e considered as evidence of even a doubtful reaction. It must, however, be noted that the precucal gland, which was already enlarged, increased considerably in size, and became tender the day after the tuberculin injection. Afterwards it resumed its previous size, and gradually became smaller, but remained still larger than the corresponding gland on the other side of the body. After September 18th the temperature became more regular, oscillating between 103° F. and 103.8° F. On October 2nd it fell still further down, ranging between 102.4° and 102.8° . On October 8th, 15 minims of tuberculin were injected; this was followed by a sharp reaction, the temperature rising to 106.2° F. after eight hours. (It is even possible that the temperature had been higher before that time.) It fell slowly to 103.8° F. in twenty-four hours.

Three days after, I had the animal slaughtered at the Manchester abattoir, where I made the *post-mortem* examination.

The chief lesions found were the following:

Abdomen.—The right precucal gland was about twice as large as the left, and more rounded. No typical tubercle was visible. There were several cheesy tuberculous masses in the large omentum near the duodenal end of the stomach. There were numerous tubercles in the pelvic peritoneum; small miliary tubercles in the suspensory ligament of the liver. The parietal peritoneum behind, and the diaphragmatic above, the spleen, also the parietal peritoneum in both iliac regions, was thickened, rough, covered with small fleshy tuberculous-looking nodules and small polypoid masses (young grapes). Parietal and visceral peritoneum generally roughened. Two of the sacro-iliac lymphatic ganglia were very much enlarged, but not necrosed. Several mesenteric ganglia were slightly enlarged and firm, but showing no distinct tuberculous lesions. The retrohepatic ganglion much enlarged, and with several necrotic patches. A few tubercles were present in the capsule of the liver at the insertion of the falciform ligament, and a few miliary tubercles in the peritoneal covering of the spleen.

Thorax.—Along the line of attachment of the diaphragm to the thoracic wall the pleura was covered with small fleshy tuberculous masses, causing in some places a considerable thickening of the costal and diaphragmatic pleura; these were most abundant over the spleen, in the neighbourhood of which the peritoneum was also most affected. Rows of small tubercles were also found along the lymphatics in the intercostal spaces up to the sixth or fifth rib; above that level only a few tubercles were found in the pleura. The pulmonary pleura was nearly normal, and the lungs were entirely free from any lesion visible to the naked eye. The pericardium was slightly affected, but round the large vessels at the root of the heart it was almost entirely covered with a layer of small rounded, fleshy tubercles. The bronchial glands were slightly enlarged, but showed no other evidence of tuberculosis. The supra-sternal ganglia were enlarged, congested, and more affected than any other thoracic ganglia, but there were only a few slightly opaque patches indicating the probable presence of tuberculous lesions.

Bacilli.—Tubercle bacilli were found on microscopical examination in the omental tubercles and the retrohepatic ganglion; none have so far been discovered in the mesenteric, oesophageal, and bronchial ganglia.

Inoculation of Guinea-pigs.—Guinea-pigs have been inoculated with several of the lesions. At the end of nine days they all showed evidences of beginning tuberculous infection. This experiment can leave no doubt as to the source of infection. All the lesions are clearly connected with peritoneal infection. They have the same distribution as those found in rabbits and guinea-pigs inoculated intraperitoneally with tuberculous products of human or bovine origin. I have in many hundred experiments obtained practically identical results with bovine and human tuberculous products injected into the peritoneum of guinea-pigs and rabbits, the focalisation of the tuberculous lesion in the pelvic and diaphragmatic regions, the gradual invasion of the pleura through the diaphragmatic lymphatics, the extensive lesions in the omentum and comparative escape of the mesenteric ganglia, are all characteristic features of peritoneal infection. The entire absence of old tuberculous lesions, the incompleteness or absence of tuberculin reaction three weeks

after inoculation, replaced by a clear tuberculin reaction six weeks later, clearly connect the lesions observed with the inoculation of human tuberculous sputum on August 1st.

