# DIPHTHERIA IN HULL

## A REVIEW OF SIX YEARS BACTERIOLOGICAL TYPING

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(With Plate 5 and 2 Figures in the Text)

This paper embodies the findings in all proven cases of diphtheria admitted to the Hull City Hospital during the years 1938–43 inclusive. All cases during those 6 years were typed and the clinical and bacteriological findings correlated. Since 1932 all severe cases had been typed and in the winter of 1932–3 a consecutive series of 313 cases was investigated and the results published (Leete, McLeod & Morrison, 1933). The 1933 paper showed a high *gravis* incidence of 59 % and an associated high case fatality rate. Not until the end of 1937 was it again possible to type every case admitted but since then we have done so, and the series now presented embodies observations on 2039 infections, the great majority of which were clinical cases.

Our routine at the Hull City Hospital is to swab all cases on admission but at the same time to make a provisional clinical diagnosis and to treat on that finding. As far as the patient is concerned he has been treated to the best of our ability before any bacteriological results are to hand. We employ an overnight Loeffler technique. If the first swab is negative it is repeated on the following day; if still negative it is repeated a third time always, sometimes a fourth. If the culture, the first or a following one, is positive, i.e. shows morphological diphtheria bacilli, a portion of the Loeffler growth is emulsified in 4·5 c.c. normal saline and a small drop of the suspension plated on Neill's tellurite medium (Neill, 1937). After 48 hr. incubation the plates are studied, using a binocular plate microscope magnifying 10 diameters so as to bring out colonial details. This technique gives well-separated colonies and enables one to utilize fully the capacity of Neill's medium to bring out characteristic colonial appearances not only of the types but of the subtypes. This feature, together with its simplicity of preparation, seems to be the great advantage of Neill's medium. We soon confirmed Neill's contention that his medium was a simple one which could be prepared in any convenient quantity with the modest resources of a small laboratory.

Appearances on a plate need further corroboration, and we make a primary culture on Loeffler from a single well-isolated colony on the tellurite plate and study the morphology of the organism after overnight incubation. From this primary culture on Loeffler a set of serum peptone water tubes and one of broth is inoculated. The four serum water tubes are (1) plain, (2) 0·5% starch, (3) 1% glucose, (4) 1 % saccharose, and the broth is a meat infusion broth containing a trace (0·1 %) of glucose. We mix a dozen litre bottles of ripened broth so as to form a large pool of blended broth which will last 2 or 3 years. This gives us a standard broth in which to observe growth whether heavy or light, smooth or granular—thus correcting error due to slight differences in the composition of individual batches of broth or in its hydrogen-ion concentration.

After inoculation the set of five tubes is incubated. The broth readings are noted at 24 hr. and the serum water tubes at 48 hr., with a final reading at 10 days. The indicator used in the serum water tubes is bromo-thymol-blue (1 % of a 0·2 % alcoholic solution) which gives a good three-colour range, blue on the alkaline side, yellow on the acid, with green in between.

Colony appearances together with the results of the fermentation tests enable us to classify most organisms. Only if there is a discrepancy or some unusual feature do we proceed to a virulence test.

Using this method we have been able to define some ten types of *C. diphtheriae* during the 6 years under review. In addition there are three or four types of diphtheroid organism occurring more or less regularly.

The diphtheria types, with one exception, fall within the classification of *gravis*, *intermedius* and *mitis* as described by McLeod and his co-workers (Anderson, Cooper, Happold, McLeod & Thompson, 1931, 1933), and would appear to be subgroups within their main groups. We describe the types tentatively as follows:

*C. diphtheriae gravis* 1. Forms a large (2 mm. upwards) grey-black or greenish grey-black colony with a white opaque edge, a semi-matt surface and a somewhat conical or conico-lenticular outline. The extreme edge is translucent and continuous. It ferments starch and forms a granular growth in broth. This is the 'Hull *gravis*' variant previously described

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as such by McLeod and his co-workers; the type 'C' of Miss Jean Orr Ewing's serological classification and type III of Robinson and Peeny. It was until 1938 by far the most important *gravis* organism in Hull. In October 1938 it disappeared and has not been isolated since.

*C. diphtheriae gravis* 2. This is somewhat like *gravis* 1 in colonial appearance, and we originally called it a 'small *gravis*', but certain characteristic features appear fairly constant. The colony is smaller and darker, black or grey-black in colour and from 1·5 to 2·0 mm. in diameter. The sectional outline is lenticular, the surface glossy and the thin growing edge is sharply defined at its margin, almost as if it had been outlined by a fine mapping pen. It ferments starch and forms a granular growth in broth. It was found in severe cases and like *gravis* 1 disappeared in 1938. Two strains tested belonged to Orr Ewing's 'C' type and one strain to Robinson and Peeny's serological type III. This serological evidence, such as it is, points to the probability that this is a colony growth variant of *gravis* 1. Nevertheless, we believe there is some value in making the distinction because of its practical epidemiological importance; familial infections and small groups, e.g. schools, show constant adherence to one or other colonial type.

*C. diphtheriae gravis* 3. This is a large light grey colony from 2 to 5 mm. in diameter with an opaque whitish edge. It is conical in shape, the surface matt and the growing edge irregular and crenated. At times it shows grooves running from the apical centre to the crenated edge and there also may be concentric grooving. The crowded colonies are flatter and light grey in colour. It suggested at once the original daisy head colony first described as *gravis* by McLeod, and we named it 'Leeds *gravis*' as soon as seen. Starch is fermented and the growth in broth is granular. Specimens submitted correspond to Orr Ewing's serological type 'A' and to Robinson and Peeny's type I. It was not found in Hull until October 1938, when within a month it replaced the *gravis* 1 and 2 strains and still remains the most frequent and important *gravis* organism in the district.

