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On the Value of the Tuberculo-opsonic Index in Diagnosis,

by

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In November, 1905, a paper by Dr. A. E. Wright and Staff-Surgeon S. T. Reid,^① discussing the "Possibility of determining the presence or absence of tubercular infection by the examination of a patient's blood and tissue fluids", was read before the Royal Society. The printed report in the "Proceedings of The Royal Society" did not reach me till several months later, and by that time a great part of the work for this Thesis was completed. Some of my investigations proved to have been over ground already covered by Wright and Reid, but this could not be considered a matter for regret as a very large collection of cases is obviously required before anything regarding the diagnostic value of the opsonic index can be either definitely proved or disproved.

These investigations were, therefore, pursued as originally intended and were supplemented by several new subjects of inquiry suggested by this very interesting paper, to which I am greatly indebted for clearing the ground and bringing order out of a somewhat chaotic collection of facts.

Two new points in particular were suggested by this paper: (a) The value of the heat test, and (b)

the
 The value of Δ differential test applied to the blood serum and to the fluid from an abscess or from a pleural or peritoneal exudate in the same patient. To these I shall allude later.

To the "Lancet" of December 9th, 1905, Dr. Lawson and Dr. Stewart ⁽²⁾ of Banchory contributed a paper entitled "A study of some points in relation to the administration of Tuberculin (TR)", and one section of this dealt with the possibility of diagnosing pulmonary tuberculosis by means of the opsonic index. They gave statistics of a large number of tubercular cases - all of them pulmonary - and the results yield an interesting comparison with my series of tubercular cases, of which the great majority are examples of so-called "surgical tuberculosis". To this paper also I shall refer further on.

The objects of the present research are:-

- (a) To determine whether there is a definite level at which the tuberculo-opsonic index stands, and beyond the limits of which it is never found, in healthy persons.
- (b) To study the tuberculo opsonic index in persons suffering from diseases other than tuberculosis
and/

and note its characteristics under these circumstances.

Also to determine, if possible, whether a so-called "tubercular heredity" or "predisposition" alters the index.

(c) To examine the index in persons known to be definitely tuberculous with a view to discovering whether it has any peculiar or distinguishing features.

(d) To compare and contrast the results got in (a), (b) and (c) so as to ascertain, if possible;

I Whether there are any levels of index which may be said to be Pathognomonic of tubercular infection and II If so, whether these levels are found in all cases of Tuberculosis.

It is obvious that if by an experimental method, such as the testing of an opsonic index, one could make, or negative, or confirm the diagnosis of tubercular disease, the fact would be of considerable clinical importance. Cases are constantly occurring in the practice of the surgeon, as well as of the physician, and in the province of the ophthalmologist, the aurist, the dermatologist (and, in these days, probably one should/

should also add, of the sociologist) where a definite statement as to the presence or absence of the Tubercle Bacillus is urgently called for and where, in the present state of our knowledge, it cannot possibly be given. I shall proceed at once to state the results of my research and shall consider at the end how far the opsonic index is capable of supplying the answer to these enquirers.

(a) Is there a definite level of the opsonic index in healthy individuals?

Three different series of observations on this point have been reported and the results are fairly uniform.

③ Bulloch examined the blood of 66 healthy people and found the index in some cases as low as .8 and in others as high as 1.2, but in no case beyond these limits. The average is .96

④ Urwick examined 20 healthy cases and agreed with Bulloch as to the limits being .8 to 1.2. His average was 1.006.

Lawson and Stewart (op.cit.) examined 25 healthy cases and found the limits to be from .9 to 1.2, except in one case which gave an index of 1.4. In no case did they/

they get a healthy index as low as .8. The average was 1.0.

I have tested the opsonic indices of 41 healthy persons and have arranged the results in the following table:-

Table I. Tuberculo-opsonic power of the blood in 41 healthy persons.

