Summary and Conclusions

The results of internal pneumolysis in an unselected group of 235 cases, in 50 per cent. of which the disease was far advanced, are reported, including twenty with bilateral artificial pneumothorax.

Division of all adhesions was possible in 34 per cent. of pneumothoraces operated on, and partial division in 55 per cent.; 11 per cent. were inoperable.

Radiologically satisfactory results were obtained in 39 per cent., 14 per cent. were improved but not satisfactory, 28 per cent. were unaffected, and in 19 per cent. partial or complete symphysis followed the operation.

In the group of 140 pneumothoraces in which only partial division of adhesions was possible, a satisfactory collapse followed the operation in 28 per cent.

Medial subapical adhesions rarely interfere with efficient collapse where the apex of the lung is below the clavicle in the upright position.

Lateral or lateral apical adhesions may be usefully divided in patients with inoperable medial apical adhesions or apical symphysis in the presence of patent cavities below the level of the clavicle.

Satisfactory results were most frequent with limited lesions in apyrexial patients.

Apart from effusions, complications were rare. Following 260 operations, effusions occurred in 32.8 per cent. of operations (8.4 per cent. transient, 10.9 per cent. persistent TB negative, 13.5 per cent. persistent TB positive). Transient effusions did not materially affect the result of the operation. Results were poor where the operation was followed by persistent effusions, particularly those in which tubercle bacilli were present and the incidence of partial or complete obliteration was high.

Effusions were most common in cases with advanced disease, any degree of pyrexia, rapid sedimentation rates, or in cases where extensive cauterization was carried out. Consideration of the first three of these factors is of importance in estimating the probability of effusion following the operation.

The radiological diagnosis of an inoperable apical symphysis in forty-six cases was confirmed by thoracoscopy. Apart from this group, radiological examination was unreliable in determining the position or extent of the adhesions present. Stereoscopic examination was more reliable than fluoroscopy and antero-posterior films, but was not of enough value to warrant routine use.

Facilities for intrapleural pneumolysis are essential for the proper conduct of artificial pneumothorax treatment, and the operation may be of value even in advanced cases.

The place of double artificial pneumothorax and phrenic evulsion in intrapleural pneumolysis is indicated.

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Disturbances of Epiphyseal Ossification.—The hip-joint is the site at which hereditary disturbances of epiphyseal ossification may most often be found, but any epiphysis in the body may be affected. The condition has to be differentiated from Perthes's disease and allied abnormalities, but the non-traumatic form of osteochondritis dissecans is thought by the author to be closely related to it.—Multiple Hereditary Disturbances of Epiphyseal Ossification. W. Müller.—*Z. Orthop.*, May 30, 1939, 69, 257.

LABORATORY METHODS IN THE
DIAGNOSIS AND CONTROL OF FEVERS
OF THE ENTERIC GROUP*

BY

J. S. K. BOYD, M.B., Ch.B., D.P.H.
Lieutenant-Colonel R.A.M.C.

In a very brief paper such as this it is impossible to do more than touch on a few of the principal points in which progress has been made in diagnosing and controlling fevers of the enteric group. To those who practise at home it may seem that the existing methods of laboratory diagnosis are adequate and satisfactory, but unfortunately in subjects who have been inoculated with typhoid-paratyphoid vaccine—and this includes practically all Europeans living over-seas—the usual serological tests give very equivocal and unreliable results. In the accompanying table the figures for the British and Indian Armies for the last ten years are shown. The cases classified as "enteric group" have been diagnosed on serological or clinical grounds, and there is good reason to believe that a considerable proportion of them are not true enteric group fevers. It is unlikely that there will be any notable increase in the number of cases diagnosed by cultural methods; for, in the Army, blood culture as well as faeces and urine culture is pursued relentlessly. In outbreaks of typhoid or paratyphoid fever, isolations are made from practically 100 per cent. of the cases: the enteric group cases in the table are mainly sporadic cases,

Table showing Incidence of Enteric Group Fevers in the Army in India (British and Indian Troops Combined)

