinins of an immune cholera serum, for instance, are completely absorbed by adding cholera vibrios to the serum, whereas the non-specific agglutinins remain free in the serum.

In our experiments, 10 loops of a cholera vibrio (CK) grown for eighteen hours on agar, were suspended in 10 c.cm. of a 5 per cent. solution of cholera serum (Berlin). After standing for two hours at the temperature of the laboratory, the mixture was centrifuged, and the clear supernatant fluid decanted. The agglutinating power of the decanted liquid was now tested on all the vibrios which, in previous experiments, had been agglutinated by the serum. As a control, the agglutinating power of the same serum, not previously saturated with cholera micro-organisms, was examined comparatively. The result was that all the vibrios agglutinated with cholera serum—whether isolated from cholera cases or not—absorbed the specific agglutinins. (See Table IV.)

Pfeiffer's Reaction.

Owing to the number of microbes to be examined, it was impossible to try this reaction on guinea-pigs. The enormous number of animals which would have been necessary, and the fact that some vibrios were not virulent, made this experiment an impossible one. Metchnikoff had noticed that if one drop of peritoneal lymph from a guinea-pig (which had received either no previous injection, or merely one of bouillon) was added to vibrios suspended in a little immune serum, a typical Pfeiffer's reaction took place. Bordet used guinea-pig's serum instead of peritoneal lymph.

Three to four c.cm. of bouillon were injected into the peritoneum of an animal, and four hours afterwards the opaque liquid, full of leucocytes, was withdrawn, and left in the ice-box until the next day. The cholera serum was prepared by injecting rabbits with vibrio CK. When a trace of this

TABLE III.

Total Number of Vibrios Isolated from Cases of Cholera : 15.		Total Number of Vibrios Isolated from Patients who had no Symptoms of Cholera : 23.		Vibrios of Doubtful Origin, including Sea-water Vibrio : 4.	
Agglutinating with cholera serum :	Not agglutinating with cholera serum :	Agglutinating with cholera serum :	Not agglutinating with cholera serum :	Agglutinating with cholera serum :	Not agglutinating with cholera serum :
11 (73 per cent.)	4 (27 per cent.)	7 (30 per cent.)	16 (70 per cent.)	0 (0 per cent.)	4 (100 per cent.)

TABLE IV.

No.	Name of Vibrio.	Origin of Vibrio.	Agglutination Test.		Saturation Test.		Pfeiffer's Reaction.	Fixation Test.		Haemolysis Test.
			Serum Berlin.	Serum CK	Serum Non-Saturated.	Serum Saturated.		Bordet's Method.	Dopter's Method.	
1	CK	Cholera stool	3,000	1,000	3,000	250	+	+	+	—
2	Aida	" "	3,000	1,000	3,000	250	+	+	+	—
3	Fatma	" "	3,000	1,000	3,000	250	+	+	+	—
4	Alioglu	" "	—	—	—	—	—	—	—	+
5	LXII	" "	—	—	—	—	—	—	—	+
6	141	" "	3,000	800	3,000	500	+	+	+	—
7	Berlin 70	" "	3,000	1,000	3,000	300	+	+	+	—
8	CV	" "	3,000	1,000	3,000	300	+	+	+	—
9	98	Dysentery (El Tor)	—	—	—	—	—	—	—	+
10	147	" "	—	—	—	—	—	+	+	+ slight after 48 hours.
11	Berlin 76	Cholera stool	3,000	800	3,000	500	+	+	+	—
12	Machaout	Pneumonia during cholera epidemic	3,000	1,000	3,000	500	+	+	+	—
13	Tor No. 1	Dysentery (El Tor)	3,000	500	3,000	300	+	—	—	+
14	V	Cholera stool	—	—	—	—	—	—	—	+
15	173	Dysentery (El Tor)	—	—	—	—	—	+	+	+ very slight.
16	Berlin 115	Cholera stool	2,500	1,000	2,500	250	+	+	+	—
17	Tor No. 2	Dysentery (El Tor)	3,000	500	3,000	250	+	—	—	+
18	CVA	Cholera stool	2,000	1,000	2,000	100	+	+	+	—
19	IV	" "	—	—	—	—	—	+	+	+
20	167	Dysentery (El Tor)	—	—	—	—	—	—	—	+
21	Tor No. 3	" "	3,000	800	3,000	300	+	—	—	+
22	145	Cholera stool	3,000	500	3,000	500	+	+	+	—
23	218	Dysentery (El Tor)	—	—	—	—	—	—	—	+
24	184	" "	—	—	—	—	—	+	+	+ after 48 hours.
25	10	" "	—	—	—	—	—	+	+	+ slight after 48 hours.
26	Tor No. 4	" "	3,000	800	3,000	250	+	—	—	+
27	Tor No. 5	" "	3,000	500	3,000	250	+	—	—	+
28	16	" "	—	—	—	—	—	+	+	+ slight after 48 hours.
29	21	" "	—	—	—	—	—	+	+	+
30	23	" "	—	—	—	—	—	+	+	+
31	Tor No. 6	" "	3,000	800	3,000	300	+	—	—	+
32	Calcutta 2	(?)	—	—	—	—	—	+	+	+ after 48 hours.
33	1	Dysentery (El Tor)	—	—	—	—	—	—	—	+
34	2	" "	—	—	—	—	—	—	—	+
35	3	" "	—	—	—	—	—	—	—	Very slight after 48 hours.
36	Calcutta 6	(?)	—	—	—	—	—	+	+	+ after 48 hours.
37	Calcutta 8	(?)	—	—	—	—	—	+	+	+
38	4	Dysentery (El Tor)	—	—	—	—	—	+	+	+ very slight
39	5	" "	—	—	—	—	—	+	+	+ " "
40	6	" "	—	—	—	—	—	+	+	+ " "
41	Mansone	Sea water	—	—	—	—	—	—	—	+ " "
42	Agra II	Cholera stool	3,000	800	3,000	250	+	+	+	—