No.	Initials.	Opsonic Index.
1	D. T.	1.2
2	D. C.	1.1
3.	M. R.	1.1
4.	P. F.	1.1
5.	C. D.	1.1
6	M. H.	1.1
7	O. S.	1.1
8	A. F.	1.09
9	J. McF.	1.09
10	M. B.	1.07
11	D. T. F.	1.05
12	J. L.	1.05
13	J. L. T.	1.00
14	D. D.	1.00
15	G. M.	1.00
16	M. B.	1.00
17	D. N.	1.00
18	J. S.	1.00
19	A. B.	1.00
20	A. T.	1.00
21	A. F.	1.00
22	J. F.	1.00
23	M. McC.	1.00

No.	Initials.	Opsonic Index.
24	M. J. R.	1.00
25	J. R.	.96
26	D. H.	.93
27	J. Y.	.92
28	M. F.	.91
29	D. McC.	.90
30	D. McG.	.90
31	D. S.	.90
32	R. K.	.90
33	T. M.	.90
34	J. McC.	.90
35	J. D.	.89
36	J. R.	.89
37	J. G.	.85
38	W. A.	.84
39	B. R.	.84
40	P. L.	.80
41	W. F.	.80

The average in this series is .98. The variation is from .8 to 1.2, as in Bulloch's cases. In no healthy person have I found an index beyond these limits.

The question as to whether the index of a healthy person varies at all from time to time is also of considerable importance when we attempt to get a standard for comparing the indices of the healthy with the indices of the diseased (~~Opsonic~~).

indices of the diseased. Urwick (op.cit.) has investigated this point, and he states that "the opsonic power of healthy people varies very slightly, or not at all, from day to day". On the other hand, Dr. G. G. Ellett⁽⁵⁾ has taken the opsonic index of the blood of men training for a boat race with the view to discovering the effect of bodily exertion on the opsonic index of healthy persons, and he states that after hard rowing the index is lowered. His report, however, includes only two cases, and therefore does not justify any conclusion.

In three of my healthy cases I made repeated examinations of the blood on different days and found the variation to be practically the same as the variation got between the indices of different healthy people examined on the same day. I am inclined to believe that, although there may be a slight variation in the level of the index in different healthy individuals and that although there may also be a variation within ~~slight~~ certain limits in the level of the index of a single healthy individual at different times, these figures do not accurately represent it. This fluctuation/

fluctuation probably represents the varying "personal equation" rather than an exact variation in the opsonic content of the blood. However, this is an element that must be reckoned with in any case, for it is evident that, when one is dealing with such minute quantities as require to be measured and with such sustained eye-strain as is necessary for the estimations, something will certainly depend on the steadiness of one's hand and the acuteness of one's eyesight. But, whether these limits of .8 to 1.2 are taken as circumscribing the field of the healthy opsonic index or as bounding the fallibility of the operator, it is at least noteworthy that, as far as present observation goes, there are such limits, and that in the series of 152 reported cases, there is no instance of a healthy blood giving an index beyond this range.

Table II Showing the variation in the opsonic index of the blood of healthy persons on a succession of days.

No.	Initials.	Opsonic Indices.										
1	J. A. C.	1.10	1.03	1.00	0.88	0.90	1.00	1.00	0.90	1.00	0.92	
2	D. McC.	0.90	1.20	1.00	1.10	1.20	0.85	0.92	0.97			
3	R. K.	0.90	0.90	1.06	0.92	1.09						

(b) Does the tuberculo-opsonic index in diseased persons - other than tuberculous patients - correspond with that

found in healthy individuals? Or does the presence of
a diseased condition, or of an infection due to ~~the~~
another micro-organism, alter the opsonic index of
the blood to the Tubercle Bacillus?

This is a subject on which, up to the present time, clinical evidence is lacking. Some valuable experimental work has recently been done by Bulloch and Western^⑥ on the "Specificity of Opsonins", and they have found that, when a micro-organism is brought into contact with normal human serum and digested for one hour at 37°C., the serum loses its opsonic power for that particular micro-organism but keeps its opsonic power for other micro-organisms practically intact. Applying this clinically, e.g. to a case of typhoid fever, one might expect to find that the quantity of tuberculo-opsonin in the blood would not be diminished by the presence of the Bacillus Typhosus. However, there is the further question to deal with: Does a condition of disease in the body not interfere with the production of tuberculo-opsonin? In the abnormal conditions prevailing in the body of the typhoid patient, is the production of tuberculo-opsonin normal? The same question may be asked in the case of any

disease at all. For instance, one might very reasonably ask, in the case of advanced malignant disease, whether, in the condition of anaemia and cachexia produced, the tuberculo-opsonic substance remains unaltered.