*C. diphtheriae gravis* 4. This is a medium large black colony (1·5–2·0 mm.) with a translucent edge. The edge has a 'ground-glass' appearance much less opaque than the white edge of *gravis* 1. In outline it is usually lenticular, and the surface is matt. It is a brisk starch fermenter and forms distinct granules in broth. Specimens submitted conform to Orr Ewing's serological type 'B'. Three out of four strains sent to Prof. Tulloch at Dundee were reported by him as belonging to Robinson and Peeny's serological type II, and the fourth was reported as agglutinating with type I serum to full titre and type II serum to half titre.

In our experience this '*gravis* 4' organism has been found almost entirely in mild cases—in sharp distinction to the other starch-fermenting strains. It was not very common, only twenty-five strains being isolated, the first in February 1938, the last in September 1939.

*C. diphtheriae gravis* 5. This is a strain of diphtheria that does not grow on Neill's medium as ordinarily prepared. We were aware of the very occasional occurrence of such strains in Hull as our tellurite work had always a Loeffler parallel and in a few cases a good Loeffler positive gave no growth on Neill's medium. Later we learned of Prof. Tulloch's experience in Dundee where strains with this characteristic were common during one outbreak. In Hull only five such strains were isolated in the 2000 under discussion. We found on repeated subculture they could be made to grow on Neill's medium or they would grow (producing a small somewhat *intermedius*-like colony) on Neill's medium if the final heating stage in its preparation was omitted. As the strains were so rare we did not find it necessary to incorporate any such modifications in our routine work.

*C. diphtheriae gravis* 6. A new colonial type somewhat resembling *gravis* 4 on Neill but with a more papillated or frosted surface was observed for a brief period in 1943. Only five cases showed this infection (all in the north-west region of Hull and a neighbouring village). Two strains submitted to Prof. Tulloch gave a Robinson and Peeny type I agglutination to full titre. Despite the serological relationship to *gravis* 3 (Leeds *gravis*) the colonial features are so different that this must be regarded as another type.

Of the six *gravis* types or subtypes 1 and 3 are by far the most important in Hull.

Coming now to the non-starch-fermenting strains we find:

*C. diphtheriae intermedius* giving a characteristic small colony on Neill's medium. In contrast with the 2–3 mm. colony of Leeds *gravis* this colony is small, usually less than 1 mm. in diameter. The colour is black with a hazy 'ground-glass' edge. The colony is conical and the surface semi-matt. Minor variations are noted but the picture as a whole is constant. A distinct granular growth in broth with a clear supernatant fluid before agitation is characteristic.

This is the most common diphtheria bacillus in Hull and has been so for many years. Though generally speaking *intermedius* is also clinically intermediate between the *gravis* strains on the one hand and the *mitis* on the other, they may at times be associated with severe toxic cases, and we have noticed one or two small groups of such cases connected with schools or districts. Our impression is that the *intermedius* is the average or standard

diphtheria bacillus at any rate in the Hull area. It is remarkably constant and has been continuously present in Hull for the last 12 years. During the 6 years at present under review, percentage of cases due to this organism were 68, 63, 65, 32, 35, 38 or for all 6 years taken together, 53.

*C. diphtheriae mitis* 1. The colonial form on Neill's medium is a large grey-black opaque-edged conical colony resembling that of *gravis* 1 from which it can only be distinguished by starch fermentation tests. The broth readings usually show smooth turbidity, but some strains show only slight turbidity and on shaking granules are seen, the picture being best described as turbidity and granularity. This differs quite distinctly from the granularity of the *intermedius* strains.

*C. diphtheriae mitis* 2. This is a medium-sized lenticular glossy colony with characteristically outlined edge resembling that of *gravis* 2. Growth in broth is uniformly turbid as a rule, though some of our earlier strains did give a somewhat anomalous turbidity and granularity as did the *mitis* 1 strains. Like *mitis* 1 it is associated with mild cases.

*C. diphtheriae E.C.* 4 (*Edinburgh Christison type* 4). A new strain of diphtheria bacillus, not previously met with in Hull, appeared at the beginning of 1941 and disappeared at about the end of 1942. It caused disease of considerable severity and high mortality. On Neill's medium it had a large daisy head colony which looked like Leeds *gravis* (our *gravis* 3) but quite failed to ferment starch. I sent an early specimen to Prof. McLeod who later told me that the organism was, on cultural and serological grounds, a Christison type 4. Further experience with this organism on Neill's medium showed small but constant colonial differences between it and Leeds *gravis*. The E.C. 4 colony is darker as a whole but tends also to have a darker outer zone or some darker concentric zoning. The small immature colonies in the more crowded parts of the plate are much darker than the corresponding sized *gravis* 3 colonies. They also tend to 'zoning' which *gravis* 3 does not. Growth in broth is usually granular though 'granules with turbidity' were seen in some strains. We prepared an agglutinating serum against this organism using a strain from a fatal case. The serum agglutinated the homologous organism to a titre of 1 in 6400. Ten E.C. 4 cultures, all that were available, were tested against this serum—four strains agglutinated to full titre, two to 1 in 3200, three to 1 in 1600 and one to 1 in 800. Twelve *gravis* 3 (Leeds) strains failed to agglutinate with this serum.

Our conclusion is that this organism is of epidemiological importance and that it falls outside the ordinary classification of *gravis*, *intermedius* and *mitis*.

*Diphtheroids.* Although this paper deals with colonial-fermentation types and their associated clinical features, a brief reference to the diphtheroids and their colonial appearance on Neill's medium may not be out of place.