N.B.—The numbers give the dilution at which the serum produced complete agglutination. + means that a given test was positive.
— means that a given test was negative.

peritoneal lymph was added to vibrios suspended in serum (CK), the vibrios which reacted at all were almost completely transformed into granules. The microscopical appearance of these preparations, therefore, differed entirely from that of control preparations. The main results are given in Table IV, which shows that all the vibrios agglutinated with cholera serum also reacted to Pfeiffer's test.

Fixation Test.

If a serum (previously heated to 56° C.), specific for the corpuscles of an animal or for a certain micro-organism, namely, cholera vibrio, be mixed with the red corpuscles of the same animal or with the cholera vibrio, the corpuscles or vibrios absorb the immune body.

Bordet also showed that if red corpuscles or microbes containing an appropriate immune body be added to fresh non-heated alexine (namely, fresh rabbit's serum) the corpuscles or microbes absorb the alexine, so that none remains free in the liquid.

Accordingly, if fresh guinea-pig's serum be added to cholera vibrios which have not absorbed any cholera-immune body, the alexine, not being absorbed, remains free in the liquid. The proof of this is that if "sensitized" corpuscles be added to such a mixture, the globules are quickly haemolysed. If, on the other hand, vibrios, which have already absorbed the cholera-immune body, be added to the same quantity of fresh serum, the microbes absorb the alexine; and, provided the amount of fresh serum is not too great, the alexine is absorbed so completely that "sensitized" corpuscles, when added to the mixture, are not dissolved. If, on the other hand, vibrios other than cholera be added to cholera serum, the immune body is not fixed, the alexine added remains free, and the sensitized corpuscles are dissolved.

Such are the fundamental facts on which Bordet and Gengou's method is based. This has been tried on various microbic species, but, as far as I know, not systematically on vibrios.

This test was tried by two different methods:

Bordet and Gengou's Method.

The immune serum was heated at 56° C. during half an hour, and fresh rabbit's serum was treated in the same manner. An agar culture, eighteen hours old, of the microbe to be tested was suspended in 2 c.cm. of physiological solution. The alexine was the serum of a rabbit, bled on the preceding day and centrifugalized until freed of corpuscles.

The following mixtures were then prepared in three tubes:

Tube I contains 0.2 c.cm. of microbic emulsion, 0.6 c.cm. of immune serum, and 0.1 c.cm. of alexine.

Tube II contains 0.2 c.cm. of microbic emulsion, 0.6 c.cm. of new (heated) serum, and 0.1 c.cm. of alexine.

Tube III contains the same mixture as the first.

All these remained for four to five hours at room temperature, and were well shaken from time to time.

One volume of a mixture consisting of two parts of a heated serum, haemolysing bovine red corpuscles, and one part of the washed corpuscles of the same animal, was then added to Tubes I and II. One volume of a mixture of two volumes of physiological salt solution and one volume of bovine, non-sensitized, red blood corpuscles was added to Tube III. After three hours the tubes were examined, and note was taken of any haemolysis which had occurred. When the vibrios fixed the immune body the contents of Tube II showed very marked haemolysis after two hours, whereas haemolysis was entirely absent in the other tubes. In Tube III haemolysis appeared after twelve to eighteen hours, if the microbes used were themselves haemolytic, but when this was not the case, no haemolysis took place. The results are shown in Table IV.

Dopter's Method.

The following mixtures were introduced into five different tubes:

Tube I.—Twenty drops of immune serum (CK) heated to 56° C., 3 drops of alexine, 6 drops of microbic emulsion.

Tube II.—Twenty drops of immune serum (CK), 4 drops of alexine, 6 drops of microbic emulsion.

Tube III.—Twenty drops of immune serum (CK), 5 drops of alexine, 6 drops of microbic emulsion.

Tube IV.—Twenty drops of fresh rabbit's serum previously heated to 56° C., 3 drops of alexine, 6 drops of microbic emulsion.

Tube V.—Twenty drops of fresh rabbit's serum heated to 56° C., 5 drops of alexine, 6 drops of microbic emulsion.