	1928	1929	1930	1931	1932	1933	1934	1935	1936	1937
Typhoid { Cases	227	293	200	176	161	137	105	82	43	42
Deaths	33	41	21	25	21	26	16	16	5	?
Para A { Cases	45	58	68	64	67	52	53	59	27	25
Deaths	—	—	1	3	1	1	—	3	—	?
Para B { Cases	18	9	6	10	10	3	4	1	2	2
Deaths	—	—	—	—	—	—	—	—	—	?
Para C { Cases	4	12	9	4	1	3	3	—	1	—
Deaths	—	2	1	—	—	—	—	—	—	—
Enteric Group { Cases	264	237	218	240	205	222	148	128	80	55
Deaths	12	9	9	11	10	10	6	3	3	?
Total { Cases	558	609	501	494	444	417	313	270	153	124
Deaths	45	52	32	39	32	37	22	22	8	?

in many of which the diagnosis has been made because nothing else seems to apply. It is obvious that a serological test capable of giving reliable positives and negatives would be of the greatest value.

The usual agglutination test made with suspensions of H or flagella antigen, eminently successful in the un-inoculated, has now been completely given up in the military laboratories of India, for it has been conclusively shown that, in subjects inoculated with typhoid-paratyphoid vaccine, febrile conditions other than enteric group fevers produce an anamnestic rise of agglutinins not to be distinguished from that given by enteric infection. Routine tests are now being performed with suspensions of O antigen. These are undoubtedly more specific in their indications, being less influenced by the stimulus of non-

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enteric infections. Unfortunately the response is somewhat sluggish, and with Dreyer's technique many proved cases fail to show a diagnostic rise in agglutinin. Trials are now in progress using the more delicate technique advocated by Felix, and the results obtained to date give reason for hope that more reliable information will be forthcoming from this test.

The Vi Agglutination Test

The most recent method of serological diagnosis, which applies at present only to typhoid and not to paratyphoid infection, is a test for the presence of agglutinins for the virulence or Vi antigen, first described in detail by Felix. This test has a more complicated technique owing to the instability of the antigen. The original and probably the most delicate method of performing the test is with suspensions of living organisms, but difficulties in standardization and in reading the results make this a method for the expert. An alternative technique has been provided by the discovery of strains of *typhosum* which are devoid of H and O antigen and possess only Vi antigen. Preparations of such strains can be preserved by formalin without losing their properties, and in this way standardized suspensions can be prepared and issued from a central laboratory.

The Vi agglutination test was first used by Felix for the detection of carriers. In fifty-six chronic carriers he found Vi agglutinins present in every case, although in forty-seven the titre was 1 in 20 and under: with few exceptions all controls were negative. I am indebted to my colleague Major H. J. Bensted, M.C., R.A.M.C., for some data, not yet published, on the results of this test carried out at the Enteric Laboratory, Kasauli, India. In the small number of permanent carriers which were investigated, appreciable amounts of Vi antibody were found in every case. In temporary and convalescent carriers, however, approximately half the cases failed to show Vi agglutinins despite the fact that the organisms were readily recovered from the stools. It would therefore appear that this test is likely to be of great assistance in detecting permanent carriers, but cannot be trusted to give a reliable negative in the routine examination of convalescents before discharge from hospital.

More recently Bhatnagar has applied this test to the diagnosis of cases of typhoid fever, and claims to have obtained an easily detected response in inoculated subjects and a less obvious result in uninoculated natives. The Vi agglutinins appear early and disappear quickly. Bensted, in investigating cases of typhoid fever proved by isolation of the organism, found that about 25 per cent. failed to show any Vi agglutinin when examined at short intervals beginning at the seventh day. In a small number of cases serum was obtained between the first and fifth days: in all of these Vi agglutinin was demonstrated in appreciable amounts. It would therefore appear that this test may be of considerable diagnostic value in the early days of the disease, and further investigations along these lines are being carried out.