*Hofmann's bacillus* grows well on Neill's medium. Some colonies are light and pearly in colour, others have a dark centre and wide pearly outer zone, others again are dark with a still darker outer zone. The two types of colony, some with a light outer zone and some with a dark outer zone, are usually seen on the same plate, and this 'reversal' or the existence of what one might call 'negative' and 'positive' colonies is very characteristic of this organism.

*Large black diphtheroid.* This is a large glossy lenticular black colony with a still darker black outer zone. Its appearance is characteristic. The morphological features from an overnight Loeffler culture are short bacilli with marked granulations.

Most strains of this colonial type ferment saccharose. A culture of *C. xerosis* from the National Collection of Type Cultures gives a similar colony on Neill's medium.

*Small faded diphtheroid.* These form small colonies comparable in size with those of *intermedius* though rather smaller and not so dark. This lack or small degree of central darkening makes them look like a faint or faded *intermedius*—hence the name. Morphologically the overnight cultures on Loeffler show cocco-bacillary forms with few granules.

Of the faded types rather more than half ferment saccharose, all ferment glucose, and most show a deposit in broth which rises in a characteristic 'stringy' fashion on agitation.

A culture of *C. coryzae segmentosum* from the National Collection of Type Cultures gave a faded type colony on Neill's medium, stringy deposit in broth and did not ferment saccharose. We conclude that some of our faded strains could be thus designated, while others showing saccharose fermentation and other slight cultural variations are members of a wider group which includes the named type.

Having given a brief account of the various colonial forms of *Corynebacteria* seen on Neill's medium in Hull during the past 6 years, it is now proposed to correlate our bacteriological with our clinical findings. To do this our diphtheria cases have been divided into faucial, laryngeal and carriers, and each section is dealt with separately. The faucial group is by far the largest, and the conclusions as to toxicity of the various bacterial types are based on this group. The laryngeal group is dealt with separately because deaths in this group are more often obstructive than toxic and should be indicated as such, and not included in the figures for toxic deaths.

The number of typed faucial cases for the 6 years was 1825. They were treated to a conclusion, and the clinical classification adopted is based on the

final outcome of the case as well as on the severity of the initial symptoms. This gives five classes which are in order of ascending severity: mild, moderate, severe without paralysis, severe paralysed, fatal. In addition, there is a small number of late cases coming under treatment after the seventh day of disease without showing clinical signs which would enable them to be placed in the above list. They can only be termed late (otherwise unclassified).

By a mild case is meant one with a trivial throat lesion on admission, membrane on one tonsil or part of a tonsil only, no adenitis, albuminuria or sign of toxaemia. This class also includes the anterior nasal case with a clean throat, a discharging nose with or without membrane showing at the anterior nares. Though these are not strictly speaking faucial cases they are included with the mild faucial cases because they are invariably clinically mild.

In the moderate cases membrane may cover both tonsils but there is no extension beyond, and adenitis and other associated symptoms are not marked.

In severe cases membrane extends beyond the tonsils, involving the pillars of the fauces, soft palate and sometimes posterior pharyngeal wall, naso-pharynx and post-nasal region, together with considerable adenitis, toxaemia and albuminuria. The further classification of severe cases is best indicated by progress, which divides the severe class into those showing recovery without paralysis, those with recovery after one or more paralyses, and those dying with toxaemia, the fatal cases being either acute toxic, cardio-toxic or paralytic. All the fatal cases in the faucial series are toxic deaths in this sense. The other manifestation of diphtheritic toxaemia is paralysis, so that if we add our non-fatal paralysed cases to our fatal cases we get the toxic incidence for any series of cases. For convenience, and if we have sufficient cases, these can be expressed as rates per cent. There is thus a case fatality rate, a paralysis incidence rate, and the two rates can be added together to give a toxic rate. It is now proposed to give the figures and compare the rates for the main types of diphtheria bacilli year by year, as the time factor is an important one.

Taking the first year of this investigation, 1938, it is seen that the general experience of toxic order, *gravis*, *intermedius* and *mitis* holds good; the toxic rate for *gravis* being 34, for *intermedius* 19 and for *mitis* nil. The four subtypes of *gravis* have been aggregated for statistical purposes. The great majority of infections were due to the Hull *gravis* organism *gravis* 1 and its colonial variant *gravis* 2. *Gravis* 3 (Leeds *gravis*) was only beginning to appear —the first time this organism was isolated was in October 1938. Nevertheless, it gave some indication of its toxic nature, two out of the four infections proving fatal. It should be noted that *gravis* 4 gave rise to ten mild and one moderate case—no toxic case. That continued to be our experience while the germ was with us. Had the incidence of *gravis* 4 cases been higher with similar clinical mildness, then our toxic rate for *gravis* would have been lower and might have been below *intermedius*. Some areas such as Liverpool have reported a lower case fatality rate for *gravis* than for *intermedius*. It is suggested that the reason may be that the subtype or leading subtype of *gravis* in such a neighbourhood may be a mild subtype similar or analogous to our *gravis* 4 in Hull. At any rate the striking difference between *gravis* 4 and the other types of *gravis* indicates the importance of studying the various subtypes of the group whether we arrive at them by colonial distinctions or serological tests. To speak only of *gravis* does not appear to be sufficient.