After the tubes had been left four to five hours at the temperature of the laboratory, 2 drops of sensitized corpuscles were added to each tube.

The results obtained are shown in Table IV, and it is noticeable that, although a distinct relationship exists

* The French word *sensibilisé*, translated here "sensitized," means that the corpuscles or microbes have fixed a certain amount of immune body.

between agglutination test and Pfeiffer's reaction in so far that the microbes reacting to one test also react to the other, there is no agreement between these two reactions and the fixation test. Fourteen of the twenty-four vibrios not agglutinated by cholera serum fixed the immune body of the same serum. Conversely, six microbes which were transformed into granules and agglutinated by cholera serum did not absorb the immune body.

Haemolysis Test.

Kraus, having noticed that certain vibrios dissolved red corpuscles, extended his researches, and concluded that no haemolytic comma micro-organism was a true cholera vibrio. He used the following method: Tubes of agar were liquefied, cooled to 40° C., and 0.3 to 0.5 c.cm. of defibrinated rabbit's blood were allowed to mix slowly and uniformly with the agar in each tube. The agar was poured into Petri's dishes, and, when cool, was inoculated with the vibrio to be examined, in such a way as to obtain separate well-defined colonies. After twenty-four hours in the incubator, the colonies, when haemolytic, were surrounded by a clear, more or less extended areola, contrasting sharply with the dark, opaque colour of the agar.

The objection to this method is that the results are not constant and not easily observed. A simpler method, by which the slightest trace of haemolysis may be readily demonstrated, was therefore used.

An agar culture, eighteen hours old, was rubbed up in 4 to 5 c.cm. of physiological NaCl solution; 0.1 c.cm. of this emulsion was mixed in a tube with 0.9 c.cm. of physiological salt solution, to which one large drop of washed red corpuscles or of the defibrinated blood of a rabbit or any other animal had been added. After twelve to twenty-four hours as a rule, haemolysis was noticeable, if it was ever to take place at all, though in some cases it did not appear for twenty-four hours. If no haemolysis had taken place after forty-eight hours, further observation was unnecessary, as such vibrios would not dissolve blood later on, and were therefore non-haemolytic.

The haemolytic properties of vibrios were tested on the red corpuscles of rabbits, goat, sheep, and guinea-pigs, and the corpuscles of all these animals reacted in the same way. The vibronic haemolysins, therefore, were not specific for one special kind of animal.

At first sight, the haemolytic properties of vibrios appear to stand in no relationship to the agglutinating and Pfeiffer's reactions, for several agglutinating vibrios haemolyse and others do not. Nevertheless, Table IV shows that no vibrio haemolyses, when the agglutination test, Pfeiffer's reaction, and the fixation test are positive.

RECAPITULATION OF BACTERIOLOGICAL RESULTS.

The vibrios examined may be divided into four groups:

1. Those which give the four principal tests with cholera serum—namely, the agglutination test, saturation, Pfeiffer's reaction, and the fixation test. They do not haemolyse, even when remaining in contact with red corpuscles for three days, at the temperature of the laboratory.
2. The second group contains the vibrios agglutinated and giving the saturation and Pfeiffer's reactions with cholera serum, but not fixing the cholera-immune body. These vibrios are strongly haemolytic. This group consists of the El Tor vibrios only.
3. The third group is formed by vibrios which are not agglutinated by immune serum, do not give the saturation or Pfeiffer's reactions, but fix the cholera-immune body. These vibrios also haemolyse, but feebly and late, often after thirty-six to forty-eight hours only.
4. The last group is formed by strongly haemolytic vibrios not reacting at all to cholera-immune serum.

DISCUSSION OF RESULTS.

The discovery at El Tor of vibrios agglutinating with cholera serum is of great importance, for two chief reasons: (1) It is the first time that vibrios agglutinating with cholera serum have been found in the absence of a local or general epidemic. (2) The discovery raises the whole question of the value of the present system of bacteriological diagnosis; for, if the agglutinating El Tor vibrios are not cholera vibrios, the reliance placed so far on the agglutination, Pfeiffer's, and saturation reactions as specific tests is not justified.

An opinion regarding the specific nature of the vibrios found at El Tor can be formed only by considering the subject from the epidemiological and from the bacteriological points of view.

Discussion of Epidemiological Data.

Three principal epidemiological questions present themselves:

First, Are there any facts to show that in 1897, 1905,

and 1906 cholera existed in the Hedjaz or in any country traversed by the pilgrims on their way to and from Mecca? The answer is: "None."

Secondly, Is it likely that the vibrios agglutinating with cholera serum come from a different place than the non-agglutinating vibrios? In my opinion, the probability is that wherever the pilgrims infected themselves with vibrios agglutinating with cholera serum there they absorbed the other vibrios also.

Thirdly, Did the pilgrims whose faeces contained vibrios agglutinating by cholera serum bring these vibrios from their homes to the Hedjaz and El Tor, or were they infected en route?

