5. B.B.S. is a more suitable diluent than phenol saline for Toxin B. It ensures less deterioration after (a) two to three days at room temperature, and also after (b) four weeks at 4° C. followed by two to three days at room temperature.

Comparison of two Dick toxins, A and B, diluted in B.B.S. or 0.4 per cent. phenol saline (a) two to three days before injection, and (b) one month before injection

			Observers		
			M.L.	McG. and K.	R.
A (B.B.S.) 2-3 days	>	B (phenol) 2-3 days	11	18	16
" " " "	>	" " " "	0	0	0
" " " "	>	" " " "	2	0	0
A (B.B.S.) 2-3 days	>	A (B.B.S.) 1 month	2	12	4
" " " "	>	" " " "	4	2	2
" " " "	>	" " " "	7	4	10
A (B.B.S.) 1 month	>	B (phenol) 2-3 days	11	18	16
" " " "	>	" " " "	0	0	0
" " " "	>	" " " "	2	0	0
B (phenol) 2-3 days	>	B (phenol) 1 month	6	7	1
" " " "	>	" " " "	2	3	3
" " " "	>	" " " "	5	2	12
B (phenol) 2-3 days	>	B (B.B.S.) 2-3 days	4	1	0
" " " "	>	" " " "	4	9	10
" " " "	>	" " " "	5	0	6
B (phenol) 1 month	>	B (B.B.S.) 1 month	1	2	1
" " " "	>	" " " "	5	6	8
" " " "	>	" " " "	7	0	7

The toxins were supplied to the various hospitals in sealed glass phials and in rubber-stoppered bottles. There did not appear to be any significant difference between the results obtained with toxins from the two types of container, which were disregarded when the above table was compiled.

Discussion

From the combined research it is obvious that one has to use large numbers of persons in comparing the dilutions which were supplied of Dick toxins A and B. Discrepancies are apparent in an analysis of the data from different hospitals, and indicate the need for care in the interpretation of comparisons based on small groups. At the same time undue emphasis must not be placed on the discrepancies reported by different workers. Many of these were explained by a difference in measurement of a very few millimetres, as was evident from the original protocols (unpublished).

The influence of the diluents is also of interest. Boric acid borate buffer solution, which is now used in Great Britain, is a better stabilizing agent than phenol saline. A similar conclusion was reached by O'Brien, Okell, and Parish (1928), although in their early work a slightly higher concentration of phenol was used and a more rapid deterioration of toxin was observed. It is now well known that phenol is an unsuitable antiseptic for various other toxins—for example, diphtheria and tetanus—and for such immunizing agents as diphtheria prophylactic, A.P.T., which may lose its antigenicity rapidly in the presence of phenol.

A comparison of various Dick toxins has also been made by Ker (1937), who commented on the stability of the material used in his tests. His work emphasizes, too, the necessity for tests on a large group of persons in any investigation of this type.

With regard to the strength of Dick toxin used normally in our clinical work, the dramatic reduction of scarlet fever among nursing staffs after the introduction of the Dick test and active immunization indicates clearly that a

Dick-negative staff of nurses has a high degree of protection against infection; but we have seen a small number of relapses to Dick-positive and a few cases of scarlet fever among nurses who had formerly, or recently, been Dick-negative. On reviewing all the evidence, however, the results of immunization indicate that the Dick toxin used is of satisfactory potency.

Summary

1. In comparing two different samples of Dick toxin, tests on small groups of persons may be misleading. We would emphasize the need for making a considerable number of tests if an accurate result is required.

2. Boric acid borate buffer solution is a preferable diluent to 0.4 per cent. phenol saline, since it ensures greater stability.

3. The Dick toxin A, used normally in our clinical work, is of satisfactory potency and stability. Negative reactions with this toxin indicate a high degree of protection, although we have observed a few cases of scarlet fever in Dick-negative nurses.

We are indebted to Dr. R. A. O'Brien and Dr. H. J. Parish of the Wellcome Physiological Research Laboratories for the Dick toxins and diluents used for the tests.