A point worth noting is the approximation between the paralysis rate and the mortality rate in the *gravis* infections; there are nearly as many deaths as paralyses. In *intermedius*, which may be taken as our average or standard organism, not only are the deaths much less frequent but the non-fatal

Table 1. *Faucial diphtheria, typed cases*, 1938

| Organism *C. diphtheriae* | Clinical condition and outcome: Mild | Moderate | Severe: Non-paralysis | Severe: Paralysis | Severe: Fatal | Late | Total | | Paralysis rate % | Mortality rate % | Toxic rate % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *gravis* 1 | 17 | 18 | 8 | 18 | 12 | 2 | 75 | | | | |
| *gravis* 2 | 5 | 6 | 1 | 1 | 3 | 1 | 17 | 107 | 17·7 | 15·9 | 34 |
| *gravis* 3 | 1 | 1 | — | — | 2 | — | 4 | | | | |
| *gravis* 4 | 10 | 1 | — | — | — | — | 11 | | | | |
| *intermedius* | 116 | 112 | 42 | 44 | 21 | 6 | 341 | | 12·9 | 6·2 | 19 |
| *mitis* 1 | 27 | 10 | 3 | — | — | 1 | 41 | 51 | Nil | Nil | Nil |
| *mitis* 2 | 10 | — | — | — | — | — | 10 | | | | |
| Totals | 186 | 148 | 54 | 63 | 38 | 10 | 499 | | 12·6 | 7·6 | 20 |

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paralyses are more than double the deaths. This ratio, deaths to paralyses, is another means of measuring clinical severity, and other things being equal, relative toxicity.

The fifty-one cases due to *mitis* infection did not show any toxic phenomena which was our usual experience in Hull up to the year under consideration. There is a hint that *mitis* 2 was more constantly found in milder cases than *mitis* 1.

The totals show that diphtheria taken as a whole was only moderate in severity due to the preponderance of *intermedius* infection. Our highest mortality rate for 12 years was in 1936, when 761 cases gave a mortality rate of 13·9 % and a paralysis rate of 10·4 %. This is a toxic rate of 24 with deaths exceeding paralyses.

*1939.* *Gravis* 1 and with it *gravis* 2 have disappeared. *Gravis* 3 has replaced it, and to this is due all the deaths and most of the paralyses. *Gravis* 4 continued chiefly mild till it disappeared in September of this year. It has not been seen since. *Intermedius* again provides most of the cases with similar rates to those of 1938. For the first time in our experience we record toxic *mitis* deaths and *mitis* paralyses and have a 7 % toxic rate for this strain. *Mitis* 2 continued to show non-toxic cases.

*1940.* *Gravis* 3 (Leeds) is now the sole *gravis* strain present. There are few cases, but the same high toxic rate of 36 % with paralyses more numerous than deaths. *Intermedius* shows an increased paralysis rate, and again there are paralyses and one death due to *mitis* strains. The first paralysis recorded for *mitis* 2 is shown. Though the numbers are small the relative toxic rates in order *gravis*, *intermedius*, *mitis* are maintained.

*1941.* A very instructive year. *Gravis* numbers are falling though its toxic rate of 24 is maintained. A new *gravis* strain, not growing on Neill's medium and so similar to the Dundee strains, was observed.

*Intermedius* is no longer the predominating organism; its death-rate is low and its paralysis rate constant, giving it a low (13) toxic rate with a paralysis rate paralyses to deaths ratio of 8 to 1. *Mitis* still shows an occasional paralysis or death giving a toxic rate of 4. A strain of *mitis* which would not grow on Neill's medium was encountered, showing that the 'Neill-shy' phenomenon is not limited to *gravis* strains. But the most striking thing in this year was the appearance of a new strain, *C. diphtheriae* Edinburgh Christison 4 (called for brevity E.C. 4). It appeared in January and we had it with us all the year and the next. It was the commonest strain during the year (a year of small numbers in any case) and it was the most deadly. It had a 31 toxic rate with deaths more numerous than paralyses, the actual case mortality rate reaching the high figure

Table 2. *Faucial diphtheria, typed cases,* 1939

| Organism *C. diphtheriae* | Clinical condition and outcome: Mild | Moderate | Severe: Non-paralysis | Severe: Paralysis | Severe: Fatal | Severe: Late | Total | Paralysis rate % | Mortality rate % | Toxic rate % |
|---|---|---|---|---|---|---|---|---|---|---|
| *gravis* 1 | — | — | — | 1 | — | — | 1 | | | |
| *gravis* 3 | 13 | 11 | 9 | 13 | 6 | 1 | 53 | | | |
| *gravis* 4 | 13 | — | 1 | — | — | — | 14 | | | |
| | | | | | | | 68 | 20·6 | 8·8 | 29 |
| *intermedius* | 82 | 82 | 47 | 35 | 18 | 2 | 266 | 13·2 | 6·8 | 20 |
| *mitis* 1 | 44 | 19 | 4 | 3 | 3 | 2 | 75 | | | |
| *mitis* 2 | 10 | 3 | — | — | — | — | 13 | | | |
| | | | | | | | 88 | 3·4 | 3·4 | 7 |
| Totals | 162 | 115 | 61 | 52 | 27 | 5 | 422 | 12·3 | 6·4 | 19 |

Table 3. *Faucial diphtheria, typed cases,* 1940

| Organism *C. diphtheriae* | Clinical condition and outcome: Mild | Moderate | Severe: Non-paralysis | Severe: Paralysis | Severe: Fatal | Severe: Late | Total | Paralysis rate % | Mortality rate % | Toxic rate % |
|---|---|---|---|---|---|---|---|---|---|---|
| *gravis* 3 | 6 | 10 | 2 | 6 | 4 | — | 28 | 21·4 | 14·3 | 36 |
| *intermedius* | 45 | 22 | 16 | 19 | 7 | — | 109 | 17·4 | 6·4 | 24 |
| *mitis* 1 | 16 | 4 | 1 | 1 | 1 | — | 23 | | | |
| *mitis* 2 | 6 | 2 | — | 1 | — | — | 9 | | | |
| | | | | | | | 32 | 6·2 | 3·1 | 9 |
| Totals | 73 | 38 | 19 | 27 | 12 | — | 169 | 16·0 | 7·1 | 23 |

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of 17·6. Had this strain not appeared we would have had record low death and toxic rates (2·7 and 12·7 %). As it was, this invasion of E.C. 4 brought the total rates up to the average of about 7 % death and 20 % toxic.

