chemical properties. During the period of this study one of us (P.R.E.) was in receipt of a grant from the Medical Research Council.

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Vi Reaction in Hong Kong

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After 30 years the value of the Vi reaction remains controversial (Public Health Laboratory Service Working Party, 1961; Bokkenheuser and Richardson, 1964), and several factual points in connexion with the test are still in doubt. As typhoid fever is endemic in Hong Kong, it was decided to conduct an investigation into the use of the Vi reaction in the diagnosis and epidemiology of typhoid under the rather unusual conditions pertaining in the colony.

Before any work could be done on the place of the Vi reaction in the detection of typhoid carriers it was essential to ascertain the normal range in the general population.

In the study of the acute phase of typhoid an attempt was made to establish whether the Vi reaction could be an aid to the serological diagnosis of the disease, special emphasis being given to the possibility of forecasting clinical relapse or the development of the carrier state. The records were also examined for correlation between Vi titres and the following: age, severity of disease, Widal reaction, and treatment.

Method and Materials

Blood was collected for Vi examination from three groups of subjects: group 1, 100 orthopaedic patients and prisoners with negative histories for typhoid and T.A.B. vaccination; group 2, 75 patients with culturally proved typhoid on whom Vi examinations were carried out at weekly intervals during their stay in hospital, and then, so far as was possible, at three-monthly intervals up to 12 months; and group 3, 17 proved typhoid carriers.

Serological Examination

The Vi antibody test was carried out with a suspension prepared from the Colindale Vi suspension (Colindale Public Health Laboratory, London) and the standard Vi sera from Colindale as the reference sera. The prepared Vi antigen suspension was tested at regular intervals with the titrated standard sera and in conjunction with the sera under test. The titre of the test sera was taken as the reciprocal of that dilution of the sera giving the same degree of agglutination as that of the standard sera at a dilution of 1,600 set up at the same time.

The test itself was performed by adding 0.3 ml. of the antigen suspension to 0.3 ml. of the test sera diluted in twofold steps from $\frac{1}{2}$ to $\frac{1}{64}$, giving final reciprocal serum concentration

from 4 to 128, further doubling dilution being set up later if necessary. Both test and controls were incubated for two hours at 37° C. and then overnight in the refrigerator.

In reading the test the three standard diagnostic criteria were used to assess the degree of agglutination: the clearing of the supernatant, the pattern of the deposit, and the resultant granularity after agitating the tube.

Results

All Vi estimations were carried out by one of us (M. J. R.).

Normal Levels

Sera were obtained from 100 subjects representative of the main economic strata in Hong Kong, comprising orthopaedic patients and prisoners, none of whom gave a history of enteric-like infection or of T.A.B. immunization. The results of this sample are shown in Table I, which also gives the titres for those in the group who were under the age of 20.

The upper limit of normal was chosen as 32. This leaves 4% of the population as positive reactors. (At the British level of 5 as positive the Metropolitan Water Board found 3.2% positive reactors (P.H.L.S.W.P., 1961).)

TABLE I

Vi Titre:	Neg.	4	8	16	32	64	
Total No. of subjects	7	16	22	24	27	4	100
No. under 20	—	4	1	3	3	1	12

Acute Disease

The patients consisted of 75 unselected consecutive cases admitted to a Government hospital with typhoid fever. Before a case was accepted into the series it was necessary for *Salmonella typhi* to have been recovered from the blood or faeces. Apart from the exclusion of treated patients transferred late in the disease from other hospitals there was no selection. The sex incidence was equal, being 38 males and 37 females.

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In Hong Kong typhoid is a disease of childhood and adolescence, only 14% of the patients being older than 20, with the peak incidence falling in the group 5 to 15 years (69%).

No deaths occurred in the series. The complication rate was low; there were four examples of melaena and 14 cases developed clinical relapses. An unusual feature was the relative mildness of the condition. Several children—even without treatment—became apyrexial and symptom-free by the 14th day. Nevertheless, despite the clinical cure, more than half of these abortive cases continued to excrete *S. typhi*.