REFERENCES

- Ker, F. L. (1937). *British Medical Journal*, 1, 852.
O'Brien, R. A., Okell, C. C., and Parish, H. J. (1928). *Publ. Hlth.*, 41, 181.

A NOTE ON DIPHTHERIA IMMUNIZATION IN LONDON

BY

MAX SORSBY, L.M.S.S.A.

The increasing attention that is being paid by public health authorities to the immunization of children against diphtheria and the satisfactory results that have been obtained by various authorities in the reduction of the incidence of the disease by this procedure have led to the present study of the extent of diphtheria immunization in the child population of London. Diphtheria is a problem of no mean order in the metropolis. For the decennial period 1926-35 the following yearly averages for the County of London show the extent of morbidity and mortality.

Approximate population (0-15 years)	1,000,190
Diphtheria cases	9,047 (Attack rate of 9.04 per 1,000)
Deaths	367 (Death rate of 3.65 per 10,000)
Case mortality, per cent.	4.05

Immunization is carried out in the County of London mainly by the authorities of the different metropolitan boroughs. Holborn has provided facilities since 1922, and it was some years before other authorities followed: even now Bethnal Green has no local facilities, but makes arrangements for applicants to be immunized elsewhere. By reason of this lack of uniformity a much larger number of children are immunized in some parts of London than in others. Taking all the London boroughs together, by the end of 1935 there were 29,616 children potentially protected against diphtheria, either because of a natural immunity or as a result of immunity acquired by inoculation. The proportion of naturally immune children is not insignificant, for of nearly 30,000 no fewer than 4,698 were found Schick-negative at the primary test. On this basis something like 20

per cent. of the child population in London is naturally immune. It is generally agreed that for the diphtheria mortality rate to be tangibly affected at least 50 per cent. of the child population must be immune. There is therefore a wide gap to be bridged—one of at least 30 per cent. Thus, taking the figures up to 1935, it would appear that only a very small proportion of the child population has so far been artificially protected—actually not more than 2.3 per cent.

Recent Increase in Rate of Immunization

Since 1935 diphtheria immunization has been practised on an ever-increasing scale, so that this small percentage is no longer valid. In 1936 about 3,000 more children were protected, and whilst the figures for 1937 are not yet available, there can be no question that this number has been surpassed. As emphasizing the increasing rate at which immunization is being practised, it is worth pointing out that whilst in 1930 there were about 9,000 protected children, by the end of 1935 this figure was nearly trebled, and in the two years 1936-7 as many children were protected as in the preceding five years.

The L.C.C. has carried out immunization among the inmates of its institutions since 1932, and by the end of 1936 approximately 10,000 children had been successfully immunized. Adding these figures together, it would appear that at the present moment about 55,000 to 60,000 children in the London area have been actively protected, representing approximately 5 to 6 per cent. of the child population. If the 20 per cent. or so of the naturally immune children are added to this there remain about three-quarters of the child population not protected. In view of the risk run by the unprotected, an intensive effort towards popularizing immunization seems to be called for. The experience of Dublin, where, in the second half of 1935, 25,000 children were immunized, including 4,500 under school age, illustrates what can be achieved. In Chester about 45 per cent. of the child population and in Birmingham about 35 per cent. have been immunized. There does not appear to be any reason why other local authorities cannot do as well or even better.

The following table gives a detailed analysis of the extent of diphtheria immunization undertaken by the