Here on a small scale only but sharply shown is what may happen when a virulent strain (in this case *not* a starch fermenter) is introduced into a district. Epidemics are probably the same sort of thing on a much larger scale.

*In 1942, intermedius* once more became the predominant strain, though its toxic rate and especially *Gravis* 3 and *intermedius*, which until this year had both been associated with considerable toxic rates, show decreased rates. E.C. 4 which carries a higher toxic rate than *gravis* also shows a decrease in toxic effect. This can only mean that the immunity level of the population is rising and that it is rising against all types of *C. diphtheriae*. This is doubtless due partly to the play of natural forces—*gravis* and *intermedius* strains have long been prevalent in Hull, and the chances of subclinical infection and naturally acquired active immunity considerable—partly to active immunization by artificial methods, now almost entirely limited to two doses of alum-precipitated toxoid with an interval of 1 month between them.

Table 4. *Faucial diphtheria, typed cases*, 1941

| Organism *C. diphtheriae* | Clinical condition and outcome: Mild | Moderate | Severe: Non-paralysis | Severe: Paralysis | Severe: Fatal | Severe: Late | Total | Paralysis rate % | Mortality rate % | Toxic rate % |
|---|---|---|---|---|---|---|---|---|---|---|
| *gravis* 3 | 14 | 9 | 1 | 6 | 2 | — | 32 } 33 | 18·2 | 6·0 | 24 |
| *gravis* 5 | 1 | — | — | — | — | — | 1 } | | | |
| *intermedius* | 34 | 20 | 7 | 8 | 1 | 1 | 71 | 11·3 | 1·4 | 13 |
| *mitis* 1 | 29 | 3 | 2 | 1 | 1 | — | 36 | | | |
| *mitis* 2 | 6 | 3 | 1 | — | — | — | 10 } 47 | 2·1 | 2·1 | 4 |
| *mitis* N.S. | 1 | — | — | — | — | — | 1 | | | |
| E.C. 4 | 28 | 19 | 4 | 10 | 13 | — | 74 | 13·5 | 17·6 | 31 |
| Totals | 113 | 54 | 15 | 25 | 17 | 1 | 225 | 11·1 | 7·6 | 19 |

Table 5. *Faucial diphtheria, typed cases*, 1942

| Organism *C. diphtheriae* | Clinical condition and outcome: Mild | Moderate | Severe: Non-paralysis | Severe: Paralysis | Severe: Fatal | Severe: Late | Total | Paralysis rate % | Mortality rate % | Toxic rate % |
|---|---|---|---|---|---|---|---|---|---|---|
| *gravis* 3 | 19 | 13 | — | 2 | 1 | — | 35 } 38 | 7·9 | 2·6 | 11 |
| *gravis* 5 | — | 2 | — | 1 | — | — | 3 } | | | |
| *intermedius* | 47 | 22 | 3 | 9 | 1 | 1 | 83 | 10·8 | 1·2 | 12 |
| *mitis* 1 | 28 | 9 | 1 | 1 | — | 1 | 40 | | | |
| *mitis* 2 | 23 | 8 | — | — | — | — | 31 } 74 | 1·4 | — | 1·4 |
| *mitis* N.S. | 3 | — | — | — | — | — | 3 } | | | |
| E.C. 4 | 13 | 16 | 3 | 6 | 4 | — | 42 | 14·3 | 9·5 | 24 |
| Totals | 133 | 70 | 7 | 19 | 6 | 2 | 237 | 8·0 | 2·5 | 11 |

the case mortality rate had dropped. Toxic 12 % as against the usual experience of 20 and death 1·2 % as against 7. Note also that the toxic rate for *gravis* is at a new low level and for the first time less than that of *intermedius*. There are no *mitis* deaths in 74 cases. The only two severe cases in the *mitis* group are *mitis* 1 infections.

E.C. 4 has dropped in numbers but still carries the highest toxic and a considerable death-rate, though paralyses are now more numerous than deaths. Despite the E.C. 4 contribution the total figures show new low levels for toxic phenomena.

In 1943, E.C. 4 disappeared in the early part of the year. It no longer affects our rates. We have got what we would have got in 1941 if it had not been for the E.C. 4 invasion—record low figures. Although *gravis* (almost all Leeds *gravis*) strains have risen and now predominate, its toxic rate has dropped to that of *intermedius*, and both are but little above that of *mitis*. Increased immunity has smoothed out the differences between the bacterial

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types when judged by toxic reactions on human beings. We see case mortality reduced to under 2% and total toxic incidence to under 10%. If we continue to increase our immunizing measures, now so simple, these figures should be further improved, and I look forward to the time when our case mortality rate in diphtheria will be under 1%. There may be in the future outbreaks due to the introduction of fresh strains, but if the antitoxic immunity of the population is maintained they will be attacks of surface or local diphtheria without toxic complications and will be of bacteriological and epidemiological rather than clinical and pathological interest.