There was no evidence of any tendency to resolution in any of the lesions. They were all young and in a progressive state; Mr. Holburn, the Manchester Chief Veterinary Inspector, who was present and assisted me, was able to satisfy himself that the tuberculous lesions were typical and had exactly the distribution which, previous to exposing the organs, I had mentioned to him as likely to be found on the supposition that the sputum injected had carried tuberculous infection in the calf.

[N.B.—This first set of experiments had only for its object to determine whether human tuberculous products are infectious to cattle or not; further experiments are being arranged for with the view of determining the conditions which influence the virulence of human bacilli for cattle and the proportion of recoveries after such infection. The author takes this opportunity of acknowledging the facilities which have been this month offered to him by the Manchester Sanitary Committee for the prosecution of more extended experiments. Very soon after the beginning of this investigation, Dr. A. Hodgkinson also generously offered to bear the cost of experiments conducted on a farm belonging to him.]

REFERENCES.

¹ Transactions of the International Congress of Hygiene and Demography, London, 1891, vol. ii, p. 185. ² BRITISH MEDICAL JOURNAL, July 27th, 1901, p. 191. ³ *Ibid.*, September 23rd, 1893.

NOTE ON THE RESULTS OBTAINED BY ANTITYPHOID INOCULATION IN THE CASE OF AN EPIDEMIC OF TYPHOID FEVER

WHICH OCCURRED IN THE RICHMOND ASYLUM, DUBLIN.

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I AM indebted to Dr. H. M. Cullinan of the Richmond Asylum, Dublin, for a detailed account of the outbreak of typhoid fever which occurred in that asylum in the autumn of last year, and for particulars with regard to the results obtained by antityphoid inoculation in connection with that outbreak. From the materials above referred to I have abstracted the following narrative of events.

Course of the Epidemic.

The first case of typhoid fever which occurred in connection with the epidemic here in question came under observation on August 7th, 1900. From that date onwards to the end of December, 54 cases of typhoid fever occurred among the patients and the nursing staff.

The chronological distribution of these cases is exhibited in the following tabular statement:

August 7th to September 6th	19 cases*
September 7th to October 6th	8 cases†
October 7th to November 6th	8 cases
November 7th to December 6th	14 cases‡
December 7th to December 24th (half month) ..	5 cases.§

Particulars with Regard to the Antityphoid Inoculations Undertaken.

Soon after the commencement of the epidemic, Dr. Conolly Norman, the superintendent of the asylum, applied to me for a supply of antityphoid vaccine. This having been placed at his disposal, a first batch of 45 patients was inoculated by Dr. Cullinan on September 6th. When these had recovered from the effects of the inoculation, another batch was taken in hand, until on November 30th, after a series of seventeen sittings a total of 511 persons had been inoculated. The inoculations were carried out exclusively upon insane inmates below the age of 55. No member of the nursing staff underwent the operation. The dose of the particular vaccine administered was in each case 0.75 c.cm., this being the dose

* Eight of these cases occurred among the nursing staff.

† One of these cases occurred among the nursing staff.

‡ Three of these cases occurred among the nursing staff.

§ All these cases occurred among the nursing staff.

which had been fixed upon as appropriate in the case of soldiers proceeding to South Africa.

The symptoms produced by the inoculation are described as follows, by Dr. Cullinan, in a paper published in the *Dublin Journal of Medical Science* in July 1901:

The constitutional disturbance following the inoculation did not prove in any of the cases in my experience to be of great severity. In every case almost the temperature rose within a couple of hours, in some few instances reaching 103° and 104° on the day of operation, while 101° and 102° were common heights for it to attain. It usually fluctuated for a couple of days, coming down gradually from the maximum, and being generally normal on the third day. In every case operated on all the temperature records were kept. Except in the cases already specially mentioned, patients were able to be up and about on the fourth day. The principal symptom was headache, from which 85 suffered, some of them very severely; vomiting or retching occurred in 63 cases; loss of appetite and refusal of food in 33; diarrhoea in 2; rather severe prostration in 3; 4 complained of abdominal pain, while stiffness in the back and soreness over the seat of inoculation occurred in 9 and 22 cases respectively. The last symptom of soreness in the flank, where each patient was vaccinated, was not in any case accompanied by local manifestation, beyond a slight redness of the part and some swelling.