Typing with the Vi Bacteriophage

In the realm of epidemiology a notable and important advance has recently been made by Craigie in the discovery of bacteriophage which has a specific action on virulent strains of *Bact. typhosum* (Kauffmann's V forms). Craigie has described four serologically different bacteriophages, and of these one, Type II, is of particular impor-

tance from the point of view of epidemiology. This phage has the property of becoming conditioned to the particular strain of *Bact. typhosum* on which it is propagated. Thus if it is propagated for some generations on the Rawlings strain it acquires a high titre for this strain, but shows a low titre for another well-known strain, Ty 2. If this same phage is now propagated for some generations on Ty 2 the position is reversed: it develops a high titre for Ty 2 and loses in large measure its power to lyse Rawlings. Extending these observations over a large number of strains, Craigie has differentiated at least thirteen phage-types of *Bact. typhosum*, some common, some rare, for each of which he has prepared a specific bacteriophage. He has also encountered a small number of strains, probably intermediate between virulent and non-virulent forms, which cannot be typed in this way. These he names "imperfect V forms."

Once the different conditioned phages are available it is a simple matter to type any strain of *Bact. typhosum*. To observe the action of the bacteriophage, a loopful of young broth culture of the organisms to be tested is spread with a standard platinum loop over an area the size of a sixpence on an agar plate. When this has dried, a drop of phage, also from the standard loop, is placed without spreading in the centre of this patch and allowed to dry. The plate is then incubated for two hours, stored in the cold room overnight, and reincubated next day. The results will be obvious in from four to six hours, and may show either a complete confluent patch of lysis the size of a drop of phage or varying numbers of small discrete plaques, or absence of any obvious lysis. For test purposes each of the different phages is carefully titrated and diluted to the strength which against its homologous type will just give a confluent patch of lysis. This "critical test dilution" usually lies between strengths of 1 in 100 and 1 in 10,000 of the original phage, and has little or no action on heterologous types—at most it produces an occasional pinhead plaque which need cause no confusion.

To type an unknown strain a series of patches are sown, from a young broth culture, on an agar plate. These are spotted separately with the different type phages, and incubated as described. A disk of lysis is produced by the phage of the type to which the strain belongs. The phages used are phage I (a polyvalent phage not hitherto mentioned, included to confirm that the strain under test contains Vi antigen) and phage II B₂, C, D₂, E₂, F₂, G, H, and J. Phage A is omitted, as *typhosum* Type A is equally susceptible to the action of all phages. Phages B₂, D₂, E₂, and F₂ act equally on Types B₁, D₁, E₁, and F₁ respectively. If the strain being tested is lysed by one of these phages it must be further tested with phage B₁, D₁, E₁, and F₁, as the case may be: these are strictly specific for their homologous types. Imperfect V forms will be lysed by phage I and imperfectly by some of the phage II types. W forms will show no lysis at all.

Accumulating experience goes to show that the phage type of a strain is a permanent character, unaffected by passage through the human being, by artificial passage through laboratory animals, or by artificial culture. Thus the Ty 2 and Rawlings strains, which are in use in various parts of the world, have proved to be Types E and F respectively, wherever tested. The Rawlings strain now used at the Royal Army Medical College has been passed through mice on innumerable occasions, and still remains F; while in outbreaks of typhoid fever the organisms recovered from all cases prove to be alike, and repeated isolations from the same case are also of one

type, although occasionally imperfect V forms and W forms may be recovered from a case which also shows V forms of a definite type. This, of course, is a quantitative and not a qualitative difference in antigen.

Applications of the Bacteriophage Test

The applications of this test are manifold. It affords evidence which may either link up on a suspected carrier with an outbreak or may disprove his connexion with it. Thus the strain which caused the Croydon outbreak was Type D. The carrier suspected of having fouled the water supply which spread the infection also harboured an organism of Type D.

Recently the laboratory assistant of a colleague, who is engaged in the preparation of typhoid-paratyphoid vaccine, developed typhoid fever twelve days after he returned from leave. The question of laboratory infection naturally arose. The strains in use in the laboratory were Rawlings and Watson (F), Ty 2 (E), and a strain called Giglioli, which proved to be A. The strain recovered from the attendant was C, thus proving that the infection had not been acquired in the laboratory, but was probably picked up while he was on leave.

A short time ago an outbreak occurred in Birkenhead which was traced to an infected milk supply; but one case, occurring under rather different circumstances, could not be fitted into this picture. The associated cases of the outbreak proved to be caused by Type E. The anomalous case harboured Type D, thus confirming that it was a sporadic case of different origin.