These are questions of great importance in deciding on the diagnostic value of the opsonic index; if an abnormal index may mean either tuberculosis or some other disease, then manifestly its value is reduced to something infinitesimal.

With a view to elucidating this subject I have examined the tuberculo-opsonic index of the blood in 43 cases of disease definitely non-tubercular. The first 23 cases were taken at random in the Hospital Wards; the remaining cases were selected as being more likely to yield a positive result.

There are certain diseases which are generally recognised as "predisposing" to tuberculosis; of these I chose Measles, Whooping Cough, Pneumonia and Diabetes, with the object of discovering whether the index was altered in any way.

From Table III it will be seen that in the non-selected cases the index was without exception within the normal limits. In the selected cases, however,

while the majority were found to be normal, there were a few instances of indices which were definitely abnormal. In my four cases convalescent from Measles - a disease well known to be the frequent precursor of tubercular disease in children - the index was normal. In the five cases of Whooping Cough, however, there is one quite marked exception with an index of 1.5. There was no evidence of tubercular infection about the child; she was convalescent and looked fairly healthy. Had the index been low it might have been explained as the factor in measles which predisposes to Tuberculosis, but, as it stands, it is difficult to explain on any of the theories which have so far been set forth.

Pneumonia was taken as another example of a disease

? which is not infrequently followed by Tuberculosis.

*The Tubercle is
there before
the pneumonia*

Of the six cases recorded, four gave a normal index and two an abnormal. The case of G. K. is specially interesting; he had had pneumonia and about the eleventh day, as the temperature remained high, I was asked to examine the opsonic index. This was found to be .57; tubercular infection was therefore suspected and was confirmed within a few weeks by the clinical course of the case. The other case "J. B." had had his

crisis seven days previously and was doing well; there was no evidence of tubercular infection.

Diabetes was the next disease chosen for examination on account of the fact that Tuberculosis is known to be the terminal event in quite a large proportion of the cases. The blood of five different patients was examined; in three cases the index was normal; in two it was subnormal. Case 30, "J. J.", was able to be about and was apparently doing well. "P. McL.", Case 34, was confined to bed and appeared to be going steadily downhill, but there was no definite indication of tubercular disease.

I do not attempt to draw any deductions from these abnormal indices; I merely record them for the purpose of shewing that such an index may be got in a patient who is suffering from a disease other than Tuberculosis.

Table III. Tuberculo-opsonic power of the blood in forty-three persons suffering from disease other than Tuberculosis.

No.	Initials.	Disease.	Tuberculo-opsonic index.			
1	M. H.	Anaemia	1.00	0.94	1.10	
2	M. F.	Emphysema & Bronchitis	1.00			
3	C. K.	Pleurisy (Pneumococcal)	0.80	0.80		
4	M. G.	Cystitis (B. Coli)	1.10			
5	B. R.	Injury to Hip Joint	0.84	1.16		

Table III continued.

No.	Initials.	Disease.	Tuberculo-opsonic index.			
6	J. R.	Acute Rheumatism	0.89			
7	J. S.	Gastritis. emaciation, etc	1.10	1.00		
8	M. McC.	Acute Suppuration	1.00			
9	B. G.	Sarcoma.	0.81			
10	J. McF.	Abscess (Staphylococcus)	1.09			
11	O. S.	After amputation of arm for accident.	1.10			
12	J. G.	Fractured Femur.	0.85			
13	W. A.	Injuries from accident.	0.84			
14	M. M.	Malignant disease of Bowel	0.90			
15	A. C.	Enteric Fever.	0.90			
16	P. G.	Enteric Fever.	0.90			
17	A. K.	Osteomyelitis.	1.15			
18	J. S.	Malignant disease of Stomach.	1.10	1.20	0.90	0.90
19	B. McC.	Cerebro-spinal Meningitis.	1.20			
20	W. C.	Osteomyelitis (radius).	1.20			
21	J. S.	Osteomyelitis (tibia)	0.80			
22	M. S.	Fistula in ano (non- tubercular).	0.80			
23	A. Y.	Rickets.	0.92			
24	A. M.°	Pneumonia (8th day).	0.85			
25	J. H.	Pneumonia (6th day).	1.10			
26	A. C.	Pneumonia (9 days after crisis; very well).	0.90			
27	A. B.	Pneumonia (7 days after crisis; very well).	0.66	0.60	■	
28	A. McL.	Pneumonia (3 weeks after crisis).	0.94			
29	G. K.	Pneumonia (11th day; temp. remaining up. Proved tubercular later on).	0.57	■		
30	J. J.	Diabetes (doing well).	0.67	■		
31	T. W.	Diabetes.	1.20			
32	W. B.	Diabetes.	0.83			
33	J. B.	Diabetes.	0.84			
34	P. McL.	Diabetes.	0.69	■		

■ Cases in which the index was found beyond the normal limits.