A few details concerning the route followed by pilgrims travelling to and from Mecca are here necessary. The pilgrims who undergo quarantine at El Tor go to Mecca by two different routes. A number of them, chiefly Turks and people from Asia Minor, land at Yambo, stay there a few days, and then proceed to Medina on foot or by camel. After resting a few days at Medina, they travel to Mecca, remaining in the holy city until the feast is over—that is, from a week to a month, or perhaps longer in some cases.

The other pilgrims, consisting for the most part of Egyptians, Moghrabys, Algerians, Syrians, and Russians, proceed the reverse way—that is, they land at Jeddah and go on to Mecca, Medina, Yambo, and El Tor.

It is an undoubted fact that the vibrios agglutinating with cholera serum have been found only among pilgrims from Turkey, Russia, and Asia Minor returning via Jeddah, and it has been argued that the latter carried the cholera vibrios from their own country into the Hedjaz and back to El Tor.

I am not ready to admit this theory, and for the following reasons. In the first place, I do not believe that the presence of vibrios among the pilgrims was limited to the years 1897, 1905, and 1906, but consider it highly probable that the phenomenon occurs every year. As a matter of fact, vibrios agglutinating with cholera serum have been found at El Tor *whenever they have been looked for, and exclusively among pilgrims returning via Jeddah*. In 1897, when the vibrios were first discovered, Asia Minor and the route followed by pilgrims were free from cholera. In 1905 and 1906 certain districts, but by no means the whole of Asia Minor, were infected with cholera; but there is absolutely no evidence to show that the pilgrims harbouring vibrios in their intestines came from a cholera-infected district, or had been in contact with cases of this disease either at home or on the journey. As will be shown presently, the conditions for the development of cholera at Mecca are simply ideal. Yet these people who excreted vibrios in every stool at El Tor did not contaminate the holy city. To argue, as has been done, that because cholera is present in some parts of Asia Minor, therefore every person coming from there must be regarded with suspicion, is equivalent to saying that because cholera exists at Marseilles therefore every one coming from St. Petersburg or Moscow may carry vibrios in his intestine. The comparison is by no means far-fetched, for a journey of one hundred miles in Asia Minor may and often does take longer than that from Marseilles to St. Petersburg. As a matter of fact, moreover, the pilgrims carrying vibrios agglutinating with cholera serum did not come from the same place, or even from the same district. Two were from Asia Minor (no place could be ascertained exactly), two were Roumelians, two Anatolians, one Russian, and one Turk.*

Rejecting as I do the theory that the vibrios were brought by the pilgrims from their homes, I would fain advance another theory based on reasons which appear to me overwhelming. I believe that the pilgrims infected themselves with vibrios at Mecca or Jeddah, and that the reason why vibrios agglutinating with cholera serum were found among pilgrims only returning via Jeddah and not among pilgrims returning via Yambo was simply that a much shorter time elapsed between the date of infection and the arrival at El Tor in the case of the former than in the case of the latter. Further, I consider it highly probable also that the infection took place by drinking the water in Jeddah, or more probably, in Mecca.

* Since this paper was written a vibrio agglutinating with cholera serum (1 in 2,000) was isolated this year from the intestinal contents of an Algerian pilgrim who had died from carcinoma of the liver and colitis.

It is necessary to consider very briefly the possible infection by water in both places. The Jeddah water comes from wells in the town, or is brought from some distance, and when I tasted it in 1905 the water sold to the pilgrims was indescribably filthy and briny. It teemed with all kinds of micro-organisms, though I cannot say for certain that it contained vibrios. Indeed, it was so bad that the Europeans drank it only when obliged to; when, in fact, water from ships was not obtainable.

At Mecca part of the ceremonies consists in drinking water from the Zemzem well. A bacteriological examination, made at El Tor, has shown this water to be swarming with vibrios, though those agglutinating with cholera serum have not been found so far. Moreover, it is part of a religious ceremony for the pilgrim to wash in certain tanks. I have obtained photographs showing the pilgrims, some drinking in these tanks, others filling their vessels, others performing their ablutions (including the cleaning of the anus) in the very place where, a few seconds afterwards, a pilgrim may quench his thirst. One pilgrim carrying vibrios may contaminate the whole water supply, and that this actually does occur is shown by the explosive character of the epidemic, and the appalling mortality following on this promiscuous bathing and drinking, when a case of cholera has occurred at Mecca. If these Asia Minor people really carried the cholera vibrios from their homes to Mecca, why did not an explosive outbreak of cholera follow on their using these tanks? More favourable conditions for the spread of cholera can hardly be conceived than water contaminated with vibrios, drunk by thousands of people of whom many are suffering from gastro-intestinal disturbances, and whose constitutions are undermined by hardships of every kind. Yet no case of cholera occurred at Mecca.