In the light of the constitutional symptoms here described and of certain events to which attention is drawn below, I think that a somewhat smaller dose of vaccine might appropriately have been prescribed by me. It must, however, be noted that the circumstances did not admit of two successive inoculations being undertaken, and no estimate could be formed as to how far the patients would at the time of inoculation be exposed to the risk of infection.

Particulars with regard to the Number of Susceptible Persons Exposed to Infection.

Dr. Cullinan estimates that after excluding all patients above 55 years of age as insusceptible, the total number of susceptible persons exposed to infection at the date on which the inoculations were begun may be fixed at 655; 541 of these were insane inmates, the balance of 114 being nurses. Of the former, as we have seen, 511 were ultimately inoculated.

Number of Cases of Typhoid Fever which occurred in the Inoculated and in the Uninoculated respectively after the Commencement of the Inoculations.

On and after September 6th 29 and 7 cases of typhoid fever respectively occurred in the uninoculated and the inoculated groups. Before considering the question as to what was the relative incidence of cases in the two groups, the circumstances of each of the seven cases which occurred among the inoculated may be briefly considered.

Case 1.—The patient was found to be ill on September 6th. "In this case," says Dr. Cullinan, "owing to an oversight the patient's temperature was not previously taken, but was found to be 101° immediately after the operation, remaining high, and at once assuming the characteristic curve of typhoid fever."

In accordance with the history this case may be transferred from the category of cases which developed in inoculated patients to the category of cases which developed in uninoculated patients.

Case 2.—The patient in question was inoculated on September 10th, and developed the disease on September 22nd. "This case," says Dr. Cullinan, "was found to have a normal temperature, and was apparently in good health before inoculation. The temperature rose after the operation, but instead of going down in a few days, persistently remained high and assumed enteric features almost at once.....I think it may be concluded that she would have contracted the disease in any case."

This conclusion that the patient had contracted the infection before inoculation would appear to be justified, inasmuch as the interval of two days usually covered by the febrile reaction produced by inoculation would appear to be much less than would be required for the incubation of the disease. None the less I have in the statistical table given below refrained from formally excluding this case from the category of cases occurring in the inoculated. I have contented myself with distinguishing it by the use of italics, brackets, and a note of interrogation, from the other cases included in that category.

Case 3.—"The patient in question was inoculated on September 2nd, and on the 24th was quite well apparently, but on the 28th was found to have a temperature of 100°, and a couple of doubtful spots. On the 30th there was a typical crop of spots. The case from that out was a severe one.....I would not" (the quotation is still from Dr. Cullinan's paper) "place this case definitely among those suffering from prodromal signs at the time of inoculation, but.....as the spots began to appear six days after the operation, I think we may fairly refrain from blaming the inoculation."

In view of the possibility that the incubation period may

run a shorter course in a patient who has in the meantime been subjected to inoculation, it will be well to retain this case in the category of cases contracted subsequent to inoculation.

Case 4.—The patient in question, "a girl, who had been inoculated on October 3rd, having left hospital three days after the operation, was attacked very severely on October 15th. She was found on this day to have a crop of spots. This patient died."

Case 5.—Inoculation was here performed on September 22nd, and the patient, "who had been quite well in the interval," developed typhoid fever eight weeks subsequently, "and was found to have a profuse crop of spots."

Obviously there can be no doubt as to how the latter of these cases is to be classified.

Case 6.—Patient was inoculated on November 12th, and "was very ill after the operation, and continued so with a high temperature. On the 20th she had a crop of spots, having had all the appearances of typhoid in the interval."

Dr. Cullinan feels disposed to regard this as a case in which the patient was sickening for the disease at the time of inoculation. This assumption seems to me justified in view of the short period which elapsed between inoculation and the development of the typhoid spots. The fact that the patient was "very ill after the operation" also points in this direction. None the less it will, as in the case of No. 3 considered above, be preferable for the purposes of our statistical comparison to retain it in the category of cases contracted subsequent to inoculation.