Table III continued.

No.	Initials.	Disease.	Tuberculo-opsonic index.
35	J. S.	Measles (convalescent).	1.00
36	S. S.	Measles (convalescent).	1.03
37	A. T.	Measles (convalescent).	1.20
38	M. M.	Measles (convalescent).	0.88
39	M. C.	Whooping Cough (convalescent).	1.00
40	J. H.	Whooping Cough.	1.17
41	R. W.	Whooping Cough.	0.90
42	W. B.	Whooping Cough.	1.20
43	S. G.	Whooping Cough. (convalescent)	1.50 [■]
* Cases in which the index was found			beyond the normal limits.

In my enquiry as to whether an abnormal tuberculo-opsonic index was ever observed in people who were not infected with tubercle, it occurred to me that in members of the case of [^]so-called "tubercular families" - who are commonly believed to be "predisposed" to Tuberculosis - some alteration in the index might be found. I therefore examined the blood of nine of such people, and the result is given in Table IV.

Table IV Tuberculo-opsonic power of the blood in nine healthy members of so-called "tubercular families".

No.	Initials.	Tuberculo-opsonic index.	
		1st observation	2nd observation.
1	D. D.	1.00	1.07
2	A. B.	1.00	
3	C. B.	1.10	
4	B. R.	0.84	1.16
5	W. B.	0.80	

No.	Initials.	Tuberculo-opsonic index.	
		1st Observation	2nd Observation.
6	A. F.	1.09	
7	J. L.	1.00	
8	M. M.	0.91	
9	D. R.	1.00	

A much larger body of evidence is necessary before any definite statement can be made on the question but, in the nine cases examined, it is noteworthy that there is no instance of an index beyond the normal limits. In at least eight of the cases the family history was very markedly tubercular, in the ninth case the so-called "predisposition" was less well-marked.

- (c) The next question is:- What level of opsonic index is found in cases where tubercular infection is known to be present?

Wright's earliest investigations ^(7 & 8) led him to believe that the index was low in cases of tubercular disease; in seventeen cases reported the indices ranged from .4 to .85. ^(1, 9 & 10) His later work, however, has shown that this does not hold good in all cases and in his most recent contribution on this subject he makes a classification of tubercular cases into (1) "Strictly localised/

localised cases" and (2) "Cases which are associated with constitutional disturbance".

Into Class 1 he puts "cases where the infection is limited to one or more lymphatic glands, most cases of lupus, most cases of tubercular abscess in the subcutaneous tissue, tubercular affections of the joints and, lastly, many stationary, or only slowly progressing cases of tubercular pthisis".

Class 2 includes "patients who are suffering from more generalised tubercular infections associated with constitutional disturbance. This group consists in large part of cases of pyrexial pulmonary tuberculosis".

In Class I he states that "the index is low and uniformly low". In a series of thirtyone cases, the index ranged from .13 to .88; in no case did it reach above the latter figure.

In Class II - the Class associated with constitutional disturbance - he finds a continually varying index. "The range of its fluctuation is from considerably under the normal to twice or more the normal height."

Urwick^④ has reported on the opsonic power of the blood in fiftyfour cases of people suffering from various tubercular infections; five of these are lupus, sixteen are cases of general surgical tuberculosis and thirty-three are cases of Phthisis. Generally speaking his results are in harmony with the conclusions of Wright. In one case of Lupus, however, he records an index of 1.9.