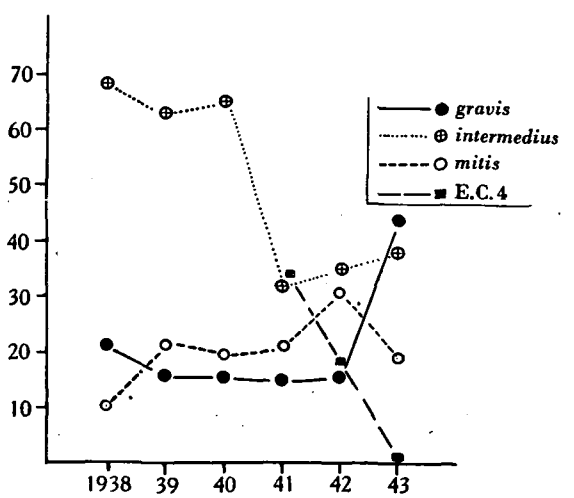
It may be of some value to summarize certain of these figures and put some of the data in graphical form (Text-fig. 1). Note the sudden drop of *intermedius* infections in 1941, and the sudden appearance and rapid drop of E.C. 4 infection, also the sharp rise in *gravis* (almost all Leeds *gravis*) infection in 1943. With this rapid rise in the number of *gravis* infections we might have expected a rise in toxic disease but it did not come.

The graphs for the various types during the 6 years also make interesting comparisons (Text-fig. 2). At the beginning of the period the high *gravis* mortality rate of nearly 16% and that of *intermedius* of about 6% was our usual experience. The sudden drop in toxic deaths in 1941 and 1942 in both strains can only be due to increasing immunity in the persons attacked, and the unprecedented low levels in 1943 reflect this increased population immunity.

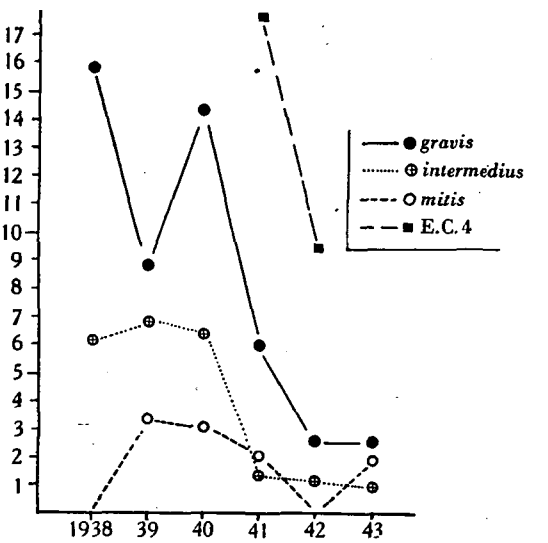
Laryngeal diphtheria is defined as diphtheria in which symptoms of laryngeal involvement or acute respiratory obstruction were present on admission or developed rapidly. The number of such cases is small—too small to consider profitably on a yearly basis, so a table is given for the whole 6 years' period.

Table 6. *Faucial diphtheria, typed cases*, 1943

| Organism *C. diphtheriae* | Clinical condition and outcome: Mild | Moderate | Severe: Non-paralysis | Severe: Paralysis | Severe: Fatal | Late | Total | | Paralysis rate % | Mortality rate % | Toxic rate % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *gravis* 3 | 52 | 45 | 2 | 8 | 3 | — | 110 | | | | |
| *gravis* 5 | 1 | — | — | — | — | — | 1 | 116 | 7·8 | 2·6 | 10 |
| *gravis* 6 | 2 | 2 | — | 1 | — | — | 5 | | | | |
| *intermedius* | 61 | 29 | 4 | 9 | 1 | — | | 104 | 8·7 | 1·0 | 10 |
| *mitis* 1 | 10 | 3 | — | 2 | 1 | — | 16 | | | | |
| *mitis* 2 | 28 | 6 | — | — | — | — | 34 | 50 | 4·0 | 2·0 | 6 |
| E.C. 4 | 1 | 1 | — | 1 | — | — | | 3 | — | — | — |
| Totals | 155 | 86 | 6 | 21 | 5 | — | | 273 | 7·7 | 1·8 | 10 |




Text-fig. 1. Percentage type distribution.




Text-fig. 2. Case mortality rates.

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There were only 73 typed cases (7 laryngeal cases were not typed) in the 6 years. There were 12 deaths and of these 10 were due to obstruction and only 2 to toxaemia. With regard to type distribution the largest group was *mitis* and then *intermedius*. The numbers in brackets show the tracheotomies (or other surgical interference) included in each group. The comparison of the percentage type distribution with that of the faucial cases for the same 6 years (shown for comparison in the last column) is interesting and shows the relative increase of *mitis* infection in obstructive cases. There is a relatively lower *gravis* incidence in the laryngeal cases. It is suggested that *mitis*, because it is relatively slow in its toxic effect, has time to exercise its surface effect and spread, so causing blockage in larynx, trachea bacilli of the various types, there is also shown those in which diphtheroids were found. In both the diphtheria carriers and diphtheroid carriers the nasal carrier is commonest.

Finally, there is a summary showing all the typed cases dealt with in this review of 6 years' experience in Hull.