The Vi titre was estimated on admission and thereafter at weekly intervals. The original aim to produce a graph showing the behaviour of the Vi reaction analogous to the rise of the H and O antibodies was not realized, owing to the very wide scatter and variation.

For clinical purposes a titre of 64 or above was regarded as positive. The number of cases whose Vi titres throughout their illness never became positive was 19 (25%). In the other 56 (75%) the Vi titre reached 64 or above at some stage in the acute illness, the pattern and height of the rise showing considerable variation. These findings are in accord with the views of the Public Health Laboratory Service Report.

The maximum Vi titres during illness are shown in Table II. As will be seen, most of the cases had a maximum titre of 64 (43%) or 128 (24%), with only 8% reaching a higher level. The earliest rise to 64 was recorded on the eighth day of illness, the latest during the seventh week of illness. An analysis of 15 cases admitted with negative Vi reactions before the 14th day of illness and which later became positive showed that 12 had reached a titre of 64 or above between the 17th and 25th days. This result is in fair agreement with Bhatnagar's (1938) findings for uninoculated subjects.

TABLE II

Vi Titre:	Up to 32	64	128	256	512
Number	19	32	18	2	4
Percentage	25	43	24	8	

Widal Reaction

The Widal reaction was carried out on every patient and in general followed the expected pattern. However, in four cases the O titre was less than 100, and in another five the H titre failed to reach a similar level. In the patients whose O levels were low the Vi titres, with one exception, reached a level of 128. Therefore these cases would seem to confirm that a high level of Vi antigen can block the O antigen. However, the numbers are too small for firm statistical conclusions. In every other respect the Vi titre and the Widal reaction showed absolutely no correlation.

Age and Clinical Severity

A breakdown into five-year age groups of the maximum Vi titres occurring in the acute phase of typhoid showed no variation from the general pattern. When the cases were divided on arbitrary clinical impression into mild, moderate, and severe, analysis of the Vi titres showed no significant difference.

Treatment

Mild cases were not given antibiotics. All moderate or severe cases were given a standard course of chloramphenicol. When necessary, ampicillin, blood transfusions, and steroids were administered. Eleven cases did not require treatment, and their serial Vi titres showed no departure from the general pattern. It is of interest that in four of these patients the titre never rose

above 32, showing that, at least in some instances, factors other than antibiotics affect the rise of Vi antibodies.

Relapses

In all, 14 cases (19%) have been described as relapses. These include five patients who were apyrexial on admission, presumably due to previous treatment, and who later developed fever and typical symptomatology. Strictly speaking, this illness should be described as "a recrudescence after inadequate therapy." However, as it is often well-nigh impossible to distinguish between this type of illness and a true (in the old-fashioned sense) clinical relapse, the two conditions are considered together.

Although on current theory clinical relapse should be associated with a high or rising titre, an analysis of the serial Vi patterns (including those within two weeks before relapse) showed no significant variation from the uncomplicated disease. (As a matter of academic interest there were four cases which, in retrospect, were undoubtedly true relapses—that is, the recurrence took place on the 35th day or later and after a full course of chloramphenicol. The serial Vi titres of these cases showed no variation from the usual pattern.)

Follow-up After the Acute Disease

Details of Vi titres for patients after discharge are given in Table III for four 12-week periods. By local standards the proportion of patients attending for follow-up was considered satisfactory. Of those who showed a positive reaction during follow-up all except two had been positive during the acute illness. These exceptions first showed positive titres at the 20th and the 40th week respectively.

TABLE III

	13-24 Week	25-36 Week	37-48 Week	49-60 Week
No. attending	46	36	24	20
Vi 64 or over	14 (30%)	7 (19%)	2 (8%)	2 (10%)
„ 32 „ less	32 (70%)	29 (81%)	22 (92%)	18 (90%)

Of the 14 cases with raised levels in the first follow-up period eight were followed to 52 weeks, and seven of these fell to normal, only one persisting at 64. Several stool and urine cultures were taken from seven cases with persistently positive titres, but always with negative results.