Bulloch^③ has investigated the opsonic indices of a hundred and fifty patients suffering from Lupus, and his results do not altogether agree with those of Wright and Urwick. In thirtynine of the cases the index was .8 and upwards, as many as ~~14~~ fourteen having a range of from 1 to 1.4

One striking point in the cases reported by these observers is the very large number of patients who are known to be tuberculous, and who yet have an opsonic index within the normal range - taking that to be from .8 to 1.2. In Bulloch's series, thirtyseven out of a hundred and fifty, in Urwick's series thirteen out of fiftyfour, and in Wright's cases seven out of thirtyone, come within these limits. It would thus appear/

appear that, in about one-fourth of the cases of tubercular infection, the opsonic index - as far, at least, as one examination of it is concerned - gives no indication of the condition. My own experiments have led me to a similar conclusion. I have examined ninety-one cases where tubercular infection was undoubtedly present, and the results are given below in Table V.

Table V. Tuberculo-opsonic power of the blood in ninety-one patients suffering from tubercular disease.

No.	Initials.	Disease.	Tuberculo-opsonic index.						
1.	S. L.	Tubercular Knee	1.20	1.28					
2	M. P.	Tubercular peritonitis	1.60						
3	F. L.	Tubercular glands in neck and in both axillae	0.50	1.40	0.90	0.60	0.60	0.96	0.78
4	L. W.	Tubercular metacarpals	1.10						
5	M. H.	Tubercular Pyonephrosis	1.90	0.60	(four days after operation)				
6	W. B.	Tubercular sinuses in thigh	0.63	0.70					
7	T. J.	Tubercular Wrist which has been excised	0.90	0.90					
8	D. O.	Tubercular Disease of Spine	0.98	1.10	0.84	1.30	1.60		
9	R. B.	Tubercular glands in neck; removed one week ago.	1.60	1.60					
10	J. H.	Multiple Tuberculosis	0.60	0.60					
11	M. G.	Tubercular Pyelitis	0.57	1.50					
12	B. M.	Tubercular Peritonitis (doing well)	1.60	1.43	1.20	1.30			
13	D. S.	Tubercular sacro-iliac disease; operated on; now discharging sinus	0.60	0.60					
14	R. M.	Tubercular elbow	1.60	0.48					
15	F. M.	Double osteomyelitis (tuberc)	1.06	1.2	0.44				

No.	Initials.	Disease.	Tuberculo-opsonic index.				
16	N. M.	Tubercular Peri- tonitis	0.80	1.20	0.80	0.60	0.67
17	P. McI.	Tubercular Ankle	1.10				
18	T. McR.	Phthisis (acute)	.60	1.70	0.75		
19	N. F.	Tubercular eye- lid.	0.50				
20	J. McG.	Tubercular Knee	0.70	0.50			
21	M. S.	Tubercular El- bow.	0.50	0.69			
22	P. D.	Tubercular Ul- ceration of Bowel	0.80				
23	No. B.	Tubercular Hip (developed tuber- -cular meningitis)	0.20	0.70			
24	J. W.	Tubercular Ab- scess	1.10	1.70			
25	J. C.	Tubercular Hip joint disease	1.00	0.70			
26	K. J.	Phthisis	1.10	1.00			
27	V. S.	Tubercular Men- ingitis	0.90				
28	J. F.	Phthisis (Sana- torium "Cure")	0.60				
29	A. K.	Tubercular Ankle	.70				
30	B. G.	Phthisis (day after Parturition)	1.25				
31	R. McC.	Pleurisy & eff- usion (no T.B. in effusion but T.B. in Sputum)	0.30				
32	P. D.	Tubercular Tar- sus and Thumb	1.20	1.10	1.10	1.20	
33	C. M.	Tubercular Peri- tonitis (Duration six weeks)	2.40				
34	G. H.	Tubercular Hip joint	1.50	1.40	1.10		
35	D. N.	Tubercular Clavicle	1.20	0.40			
36	J. D.	Tubercular El- bow	0.90				
37	R. G.	Tubercular Hip joint disease (duration six weeks)	0.66	1.00			
38	D. McG.	Tubercular Ankle	.50	0.90			
39	J. O'N.	Tubercular Peri- tonitis	.70				
40	T. L.	Tubercular glands in neck	1.00				
41	R. C.	Tubercular glands in neck	.36				
42	W. W.	Tubercular Spine	.60				
43	P. G.	Tubercular Hip joint disease (9 month's dur- -ation)	0.60	0.86			