Should the pilgrim return home via Jeddah, he arrives at El Tor after a period averaging three weeks; should he return via Yambo, he does not reach El Tor till six weeks at least have elapsed after leaving Mecca. In his report on the pilgrimage and the cholera epidemic at El Tor in 1902, Dr. Crendiropoulo drew attention to the fact that the faeces of almost every pilgrim entering the hospital contained vibrios, but that this was only the case during the five to eight days following the arrival of the pilgrims. As time went on, the vibrios became rarer and rarer, and after thirteen to fourteen days at El Tor (corresponding on an average to thirty-three to thirty-four days after leaving Mecca) none were found in the faeces. The pilgrims returning via Yambo, therefore, whose journey to El Tor lasts from five to eight weeks have almost certainly to eliminate many of the vibrios absorbed at Mecca.

Lastly, a most important fact is that not a single case of cholera occurred on the voyage home, although some of these ships were overcrowded with people coming from Asia Minor. I conclude, therefore, that, epidemiologically, there is no evidence to show that the vibrios found at El Tor were true cholera vibrios.

Discussion of Bacteriological Results.

In the literature concerning the part played by Koch's vibrio in the causation of Asiatic cholera, there is one fact, and one only, which stands out as being of supreme importance; namely, that at a time when no epidemic of Asiatic cholera existed in Europe, certain persons wilfully or accidentally swallowed a small quantity of microbes isolated from cases of cholera, and that these persons either died or presented more or less acute symptoms of the disease. The rest of the evidence, as compared to this cardinal fact, is of minimal importance.

The value of even this observation, however, may be over-estimated; for the symptoms of cholera, whether mild or acute, are only those characteristic of other intoxications of intestinal origin. These symptoms have been produced also by vibrios isolated, not from cholera patients, but from water; and at a time when the disease did not exist anywhere near the locality where the vibrios were found. In this connexion the experiments of Metchnikoff are particularly valuable. This observer produced in man the symptoms of cholera with vibrios isolated from Seine water, at a time when there was no cholera in Paris. Nevertheless, these experiments do not invalidate those previously noted, as the symptoms produced by Metchnikoff's micro-organisms were neither so

definite nor so acute as those due to vibrios isolated from cholera cases.

I admit, therefore, that the cause of cholera is the microbe which has produced typical cholera, experimentally so to speak, in several human beings.

The serums of animals inoculated with this vibrio acquire new and definite properties. Minimal doses agglutinate cholera vibrios; if cholera serum and cholera vibrios be introduced into the peritoneum of guinea-pigs, the micro-organisms are first converted into granules, and ultimately dissolved; when the cholera vibrios are added *in vitro* to this serum, they absorb the specific agglutinins. The conclusion usually drawn from these facts is that any micro-organism giving these reactions with serums so pre-

pared is the true vibrio of cholera, and that any vibrio not so reacting belongs to another class. Several reasons compel me to reject such a conclusion.

Ever since the discovery of biological reactions, more especially of the precipitation and agglutination tests, attempts have been made to attach an absolutely specific value to these reactions. To my mind, such attempts have failed. The precipitation test, for instance, is not entirely specific; for although it is easy to obtain a serum precipitating that of humans only, yet a serum which precipitates that of other animals also—for example, monkeys—may be prepared at will. The test is therefore specific under certain conditions only; conditions ill-defined, but nevertheless existent.

TABLE V.—Showing the Port of Departure of the Ships and the Origin of the Water containing these Vibrios.

Date of Arrival at Port Said.	Name of Ship.	Flag.	Port of Departure.	Origin of Drinking Water.	Observations.
July 15, 1905 ...	<i>Clan Ronald</i>	British	Liverpool	Glasgow	In a preceding journey the ship sailed from Calcutta and called at Port Said on May 12, 1905.
August 23, 1905...	<i>Torbryan</i>	British	Swansea	Swansea	Usually runs between Yokohama and Singapore.
September 22, 1905 ...	<i>Benarty</i>	British	Colombo	Colombo	Usually sails to Japan, calling at Yokohama, Singapore, Bombay, Colombo.
September 26, 1905 ...	<i>Knowsley Hall</i>	British	Karachi, Colombo	Karachi	—
October 19, 1905 ...	<i>Congo</i>	French	Alexandria	Alexandria	Runs between Marseilles, Alexandria, Port Said, and Beyrout. Had not crossed Suez Canal for many years.
October 20, 1905 ...	<i>Vesta</i>	Russian	Odessa	Constantinople	Runs between Odessa, Constantinople, Smyrna, Beyrout, Jaffa, Port Said, Alexandria. The ship had not been through the Suez Canal in 1905.

TABLE VI.—Showing the Chief Morphological and Cultural Characteristics of the Vibrios.