COUNTY OF LONDON

Diphtheria Immunization. Totals to end of 1935

Local Sanitary Authority	Approx. Average Population 0-15 Years 1926-35	Date of Commencement of Immunization	Numbers Schick-negative at Primary Test	Numbers Given Full Course of Prophylactic	Numbers Fully Inoculated and Subsequently Schick-negative	Cases of Diphtheria Reported among Immunized	Diphtheria Attack Rate per 1,000 Immunized	Deaths from Diphtheria among Immunized Children	Total Known to be Protected (Immunized or Schick-negative at Primary Test)	Percentage of Known Protected to Total Population (0-15 Years to End of 1935)	Number Potentially Protected
City of London ..	1,400	1935	None tested	26	24	0	—	—	24	1.71	26
Battersea	37,700	1927	230	1,297	1,027	4	3.89	—	1,257	3.33	1,527
Bermondsey	31,500	1929	91	295	295	1	3.39	—	386	1.23	386
Bethnal Green* ..	30,500										
Camberwell	59,000	1926	361	1,369	1,028	4	3.89	—	1,389	2.35	1,730
Chelsea	9,800	1934	22	215	184	0	—	—	206	2.10	237
Deptford	26,300	1927	316	950	384	0	—	—	700	2.66	1,266
Finsbury	19,130	{ 1928-31 1934 }	24	143	96	0	—	—	120	0.63	167
Fulham	33,230	1934	219	757	619	0	—	—	838	2.52	976
Greenwich	26,300	1936	—	—	—	—	—	—	—	—	—
Hackney	49,670	1928	1,043	4,510	3,817	6	1.57	—	4,860	9.78	5,553
Hammersmith	30,500	1935	22	1,170	546	0	—	—	568	1.86	1,192
Hampstead	13,300	1933	—	603	218	0	—	—	218	1.63	603
Holborn	6,160	1922	384	1,542	1,170	4	3.42	—	1,554	25.2	1,926
Islington	75,150	1936	—	—	—	—	—	—	—	—	—
Kensington	32,000	1934	102	2,318	1,657	1	0.60	—	1,759	5.5	2,420
Lambeth	67,650	1928	849	2,164	1,970	0	—	—	2,819	4.16	3,013
Lewisham	53,300	1935	36	236	235	0	—	—	271	0.5	272
Paddington	25,300	(June) 1933	322	664	627	4	6.37	—	949	3.75	986
Poplar	45,000	{ 1928-30 1933-35 }	58	215	202	0	—	—	260	0.57	273
St. Marylebone ..	15,400	1928	107	2,132	1,451	3	2.07	—	1,558	10.12	2,239
St. Pancras	41,800	1936	—	—	—	—	—	—	—	—	—
Shoreditch	28,650	1933	262	588	197	1	5.10	—	459	1.60	850
Southwark	45,800	1929	315	1,726	1,232	2	1.62	—	1,547	3.37	2,041
Stepney	61,100	1936	—	—	—	—	—	—	—	—	—
Stoke Newington ..	10,000	1927	68	537	512	0	—	—	580	5.80	605
Wandsworth	71,700	1928	1,258	5,362	4,013	9	2.24	—	5,271	7.35	6,620
Westminster, City of	16,400	1926	327	1,619	833	2	2.40	—	1,070	6.53	1,856
Woolwich	36,450	1934	172	1,135	781	0	—	—	953	2.61	1,307
	1,000,190	1922-35	6,588	31,573	23,118	41	1.77	—	29,616	2.96	38,071

* No facilities for immunization yet in Bethnal Green. Applicants are referred to the Hospital for Sick Children, Great Ormond Street.

metropolitan boroughs up to 1935. It will be seen that in comparison with the general child population the incidence of diphtheria among immunized children is distinctly low (an attack rate of 1.77 per 1,000 immunized against 9.04 for the general child population) and that there has not been a single death from diphtheria in the forty-one cases occurring in the immunized group.

I am indebted to the Special Hospitals Department of the London County Council for the information contained in the table, and to Dr. G. H. Dart, medical officer of health for Hackney, for much helpful advice.

VASOMOTOR RHINORRHOEA, WITH ASTHMA, ASSOCIATED WITH MENSTRUATION

BY

A. S. HOSEASON, M.D., M.R.C.P.

Clinical Assistant in the Dietetic Department, lately Laking-Dakin Research Fellow, St. George's Hospital

The relation between nasal disorders and activity of the sexual organs, both in the male and in the female, was recognized by Hippocrates, Celsus, and Aristotle, and also in the Ayurveda, the ancient Hindu medical classic. J. N. Mackenzie (1884), an ear, nose, and throat surgeon of Baltimore, was the first writer of more modern times to make a systematic clinical study of this subject and to survey the literature. He observed in a certain number of women, whose nasal organs were otherwise healthy, that the nasal erectile tissue became congested at the time of the period, and even when the period was expected but happened temporarily to be suppressed. He said that his own experience was not great enough for him to say whether these changes also took place during pregnancy; but they have now, in fact, been seen to occur (Mortimer, Wright, and Collip, 1936a, 1936b, 1937). Moreover, the change is a steadily progressive one, with exacerbations when the periods would have been expected to be due but for the pregnancy. Mackenzie was of the opinion that nasal congestion was not confined only to women at the time of the periods, but that it might also occur during or after sexual activity in both sexes.