Carrier State

A carrier can be defined as a healthy subject excreting *S. typhi* who has not in the previous six months had an attack of acute typhoid. (In practice, only a proportion of carriers give positive histories, and in fact the majority of our carriers were unable to do so.) As the organism is so rarely recovered from the urine in Hong Kong, the term here means, for practical purposes, a faecal excretor.

A detailed discussion of the pathology of the carrier state is outside the scope of this paper. However, recent work in Hong Kong University (McFadzean and Ong, 1966) has incriminated *S. typhi* in the aetiology of recurrent pyogenic cholangitis and has shown that this condition is occasionally associated with the carrier state. Unfortunately, our subjects were not specifically asked about recurrent pyogenic cholangitis; nevertheless it is of interest that two of the series were still excreting the organism several weeks after cholecystectomy and lavish courses of chloramphenicol.

It is not possible to make an accurate estimate of the number of carriers in the colony, and the following figures are put

forward with appropriate reserve. Contacts of cases of bacillary dysentery are screened by single stool culture. In one area during 1965 the contacts aged 14 or over numbered 584 and stool culture from these detected three confirmed typhoid carriers, or 1 in 195. Presumably the fact that most carriers excrete intermittently makes it likely that others were missed. A correction for this factor can be made on the basis of figures published in the P.H.L.S. Report, in which serial stool cultures of 29 carriers showed that one stool culture would detect an average of 57% of the carriers. If this correction is applied the estimated frequency of carriers in Hong Kong is 1 in 111, or 9 per 1,000 of the population aged 14 or over.

The 17 examples listed in Table IV were collected during the 18 months' routine practice of one infectious diseases hospital. The criteria applied were intentionally rigid. Before a case was accepted the diagnosis had to be confirmed on an inpatient basis to avoid substitution of stools. The usual predominance of elderly women was confirmed, 15 of the subjects being women, only five being under 50 years of age. With two exceptions (Cases 11 and 13) all the carriers, even on direct questioning, denied ever having suffered from any illness resembling enteric fever. Case 6 is of particular interest because this patient was the only excreter found among seven ice-cream vendors with positive Vi titres (five had titres of 128, two of 64), and was in fact the only carrier detected through the Vi titre. As a special research project these ice-cream vendors were intensively investigated as inpatients. Even in these special circumstances the false-positive Vi rate in this group was over 85%, which is fairly close to expectation on our other findings.

On the few occasions when it was possible to estimate the Vi titre over a period of months a disconcerting fluctuation was observed. Similar variations have been noted elsewhere (Toussaint, 1966), and it would seem highly desirable to have further information on this important point. In the normal practice of epidemiological screening it is possible to do only one estimation of the Vi titre, therefore in this paper only the initial reading is discussed.

Taking the upper limit of normal in Hong Kong as 32, there were 9 carriers (53%) with titres above this level.

TABLE IV.—*Proved Excretors of S. Typhi*

Case No.	Sex	Age	In-patient Cultures			Remarks
			Urine	Stool	Vi Reaction	
1	F	64	—	+	64	History negative
2	F	61	—	+	32	" "
3	F	70	—	+	128	" "
4	F	73	—	+	32	" "
5	F	58	—	+	16	" "
6	F	40	—	+	128	" "
7	M	59	—	+	64	Postcholecystectomy. History negative
8	F	58	—	+	16	History negative
9	F	72	+	+	16	" "
10	F	32	—	+	64	" "
11	M	48	—	+	16	Typhoid 6 months previously
12	F	63	—	+	8	History negative
13	F	68	—	+	128	Typhoid 4 years ago
14	F	63	—	+	64	History negative
15	F	32	—	+	32	" "
16	F	36	—	+	64	" "
17	F	61	—	+	128	Postcholecystectomy. History negative

Discussion

Felix (1938) stated that a Vi titre of 5 was significant in England. Since then a number of papers have been published in which the test has been described as "positive" or "negative" on this basis. In Hong Kong this approach would give a figure of 93% of the population as positive, a relatively useless figure for practical purposes. It seems much more useful to treat the test as being similar to a biochemical test with a normal range in the community and a normal upper limit of 32. This accords with the views expressed by the late Dr. Felix regarding

the TO titre. "In numerous discussions . . . [he] claimed that anything below 100 was insignificant and that 100 was only slightly suspicious. He regarded 200 as being the upper limit of the so-called 'normal' TO titre." (P.H.L.S.W.P., 1961).