Name of Culture.	Form and Size.	Motility.	Cilia.	Reaction with Gram.	Optimum Temperature.	Culture in Bouillon and Peptone Water.	Cholera- roth.	Gelatine Culture.	Cultures on Potatoes.	Cultures in Milk.	Invert- ing Action.	Haemo- lytic action.
Clan Ronald	Same form and size as <i>V. cholera</i> . Involution and S. forms	Motile. Serpentine movements quick. Slow rotatory and forward movements	Monociliated	Does not retain stain	Optimum, 73° C.	Well-developed surface veil.	Present	Growth slow. Colonies transparent, yellowish-brown, with irregular borders, characteristic bulla in stab cultures.	Whitish layer	No coagulation. Slight acidity.	Well-marked reaction	Very marked, clear; 3 mm. areola round colonies)
Torbryan...	Same length, but thinner. Curve accentuated. Many S-shaped forms	Very motile. Movements like those of preceding one	Multiciliated (2)	Ditto	Ditto	No surface veil. Uniform clouding	Present, but feeble and slow. More marked by addition of pot. nit. solution	Very slow liquefaction. Brown culture, with irregular contours and dark nucleus. No bulla in stab cultures	Yellowish dark brown layer	No coagulation. Reaction unaltered.	Reaction very feeble	None.
Benarty ...	Same length, but thinner. S-shaped and filamentous forms	Motile. Slow serpentine movements. Slow rotatory and forward movements	Multiciliated (2)	Ditto	Ditto	Ditto	Ditto	No liquefaction. Brown-yellowish colonies, granular, with irregular contours	Yellowish layer	Ditto	Ditto	Very slight; not clearly shown.
Knowsley Hall	Short curve very marked. No filaments or S-shaped forms	Motile. Movements slow	Multiciliated (2)	Ditto	Ditto	Ditto	Ditto	No liquefaction. Brown colonies, with irregular contours and central nucleus	Yellowish-brown layer	Ditto	Ditto	Ditto.
Congo ...	Short, but slightly longer than precedent one	Very motile. Serpentine movements very quick. Rotatory and forward movements quick	Multiciliated (4)	Ditto	Ditto	Ditto	Ditto	Very slow liquefaction. Brown-yellowish, transparent colonies. No bulla in stab cultures	Very light yellowish layer	Ditto	Ditto	Ditto.
Vesta ...	Short, curve accentuated. No filaments or S-shaped forms	Very motile. Serpentine movements very quick. Rotatory and forward movements quick	Multiciliated (4)	Ditto	Ditto	Ditto	Ditto	Liquefaction very slow. Colonies reddish-yellow with irregular contours. No bulla in stab cultures	Dark yellow layer	Ditto	Ditto	Ditto.

It will be noticed that four of these vibrios differ from the cholera vibrio in the important fact that they are multiciliated. Their other characteristics are by no means characteristic of cholera.

Similarly, typhoid serum agglutinates, less actively it is true, paratyphoid bacilli also. The agglutination test, therefore, is only relatively but not absolutely specific.

Further, it is unusual to rely on one or two characteristics only in the classification of plants and animals. In every classification every characteristic should be taken into consideration, and its possible value weighed.

A comparison of vibrios found at El Tor in cases of dysentery with those of the specific vibrios of cholera, shows that although both are equally affected by the agglutination, Pfeiffer's, and saturation tests, they react differently to the haemolysis and fixation tests. These reactions appear to me as important as the former.

All the El Tor vibrios haemolyse under certain conditions, but all the vibrios isolated from cases of cholera and agglutinating with cholera serum, do not. This fact, in my opinion, is a sufficient reason for classing the El Tor and the cholera vibrios into two distinct groups.

It has been urged, however, that haemolytic vibrios, agglutinating with cholera serum, have been isolated from cholera stools, and the conclusion drawn that the true cholera vibrio may occasionally be haemolytic. The fact is correct, but the conclusion would be true only if typical cholera stools contained but one kind of vibrio. In the East, at any rate, this is far from being so, and many cases of cholera are cases of mixed "vibronic" infection. In many stools one finds not one but several comma-shaped bacilli; some agglutinating with cholera serum and others not; some monociliated, others multiciliated, etc. It is possible, nay likely, that in some cases both the cholera and the El Tor vibrios exist in the same stool.

In this connexion I may state that some years ago I wrote to a distinguished bacteriologist, who was watching an epidemic of cholera in the East, to send me cultures isolated from cholera stools. Four cultures of vibrios were sent, of which only one agglutinated with Berlin serum. The three others, although monociliated, did not agglutinate, but were intensely haemolytic. I quote this fact only to show how very complicated the bacteriological examination of a cholera stool is in reality.

The fact, therefore, that a vibrio, not only agglutinating but haemolytic also, is occasionally found in cholera stools does not necessarily prove that a cholera vibrio haemolyzes at times, but it may simply show that several kinds of vibrios, some haemolytic and some non-haemolytic, may be isolated from cholera stools. Indeed, in view of the facts recited in this paper, the last conclusion seems to me the only possible one.

What has been said regarding haemolysis applies equally to the fixation test. All the vibrios isolated from the cholera stools which agglutinated with cholera serum, gave the fixation test; all the El Tor vibrios, without exception, did not. On the other hand, several vibrios, though neither agglutinated nor converted into granules by cholera serum, reacted to both the fixation and the haemolysis tests.

I conclude, therefore, that all these reactions are relatively and not absolutely specific, and that any one test or group of tests is insufficient to establish a true classification. The only possible classification is to group together all the vibrios reacting in the same way to all tests, separating them from those which, under the same conditions, behave in a different way. If this method be applied to the vibrios found at El Tor, there is no difficulty in distinguishing them from the true cholera vibrios in spite of several of the reactions of both being similar. And it follows that the agglutination, saturation, and Pfeiffer's tests are not in themselves of absolute diagnostic value for cholera vibrios.