The review represents on the whole mild and decreasing diphtheria. At the beginning, 1938, there were still indications of the severe and toxic diphtheria which ravaged Hull in 1932 and again in 1936; at the end, last year, 1943, showed a record low death-rate for all types. So the picture is of diminishing diphtheria due, I believe, to the increasing immunity of the population and not to type variation. If that immunity is maintained by

Table 7. *Laryngeal diphtheria, typed cases*, 1938–43

| | Clinical condition and outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Recovered | | Died | | | Case mortality rate | Type distribution | Faucial type distribution |
| *C. diphtheriae* | Non-paralysis | Paralysis | Obstructive | Toxic | Total | % | % | % |
| *gravis* | 7 (4) | — | — | — | 7 | — | 10 | 21 |
| *intermedius* | 22 (8) | 1 (1) | 5 (3) | 1 (1) | 29 | 20·7 | 40 | 53 |
| *mitis* | 26 (7) | — | 5 (4) | 1 (1) | 32 | 18·8 | 44 | 19 |
| E.C. 4 | 5 (2) | — | — | — | 5 | — | 7 | 7 |
| Totals | 60 | 1 | 10 | 2 | 73 | 16·4 | — | — |

*Carriers*, 1938–43

| *C. diphtheriae* | Throat | Nose | Both | Other | Total | Type (%) |
|---|---|---|---|---|---|---|
| *gravis* | 13 | 7 | 8 | — | 28 | 20 |
| *intermedius* | 6 | 18 | 8 | 2 (E) | 34 | 24 |
| *mitis* | 16 | 31 | 9 | 1 (E) | 57 | 40 |
| E.C. 4 | 14 | 2 | 5 | 1 (E) | 22 | 16 |
| Totals | 49 | 58 | 30 | 4 (E) | 141 | — |
| Diphtheroids | 4 | 28 | 11 | 2 (E) | 45 | — |
| Negative at Hospital | — | — | — | — | 47 | — |

| Summary | |
|---|---|
| Faucial | 1825 |
| Laryngeal | 73 |
| Carriers | 141 |
| Total | 2039 |

or even bronchial tubes. Invasion by *gravis* and other toxic strains in a non-immune tends to cause toxaemia and death before considerable surface extension has had time to develop. On the whole *mitis* has more chance of producing mechanical effects and so figures prominently in such a table as this.

Much the same thing may be said about the *carriers*. The term carrier is used strictly for those subjects harbouring the organism who have had no symptoms of disease and show no sign of present or past disease. Here again *mitis* shows a 40 % type distribution rate against the 19 % of the faucial series. The less toxic organism seems more likely to establish a non-pathogenic relationship to its host.

In addition to the cases carrying true diphtheria the artificial methods now available we shall see no more outbreaks in Hull like those of 1932 and 1936, when the actual toxic deaths were 113 and 106 respectively compared with 6 for 1942 and 5 for 1943.

To summarize the main impressions of this experience one would stress:

(1) The value of Neill's medium, not only as an excellent selective medium for the *Corynebacteria*, but for its capacity to allow organisms of that group to produce characteristic and distinctive colonies. Thus not only are the diphtheroids sharply and easily distinguished from diphtheria bacilli, not only are *gravis*, *intermedius* and *mitis* colonies sharply defined (subject to a check on starch fermentation) but subgroups within the *gravis* group, and subgroups outside of the *gravis*, *intermedius*, and *mitis* types,

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such as E.C. 4, can be recognized by their colonial form together with the fermentation tests. The inability of Neill's medium to grow certain strains is a possible disadvantage—though we did not feel it because of the virtual absence of such strains from the Hull district. If such strains are suspected a slight modification gets over the difficulty. Neill's medium does not appear to be peculiar in this defect; other media may not grow certain strains. Goldie & Maddock (1943) recently reported a *gravis* strain of diphtheria derived from a milk-borne outbreak which would not grow on Loeffler's medium. It is questionable if there is even yet a universal medium for all types and subtypes of this large group.

(2) The recognition of subtypes within the *gravis* group is important. There are starch-fermenting strains that do not appear to give rise to the severe toxic disease that is associated with the Leeds and Hull *gravis* subtypes. The *gravis* 4 described is an example.

(3) We were struck by the constancy of the *intermedius* type. Present in 1932 and every year since, it seems to be, in Hull at any rate, the constant, stable, 'average' diphtheria bacillus.

(4) We saw in the appearance and disappearance of the toxic E.C. 4 strain an example of what must be the mechanism of the diphtheria epidemic. In this case a strain of high virulence (though not a starch fermenter) was superimposed upon the existing local bacterial flora and caused a sharp rise in the declining case mortality rate.

(5) Most important of all are the declining case mortality rates. The *gravis* case fatality rate in 1938 was 15·9, in 1943 it was 2·6. Similarly, *intermedius* case fatality rates fell from 6·2 to 2·0. This can only be due to rising immunity in the population as a whole—an immunity that can be maintained and increased by artificial means.

As mass immunity rises variations in bacterial type become less significant. Typing will remain of value in epidemiology as in the field work of tracing sources of infection. To the bacteriologist it must remain important because of the light type variations throw on bacterial metabolism, ecology, variation, and indeed the wider biological implications of his subject. Even if the bacteriologist loses the human non-immune as his test animal for virulence variations he has still numerous comparative criteria left.

If our experience in Hull is similar to that of the country generally, and the decreasing diphtheria figures and mortality rates of the national returns suggest that it is so, then diphtheria is well on the way to being conquered and the public health worker is beginning to see some results from prophylactic methods which have been available for a quarter of a century.

Thanks are due to Prof. J. W. McLeod of Leeds, Dr Jean Orr-Ewing of Oxford and Prof. W. J. Tulloch of Dundee for kindly examining and reporting on strains of diphtheria bacilli submitted to them. I must also express appreciation of the work of Mr G. J. Acton, F.I.M.L.T., Technologist at the Hospital, for his care in carrying out the routine bacteriological work and for the photographs which illustrate this paper.

## REFERENCES

ANDERSON, J. S., COOPER, K. E., HAPPOLD, F. C. & MCLEOD, J. W. (1933). *J. Path. Bact.* **36**, 169.