For fifty years the significance of Mackenzie's and other similar work has passed unnoticed and unexplained, but these clinical observations have now acquired a fresh significance in the light of recent advances in endocrinology, and are supported by a large body of experimental evidence, obtained mostly from work on monkeys (Mortimer *et al.*, 1936a, 1936b, 1937).

Hormonic Action on the Nasal Mucosa

Nasal turgescence is one of the "specific skin responses" to increase of circulating sex hormone occurring at oestrus. It can be provoked by injection of the appropriate oestrogenic hormones into male and female monkeys, including, as controls, those which are immature or castrate. Specific skin reactivity can be shown by simple transplantation experiments, where, for example, a piece of specific skin transplanted into a non-specific area still shows the specific response, and vice versa. Thus, non-specific skin transplanted into the perineal area of a monkey stands out as a "pale island

of skin in brilliantly coloured surroundings" (Bachman, Collip, and Selye, 1936).

This specific action of oestrogenic hormones on the nasal mucosa has been investigated and put to a therapeutic purpose by Collip and his co-workers in cases of atrophic rhinitis and ozaena. They observed much improvement after a course of local application of the hormones (oestrone or oestradiol in an oily solution). Incidentally, this series of cases showed an unusually high percentage of deafness and otosclerosis, which in a few cases responded to treatment, although otosclerosis is generally considered to be a most intractable cause of deafness.

The nasal congestion which is such a feature in the oestrous cycle of the higher primates has to a very large extent been lost in human phylogenetic development. None the less, it seems that the majority of women have some degree of nasal turgescence during menstruation and pregnancy. The bleeding of "vicarious menstruation" has been observed to come not from Kiesselbach's septal triangle, as is usually the case, but from the congested middle and inferior turbinates (Mortimer *et al.*, 1936b).

Many women complain that their noses are "stuffed up" or "run" immediately before or during their periods. In an unlucky few the turgescence may give rise to even more severe symptoms. In some women the nasal congestion may result in an attack of vasomotor rhinorrhoea; this is not an allergic reaction, but an exaggeration of a normal physiological response. Why this should be so one cannot explain: cellular pathology is even less understood than cellular physiology. "The reactivity of the tissues . . . is an important factor in determining the effects of hormone secretion" (Levy Simpson, 1938).

This type of vasomotor rhinorrhoea which occurs in association with the menstrual function might be termed "oestrogenic rhinorrhoea"; but this does not mean to say that an allergic factor is necessarily excluded. It usually occurs regularly about two days before the onset of the menstrual period, during which an attack of asthma may develop. The asthma is often slow in termination because, as frequently happens, a catarrhal bronchitis of bacterial origin may supervene. The whole illness is likely to take some time to resolve, only to recur with the next menstrual cycle. As this syndrome often first appears in children of school age who are taking their higher examinations, the resultant disability is serious. The patients are seen for treatment usually on account of their asthma only; the preceding rhinorrhoea, which is much less spectacular and disabling than the asthma, is either disregarded or self-diagnosed as a "cold in the nose." If this self-diagnosis is accepted as such and the asthma treated symptomatically, then the general prognosis as regards future attacks of asthma is not hopeful. But a careful questioning will reveal the true nature of the "cold"—that is, typical vasomotor rhinorrhoea, with no malaise or fever—and the prognosis is then materially altered.

Nasogenic Asthma

Asthma produced in this manner, by a nasal affection, is termed "nasogenic asthma," and its mechanism is reflex through the naso-pulmonary reflex arc. The control of bronchial calibre and the influence upon it of nasal stimulation has been studied with the bronchoscope in experimental animals and the reflex paths worked out