ON VIBRIOS FOUND IN SHIP WATER.

During the second quarter of the year 1905, the drinking water of ships calling at Port Said was examined for vibrios by Dr. Zirolla. The samples of water submitted to bacteriological examination were 384 in number, and in 82 cases vibrios were found. Six only of these eighty-two vibrios gave a positive result with various high dilutions of cholera serum. (Fluid horse serum kindly sent by Dr. Gaffky of Berlin, Standard 1 in 3,000, date September 23rd, 1905.) Special attention was therefore paid to these six vibrios, as representing in a natural classification a group most closely related to that of the cholera vibrio.

Agglutination Test.

Cholera serum was diluted in physiological salt solution. The macroscopic test only was applied. In 1 c.cm. of the solution of serum, one loop or 2 mg. of agar-culture, grown for eighteen hours at 37° C., was suspended. The result was considered as positive when agglutination took place in two hours' time at 37° C.

As the Berlin cholera serum contained carbolic acid, it was necessary to see whether carbolic acid possessed any agglutinating properties on these microbes. For this purpose, chemically pure carbolic acid was tested in 0.5 to 0.25 per cent. solutions either in distilled water or physiological salt solution, but none of these vibrios were agglutinated by carbolic acid, not even by a 0.5 per cent. solution.

Several rabbits were immunized also by intravenous injections of gradually-increasing doses of living and dead cultures, against each of these six vibrios and a cholera vibrio isolated during the last Egyptian cholera epidemic of 1902.

TABLE VII.—Showing the Results of the Agglutination Test of these various Vibrios with different Serums.

Name of Serum.	V. Clan Ronald.	V. Torbryan.	V. Benarty.	V. Knowsley Hall.	V. Congo.	V. Vesta.	Cholera.
Serum cholera (rabbit) agglutinates	500	100	—	—	500	100	500
Serum cholera (horse) ...	10,000	500	500	500	500	100	3,000
Clan Ronald	10,000	50	—	100	500	—	2,000
Torbryan... ..	—	2,000	1,000	—	—	—	—
Benarty	500	—	20,000	—	100	100	2,000
Knowsley Hall... ..	500	500	—	50,000	—	—	—
Vesta	100	1,000	—	—	500	2,000	100
Congo	2,000	—	100	50	1,000	—	50

Pathogenic Effects and Pfeiffer's Reaction.

Pfeiffer's reaction was obtained with the V. Clan Ronald only, and the result is shown in the following table. In the case of the other vibrios the requisite virulence could not be obtained.

TABLE VIII.

Name of Culture.	Result of Injection into Pigeons.	Result of Injection into Guinea-Pig.		Pfeiffer's Reaction.
		Result.	Minimum Mortal Dose.	
Clan Ronald ...	Negative	Positive	4 loop of culture 24 hours (guinea-pig 300 grams)	Positive
Torbryan	"	"	3 loops	—
Benarty	"	"	2 "	—
Knowsley Hall...	"	"	2 "	—
Congo	"	"	3 "	—
Vesta	"	"	3 "	—

The conclusion to be drawn from the recital of the more marked characteristics of these 6 vibrios is that V. Clan Ronald possesses, more than any of the others, the characteristics of the true cholera vibrio. The five other vibrios markedly differ from cholera vibrios by their general properties. Their most marked characteristic—namely, their agglutination by a very active cholera serum in 1 in 500 solution—means that there is a certain degree of relationship between them and the true cholera vibrios. In other words, the agglutination reaction must not be regarded as a specific test but as a group reaction.

The results of agglutination tests made with the seven serums, although apparently surprising, show there is a distinct relationship between the V. Clan Ronald and

cholera vibrios, as the serums of animals injected with either vibrio agglutinate both. I do not believe that V. *Clan Ronald* is a true cholera vibrio, as it is haemolytic.

The experiments also show the degree of relationship existing between the six vibrios and between each and the cholera vibrio.

The conclusions which I base on the experiments carried out at Port Said are as follows:

1. A certain number of vibrios, although agglutinating to some extent with cholera serum, are sharply differentiated morphologically from the cholera vibrio, by the fact that they are multiciliated.

2. Whereas some vibrios found in ship water are agglutinated by very dilute solutions of cholera serum, others are agglutinated by far stronger solutions only. The latter form a transition stage, so to speak, between the non-agglutinating and the highly agglutinating vibrios.

3. Although an active cholera serum agglutinates all the vibrios to some extent, yet only two of these vibrios when injected into animals produce serums having a powerful agglutinating effect on cholera vibrios; two serums had the same property but to a slighter extent, and two had none.

These experiments therefore support the conclusion previously arrived at—namely, that it is not advisable to trust to the agglutination test only in the bacteriological diagnosis of cholera. The test is useful but not specific.