ANDERSON, J. S., HAPPOLD, F. C., MCLEOD, J. W. & THOMPSON, J. G. (1931). *J. Path. Bact.* **34**, 667.

GOLDIE, W. & MADDOCK, E. C. G. (1943). *Lancet*, **1**, 285.

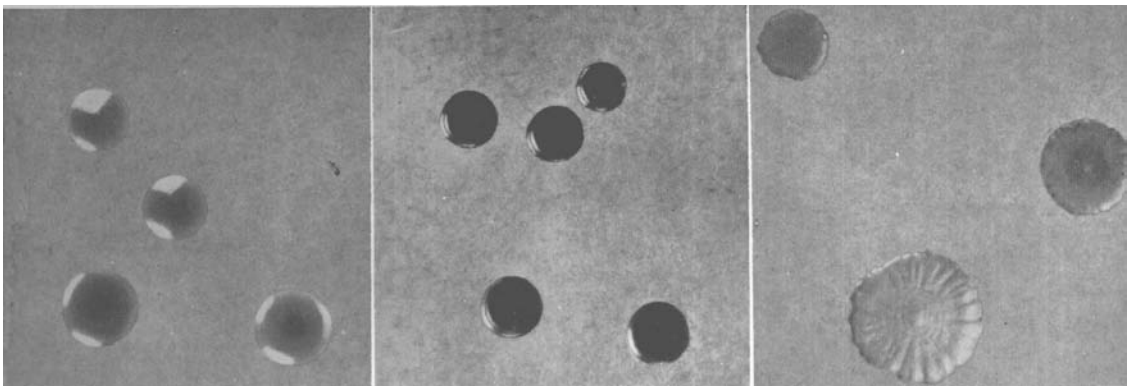
LEETE, H. M., MCLEOD, J. W. & MORRISON, A. C. (1933). *Lancet*, **2**, 1141.

NEILL, G. A. W. (1937). *J. Hyg., Camb.*, **37**, 552.

(*MS. received for publication* 21. VIII. 44.—Ed.)

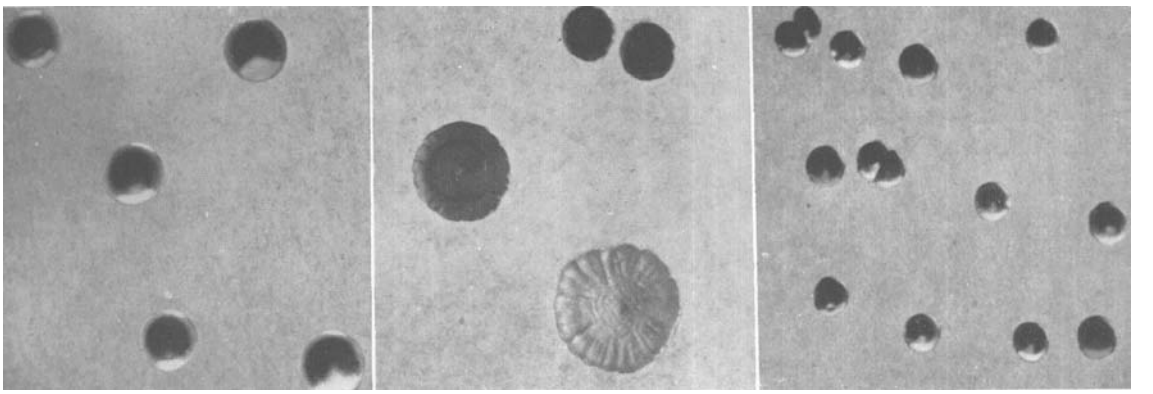
*Corynebacterium*

Hull | Hull | Leeds



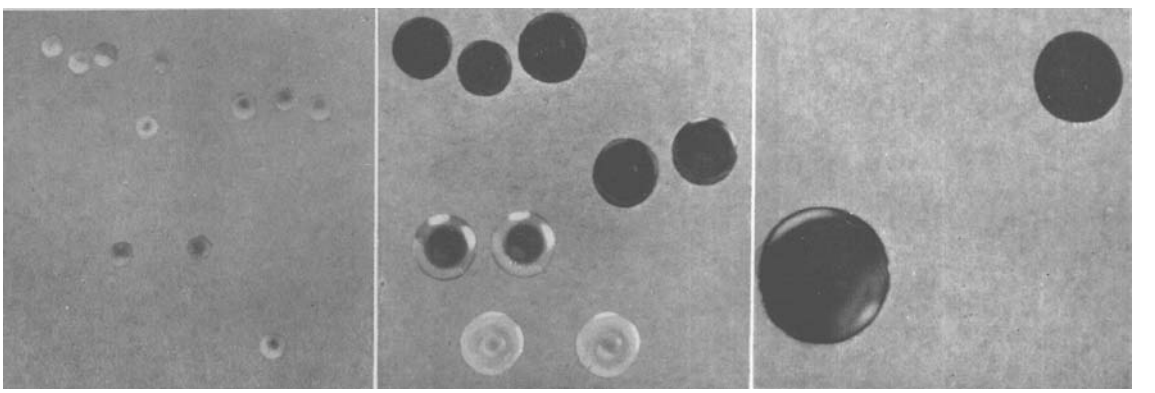
*gravis* 1 or *mitis* 1 | *gravis* 2 or *mitis* 2 | *gravis* 3

Hull | Edinburgh



*gravis* 4 | 'Christison' type 4 | *intermedius*

Diphtheroids



Faded types | Hofmann's bacillus | Large black diphtheroid

MASON LEETE—DIPHTHERIA IN HULL

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