Case 7.—The patient, "a woman of about 50 years of age, operated upon on November 5th, and getting over the effects in three days, was found on November 17th with a temperature of 101°, and had a very severe attack followed by a relapse from which she nearly died. I consider," says Dr. Cullinan, "that on this case the serum"—meaning thereby the typhoid vaccine—"acted detrimentally, and probably accentuated the severity of the attack."

Having in a very recent communication² discussed the general issue raised by Dr. Cullinan's comment, I may here leave the italics in the above protocols to speak to the attentive reader, and proceed at once to summarise the results of the above analysis. That analysis has shown that of the inoculated persons attacked by the disease, the *first* had certainly developed the fever before inoculation; the *second* had almost certainly contracted the infection before inoculation; and the *third* and *sixth* had also probably contracted it before inoculation. In the case of the *fourth* and *seventh* patients if the infection was, as would seem probable, contracted subsequent to inoculation, it must have been contracted immediately afterwards while the patients were still suffering from the effects of the operation. Thus the *fifth* patient would appear to have been the only one among the seven inoculated patients attacked who contracted the infection after the clinical symptoms due to the operation had passed off.

Let us, however, for the purposes of our statistical comparison, admit that the last 5, or even the last 6, of the 7 inoculated patients who were attacked may have contracted the disease subsequent to inoculation.

Manner in which a Comparison can be instituted between the Incidence of Cases in the Inoculated and in the Uninoculated.

Our task will then be to express in the form of a valid comparison the fact that, out of a body of 655, who consisted in part of inoculated and in part of uninoculated persons, 5—or, if we include Case 2 mentioned above, 6—cases of typhoid fever occurred in the inoculated; while 30—or, if we exclude Case 2 just referred to, 29—cases occurred in the uninoculated.

The first point which comes up for consideration in this connection is the question as to whether the 114 uninoculated nurses, who are included in the total of 655 susceptible persons, were exposed to a greater risk of infection than the insane inmates. If they were not exposed to greater risk they may obviously be included among the "controls." In connection with the risk incurred by the nursing staff Dr. Cullinan writes that "none of the nurses who contracted the disease contracted it by attendance on inmates suffering from enteric. All the nurses attacked were ordinary divisional nurses, who spent their days in the same room as the inmates, and for the most part slept off the dormitories, being in all respects as liable to infection as the inmates, except in the respect that

sane persons have, from the point of view of the risks undergone by them, in my opinion a considerable advantage over the insane."

It may, therefore, be taken that the nurses were at any rate not exposed to greater risks of infection than the patients, and hence the figures relating to these, may equally with the figures relating to the uninoculated insane, be utilised for the purpose of instituting a comparison between the inoculated and the uninoculated.

The complete data which have been furnished to me by Dr. Cullinan, admit of two such comparisons being instituted. The first of these comparisons is a comparison between the number of cases occurring subsequent to the date of the completion of the inoculations, in 504 inoculated persons³ (insane inmates) and 114 uninoculated persons⁴ (nurses). This comparison is as follows:

Number of Cases occurring in the Uninoculated and Inoculated respectively in the Interval between the Completion of the Inoculations on November 30th and the Development of the last Case of Enteric Fever on December 24th.

	Number of Persons under 55 Years of Age under Observation.	Number of Cases.	Number of Deaths.
Uninoculated ...	114	5	0
Inoculated ...	504	0	—

The comparison in question brings out in a striking manner the comparative immunity of the inoculated; it is, however, robbed of a great deal of its interest by the fact that the period of observation which is covered by the comparison is here a very short one.

A comparison based on the average daily strength of the inoculated and the uninoculated will, therefore, be of greater interest, covering as it does the whole period of three and a-half months from the commencement of the inoculations to the termination of the epidemic.

For the purposes of such a comparison Dr. Cullinan has kindly furnished me with (a) the number of patients operated upon by him at each sitting, and the dates of these inoculations; (b) a list of nurses and patients attacked with typhoid fever; and (c) a list of patients who died from other diseases, or who were admitted or discharged during the period of observation.

The latter document may be left out of account, as it shows that the number of individuals of a susceptible age who were admitted or discharged, or who died from other diseases during the period of observation was so small as to be incapable of exerting any appreciable effect upon the general result.