The Lumleian Lectures ON INSANITY, ITS CAUSES AND INCREASE.

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS
OF LONDON.

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LECTURE III. ETIOLOGY.

Alcoholism as a Cause of Insanity.

ALCOHOLIC excess has long been considered to be one of the most powerful causes of insanity; any increase among the insane was looked upon as depending upon such self-indulgence. England is now much more temperate than it was; this is shown by the greatly-diminished consumption of all forms of alcohol, and by a general consensus of opinion that it is good to be temperate or teetotal. Notwithstanding all this there has been no decrease among the insane, but a fairly steady increase.

As a consulting physician I am much struck by the large numbers of teetotallers by whom I am consulted. This does not prove that such persons are unstable in consequence of their temperance, but it shows that teetotalism alone does not decrease insanity. Dr. Mott has expressed the same opinion. Doubtless alcohol affects the nutrition of the brain, and may be called a nerve toxin. It produces acute symptoms which may pass from delirium to mania, and this may pass into a chronic hallucinated state. Prolonged indulgence in certain persons leads more or less rapidly to mental weakness which has special characteristics. These are interestingly associated with sensory disorders, the ideas of time and place becoming confused. In many respects alcoholic excess resembles in its results senile mental decay. It may give rise to neuritis which may be misinterpreted so as to give rise to ideas of cutaneous annoyance or electrical interference. Chronic alcoholism leads to a state of the nervous system which is allied to that produced by strong neurotic heredity. Alcoholic parentage tends to produce mental weakness and criminality in the offspring. Dr. Mott, supported by Dr. Bevan Lewis, has shown that alcoholics admitted into general hospitals have kidney and liver disease, whereas the insane alcoholic dying in an asylum rarely has evidence of his excess in his viscera. It seems as if the brain of those becoming insane from alcoholic excess is a weaker organ or one more easily affected than that of the drunkards who escape. We

all know that injury to the head may render a person very easily influenced by drink, and it is easy to think that there are specially susceptible persons who readily suffer from alcoholic excess.

Alcohol leads to delusional insanity, to recurring mania, to delirious mania, and later to dementia of a peculiar type. It plays an important part in the production of general paralysis of the insane, for though I have never been able to satisfy myself that any one case was due to this cause alone, yet with syphilis it is common. The special report of the Irish Commissioners expresses very strongly the opinion of the Irish medical superintendents that alcohol is a real cause of insanity in that country, though they also mention the excessive indulgence in tea as a cause.

Influenza as a Cause of Insanity.

In the earlier epidemics it was thought that the insane were less liable than the sane to this disease, but later it was proved that their comparative freedom depended on their isolation. I am much struck by the numerous cases of mental disorder which always follow an epidemic. My own opinion is that the influenzal poison has a special and most potent effect on the nutrition of all parts of the nervous system. It acts most perniciously as a destroyer of sleep, and also has serious effects by its influence on the digestion and general nutrition. It is noteworthy, too, that the number of suicides rises rapidly at and after an epidemic of influenza.

It may produce any form of psychopathy; it may act either as a predisposing or exciting cause; it may precipitate impending dementia or general paralysis of the insane; it may be the starting point of dementia of adolescence. In a few cases it causes an alternation in neuroses, so that it relieves an asthma but develops melancholia.

The severity of the influenza has no direct relation to the form or gravity of the insanity. As a rule, however, the prognosis is rather better when the insanity depends on influenza. The point to which I would make most reference is that, in my opinion, influenza, like alcohol, seems to have a specially dangerous influence on some persons and prepares a very large number of such persons for some form of nervous disorder. It puts them at a disadvantage to resist any physiological or social strain.

Sexual Causes.

I have not time to go into the question of sexual causes of insanity, but it would not be right if I did not express my opinion that the tendency to late marriages in men; the great limitation in the number of children, and the distaste of the mothers to nurse their children all have potent influence in producing mental instability.

Increase in the Number of the Insane.

There is sufficient evidence to show that there is a steady increase in the numbers of the insane in England, Ireland, and Scotland, though in the most recent reports there has been shown to be a reduction in the proportion of insane recognized, but I shall point out reasons for the apparent reduction.

Among the more wealthy in England particularly, there is a growing disinclination to send their insane relations into asylums. There is certainly no change in relationship to the feeling against asylums and against certification. With the more educated the dread of the transmission of insanity is very great, but if the malady is called by any other name and treated by other than alienist physicians people are satisfied.

Statistics are dry bones, but one must make use of some of them. On January 1st, 1906, there were 121,976 certified patients in England, this being an increase of 2,150 on the previous year, the rate of increase being less than that of the average for the former five and ten years.

The decrease was most in the private patients. Nowadays fewer insane patients are retained in workhouses; fifty years ago half of the pauper lunatics were in workhouses, now only a small number are detained there. The chief increase among the insane is seen in the metropolitan area. The capital attracts the weak as well as the strong.

The increase is shown by my tables to be very large in fifty years. In 1859 there were in England and Wales 36,762 certified insane persons. The increase in that time in proportion to the general population has been 231 per