In commenting on Craigie's work an annotation in the *British Medical Journal* (1938, 2, 1212) suggested that his methods were unlikely to come into common use, presumably in the belief that the test was very intricate. This is far from being the case, and I hope that the remarks I have made and the demonstration I have put out will dispel this idea and will show that the test is simple and the results refreshingly clear-cut.

To summarize, we have in the Vi agglutination test a promising method of detecting permanent carriers, and in Vi bacteriophage an extremely delicate and accurate means of studying certain aspects of the epidemiology of the disease.

The Joint Committee set up under Subsection (1) of Section 4 of the Therapeutic Substances Act, 1925, has made further regulations (Statutory Rules and Orders, 1939, No. 1395). These Therapeutic Substances Amendment Regulations, 1939, come into operation on December 1 next. They require every holder of a licence to manufacture therapeutic substances, who for any purpose engages in the culture or manipulation of pathogenic spore-bearing micro-organisms, to provide separate laboratories and utensils and apparatus for the culture or manipulation of such micro-organisms. These laboratories and appliances are not to be used for the manufacture of any other therapeutic substance. Part I of the attached schedule lays down provisions applicable to tetanus toxoid, and Part II provisions applicable to gas-gangrene antitoxin. Tetanus toxoid is defined as "tetanus toxin (the sterile filtrate from a culture on nutrient broth of *Clostridium tetani*) the specific toxicity of which has been completely removed by the action of chemical substances in such a manner that it retains efficient properties as an immunizing antigen. Its proper name is 'tetanus toxoid.'" Gas-gangrene antitoxin is defined as "the serum, or the antitoxic globulins, separated from the blood of animals which have been immunized against the specific toxin prepared by the growth of *Clostridium histolyticus* in a fluid medium. The proper name of the substance is 'gas-gangrene antitoxin (histolyticus).'"

CANCER: A CONSIDERATION OF CURABILITY AND OF THE ROLE OF RADIOTHERAPY IN TREATMENT*

BY

RALSTON PATERSON, M.D., F.R.C.S., F.F.R.

(From the Christie Hospital and Holt Radium Institute, Manchester)

The main purpose of this paper is to try to analyse the part which radiotherapy is capable of playing in the treatment of malignant disease, and to consider certain of its limitations. The term "radiotherapy" should be used to include both radium and deep x-ray therapy; to obtain maximum efficiency of treatment policy these agents must be in the same hands. In particular I feel that the respective fields of surgery and radiotherapy—and these two between them remain the only available methods of curing cancer—are much better defined than is generally supposed. Analysis of the proper part which each should play is therefore practicable. Certain of the ideas which I propose to lay before you were suggested by study of a most interesting Ministry of Health publication, "Cancer: An Inquiry into the Extent to which Patients receive Treatment," by Sholto Mackenzie.† I shall have occasion to make frequent reference to that report.

The best approach to the main theme of the role of radiotherapy in malignant disease seems to require as preliminary some consideration of the more basic questions of the extent to which malignant disease is normally curable by any means; to what extent it calls for some treatment even though not necessarily curative in intent; and, lastly, the extent to which in spite of all our knowledge and accomplishments of the last twenty-five years cancer is still a hopeless disease. In Mackenzie's report the subject was approached from the completely objective standpoint of finding out the extent to which certain types of cancer were in fact receiving treatment in this country to-day, as assessed from a detailed analysis of all the cancer deaths in a number of sample areas, no account being taken of possible cured cases. It seemed to me, however, that collateral evidence of value could be built up from a rather more subjective point of view by considering how far the various methods and technical facilities at our command have been proved in practice to be effective or otherwise in dealing with each of the known types of malignant disease.

This subjective survey shows that for each disease type the many manifestations of malignancy fall into groups so near those proposed by Mackenzie that I have taken his three groups as a satisfactory index of the present-day state of affairs. These three groups are shown in Tables I, II, and III. It must be noted that the percentages shown on these tables are not results of treatment, but are the percentages of all cases of registered cancer deaths in the sample communities tested which were found to have received treatment. For his analysis Mackenzie took "treatment" to mean treatment of practically any sort, except palliative surgery, under-

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† Reports on Public Health and Medical Subjects, No. 89.