Having simplified our task in this way, we arrive at the number of the inoculated and uninoculated on each successive day by taking into account (a) the alterations in the numbers of the inoculated and uninoculated brought about by the successive inoculations; and (b) the alterations in these numbers brought about by the development of typhoid fever in members of each group.

Taking the numbers thus arrived at, we now multiply in each case by the number of days during which that particular strength was maintained. Finally we add together the figures relating to each group and divide in each case by the number of days included within the whole period of observation. In this manner we arrive at a daily average strength of 339 for the inoculated, and of 298 for the uninoculated.

We now institute our comparison by dividing the number of typhoid cases which occurred in the inoculated and uninoculated groups respectively into the average strength of each group.

Before considering the statistical result thus arrived at, it will be well to realise why we are here justified in regarding a result obtained in the manner which has just been indicated as a result which correctly represents the relative incidence of typhoid fever in the inoculated and uninoculated groups.

We shall realise this if we consider what is the assumption to which we are committed by the method of calculation here

adopted. That assumption is that the cases of typhoid fever among the inoculated would not have been more numerous if the number of inoculated had stood throughout at 339, instead of standing, as it in reality did, at a lower figure on all dates previous to November 5th, and at a higher figure on all dates subsequent to this particular day. Now this assumption is manifestly justified if the risk of contracting typhoid fever was as great in the period between November 5th and December 24th, when the inoculated numbered more than 339, as in the period between September 6th and November 5th, when the inoculated numbered less than 339.

Dr. Cullinan's list of cases and dates of attack shows that this condition was satisfied and more than satisfied, 16 cases of typhoid fever having occurred in the smaller number of uninoculated exposed to infection in the period subsequent to November 5th, as against 14 cases in the larger number of uninoculated exposed in the earlier period.

In conformity with this it may be confidently assumed that the comparison based on the average daily strength is a comparison which does not here exaggerate in favour of the inoculation procedure.

The comparison in question is as follows:

Comparative Incidence of Typhoid Fever in Inoculated and Uninoculated calculated upon the Average Strength of the respective Groups during the period intervening between the Commencement of the Inoculations and the Termination of the Epidemic.

	Average Strength	No. of Cases.	No. of Deaths.	Percentage of Cases.	Percentage of Deaths.
Uninoculated ...	298	30 (— 1?)	4	10.1	1.3
Inoculated ...	339	5 (+ 1?)	1	1.5	0.3

It may be noted, in conclusion, that the result is in conformity with that of all the statistical returns of antityphoid inoculation which have reached me.

NOTES AND REFERENCES.

¹ The reference is to Cases 1, 2 and 6, reported below. ² *Lancet*, September 14th, 1901. ³ This number is arrived at by subtracting the 7 inoculated patients who developed the disease from the total of 511 who were inoculated. ⁴ The number of nurses was kept up to 114 by replacing those attacked by the fever.

PRIMARY CHANCRE OF THE TONSIL.

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THE case of primary sore of the tonsil, reported by Dr. Abercrombie in the *BRITISH MEDICAL JOURNAL* of September 21st, p. 809, interested me very much, as I met with a similar instance two years ago—that is to say, there was a history that after tonsillotomy one side never got properly well, and enlarged glands appeared at the angle of the jaw, causing the patient to seek other advice, and in due course he came out in the full bloom of secondary syphilis. Careful searching of other parts of the body by me failed to reveal the presence of a chancre on the genitals or elsewhere.

I suspect that infection occurs in the following ways: Either hereditary syphilis may be overlooked in a child, or if a young adult with largish tonsils and in the very early stage of secondary syphilis seeks advice for what is really an incipient specific throat, two things are very likely to happen, namely, tonsillotomy to be performed, and the syphilitic character of the disease not recognised. Consequently, special notice may not be given to cleansing the tonsillotome, which instrument, with its deep groove, is peculiarly adapted for retaining and inoculating virus. The moral is, of course, as has been pointed out, to make it an invariable rule to see personally that instruments are efficiently sterilised immediately before use. The question arises whether some of the mysterious red rashes which are recorded as appearing after operation on tonsils and adenoids may not be due to other poisons introduced in this way.