The figure of 32 is much higher than the usually accepted upper limit of normal. Eliot (1940) took 20 as suspicious of the carrier state in the U.S.A. Horgan and Drysdale (1940) accepted 10 as the upper limit of normal for the Sudan, while even in India 25 has been regarded as positive (Bhatnagar, 1938). Probably of even greater significance is the fact that only a minority of proved excretors in the British Isles have titres of over 40. In the series reported by P.H.L.S.W.P. (1961) only 4 out of 24 cases were above this level.

In the diagnosis of the acute case in Hong Kong the Vi titre is of little or no value, for the following reasons: (a) the margin is narrow between levels reached in the disease and titres obtained in normal subjects; (b) positive titres are often obtained only at a late stage; and (c) in 25% of cases the reaction does not become positive. The possible exceptions to this assessment are those very few cases where the Vi titre is raised while the O titre remains negative.

For the purposes of anticipating or diagnosing a relapse the Vi titre was of no help. The exact mechanism of the relapse in typhoid is obscure. Nevertheless, it is usually accepted as being due to a resurgence of the organism which has been temporarily controlled by antibiotic therapy or the natural defences of the body. Moreover, it is generally taught that high-level or rising titres imply the presence of living *S. typhi*. Therefore, according to theoretical considerations, relapses should be associated with high Vi titres. However, among the 14 examples of relapse which occurred in the series, no statistical correlation with the Vi titre could be demonstrated. Furthermore, from a clinical point of view, it can be categorically stated that the Vi reaction is of no assistance in forecasting relapses in Hong Kong.

In a follow-up of the acute cases to detect the incipient carrier state the Vi titre was approaching the normal distribution of the general population in Hong Kong by the 37th to the 48th week after illness. Since no carriers were detected in this group, no comment can be made on the value of the Vi titre for this purpose.

In the detection of the chronic carrier the Vi test is essentially a screening test, the value of which is related to two main features:

1. *Accuracy or Specificity of Test.*—Though Vi antigen is usually found in cultures isolated from human infections, a Vi antigen characteristic of the form occurring in *S. typhi* is also known to occur in many strains of *Salmonella* and other Gram-negative bacteria, many of which are non-pathogenic species (Wilson, 1928; Luippold, 1944). These include *S. paratyphi* A, B, and C, *S. typhimurium*, some strains of *Escherichia coli*, and the Ballerup group of paracolon bacilli. *S. paratyphi* A and *S. typhimurium* are relatively often found in Hong Kong. Though such Vi antigens often differ in specificity, it is of interest that immunization with strains of the Ballerup group can produce antibodies affording some protection against virulent typhoid bacilli (Longfellow and Luippold, 1943). It seems likely that the prevalence of some of these organisms in Hong Kong may account, in part at least, for the frequency of false-positive Vi titres in the general population.

2. *Time and Effort Saved by Using Vi Test in place of Stool and Urine Cultures, which it replaces.*—To assess the time and effort saved by the Vi test, the following points must be determined: (a) the range of the Vi titre in the normal population (this determines the upper limit of normal and the percentage of false positives), (b) the incidence of the carrier state in the population, and (c) the false-negative Vi rate among the carriers.

If we consider the extremely hypothetical exercise of screening 100,000 of the adult population of Hong Kong by Vi titre we would expect the group to contain 900 carriers, of whom 53%, or 477, should have positive Vi titres. A further 4% of the total—that is, 4,000 normal people—would also be Vi positive. If single stool cultures were carried out on the 4,477 people 57%

of the 477 carriers present should be detected—that is, 271. Thus 100,000 Vi titres would have saved 95,523 stool cultures as compared with screening the whole group by stool culture, though 513 carriers would have been detected by the later method (57% of 900).

A similar exercise in Britain would result in 100,000 Vi titres saving 98,829 stools, with a 40% chance of detecting the one expected carrier. (Calculated from figures in the P.H.L.S.W.P., 1961).

To put it in another way which takes no account of the number of carriers who are missed, the group with positive Vi titres contains in Hong Kong 477 carriers in 4,477 people, or a carrier rate of more than 1 in 10, as compared with a carrier rate of 1 in 111 in the general population. In Britain the Vi-positive group has a carrier rate of 1 in 1,171, as compared with 1 in 100,000 in the general population.

For screening special groups in which a missed carrier would constitute a serious risk to the community it would seem appropriate to concentrate first on the positive Vi reactors and then to carry out stool and urine culture on the negative Vi reactors. If the ideal of three stool and urine cultures—expected to detect 72% of carriers (P.H.L.S.W.P., 1961)—is not practicable at least one culture of each kind would offer a good prospect of detecting the most dangerous type of carrier in whom excretion is practically continuous. For larger groups the Vi test is the only practical screening test available.

The assessment of the value and limitations of the Vi test in different circumstances calls for judgement based on consideration of all the factors involved, theoretical and local.

In general it can be said that the Vi test is less reliable as a screening test in Hong Kong than in Britain, though the increased incidence of carriers in Hong Kong results in a greater number being detected. Other countries for which figures are available appear to come somewhere between these two extremes. We consider that our findings confirm the need to make a fresh assessment of the value of the Vi test for each area.

Summary and Conclusions

The upper limit of normal for the Vi titre in Hong Kong has been assessed at 32. Four per cent. of the population showed titres above this level. These figures are higher than have been recorded elsewhere.

In a series of 75 proved cases of typhoid the Vi reaction was found to be of no value either in the diagnosis of the acute attack or in the forecasting of clinical relapses.

The carrier rate in the adult population of Hong Kong has been estimated to be in the region of 9 per thousand (1 in 111).

The Vi test makes it possible to suspect 53% of the carriers in Hong Kong. However, the presence of 4% false positives adds considerably to the amount of work required to confirm the carrier state.

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The Thymus in Systemic Lupus Erythematosus: a Quantitative Histopathological Analysis and Comparison with Stress Involution*

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The recent demonstration that the thymus is concerned with the function of the immune system has stimulated interest in thymic pathology. Burnet (1962) found germinal centres and “lymphocyte proliferation” in the thymic medulla of NZB mice with autoimmune haemolytic anaemia; he speculated that “the forbidden clones concerned with systemic lupus erythematosus arise in the thymus and that in an early untreated case the thymus would be found to be enlarged and to contain numerous lymphoid follicles.”

Mackay, Masel, and Burnet (1964) and Burnet and Mackay (1965) reported two cases of systemic lupus erythematosus with abnormalities in the thymic medulla, these being aggregates of epithelial cells and numerous plasma cells in one case and

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typical germinal centres in the other, and Hutchins and Harvey (1964) described 13 cases in which the medulla contained epithelial aggregates and numerous plasma cells. Goldstein and Mackay (1965) made a quantitative study of the thymus in systemic lupus erythematosus; the significant changes included cortical atrophy, epithelial cell aggregates in the medulla, cystic Hassall's corpuscles, and numerous plasma cells. However, we could not be sure of the specificity of these changes, since the histological appearance of the thymus changes greatly with age and stress (Hammar, 1921). We therefore analysed quantitatively the thymic changes in 198 control cases grouped according to age and the expected degree of stress involution. With this basis for comparison we found that the thymus in systemic lupus erythematosus showed the combined features of extreme involution and of immunological reaction within the medulla.

Cases Studied and Controls

The thymus was obtained from 13 patients with classical clinical and serological features of systemic lupus erythematosus. All the patients were females aged from 15 to 56 years; there were three surgical specimens (Mackay and Smalley, 1966) and