No.	Initials.	Disease.	Tuberculo-opsonic index.			
44	N. C.	Tubercular Hip & abscess	0.40			
45	J. B.	Tubercular Tibia	.50	1.20	0.90	
46	K. D.	Scrofuloderma	0.70	0.94		
47	J. K.	Tubercular Laryngitis (several year's duration)	1.00	1.08		
48	A. McG.	Phthisis (early)	.80	0.92		
49	R. B.	Phthisis	1.20	1.10		
50	M. N.	Cerebral Tumour (Tuberc.)	.57	0.60	1.30	1.04
51	J. L.	Tubercular Osteomyelitis	1.10	0.40	0.33	
52	M. B.	Tubercular Pleurisy.	1.54			
53	M. F.	Lupus of Nose	0.47			
54	J. T.	Scrofuloderma (20 years' duration)	0.50			
55	G. R.	Phthisis	0.90			
56	J. R.	Phthisis (acute)	.80			
57	A. D.	Tubercular Ulcer of Bowel; diagnosed at operation.	.60	0.70		
58	J. McE.	Psoas Abscess	0.43			
59	D. B.	Tubercular foot	.86	1.00		
60	V. C.	Psoas Abscess	0.65	0.80		
61	J. McI.	Phthisis (early) & Haemoptysis	1.20			
62	H. S.	Phthisis (10 months duration)	1.23			
63	J. C.	Phthisis (early)	.78			
64	M. B.	Tubercular Meningitis	1.50			
65	P. McL.	Tubercular Peritonitis	.80			
66	M. Knox	Lupus & Pneumonia	1.40			
67	J. L.	Pleurisy (recovering; T.B. in sputum)	1.00			
68	M. S.	Tubercular Laryngitis	0.90	1.08		
69	L. R.	Tubercular cervical glands	1.60	1.30		
70	M. G.	Phthisis & Empyema	.78			
71	M. C.	Tubercular ankle (duration 1 year)	.78			
72	D. B.	Tubercular peritonitis (cured)	.77			
73	J. D.	Tubercular hip joint (no constitutional disturbance)	1.70			

No.	Initials.	Disease.	Tuberculo-opsonic index.	
74	M. McA.	Tubercular Peri- tonitis	1.20	1.40
75	A. S.	Tubercular Men- ingitis	1.50	1.08 (almost comatose; just before death)
76	R. W.	Tubercular pleu- risy	.65	
77	A. C.	Tubercular Peri- tonitis	1.50	1.50
78	G. K.	Phthisis (acute)	.57	1.20
79	J. B.	Osteomyelitis (tubercular)	0.95	
80	J. F.	Lupus vulgaris	0.73	
81	J. S.	Pleurisy (tu- bercular)	1.04	
82	W. G.	Phthisis	1.30	
83	K. H.	Pleurisy (tu- bercular)	1.60	
84	M. P.	Phthisis (ad- vanced)	0.67	
85	B. D.	Phthisis (early)	0.90	
86	A. N.	Tubercular cer- vical glands	0.60	
87	F. C.	Tubercular Pleu- risy	1.20	
88	M. Y.	Phthisis (very early)	0.50	
89	M. S.	Tubercular Peritonitis	0.50	
90	R. P.	Phthisis	0.70	
91	P. M.	Tubercular ulceration of Bowel	0.94	

I have endeavoured to arrange my cases according to Wright's ^① classification into strictly localised cases, with a uniformly low index, and cases with general constitutional disturbance and a fluctuating index, but, so far, I have quite failed to do so. Many of the cases which yielded a normal index were examples of localised tuberculosis and had no constitutional disturbance, e.g., cases 4, 7, 17, 40, 47, 59 & 68. Also in some cases of strictly localised lesion, the index was con-

siderably above normal, e.g., Cases 9^x, 66, 69 & 73.

An analysis of the figures in Table V will shew that in fiftyeight out of the ninetyone cases, the opsonic index is beyond the limits found in health; in thirtythree cases it is within these limits on the first examination. In a number of the cases in this latter category, repeated examinations of the blood were made in order to observe whether the index was stationary or fluctuating. Six of these cases yielded an abnormal index on second examination, and several others behaved similarly when the examinations were repeated four or five times.

E.g., "D. O.", Case 8, was a child who had had tubercular disease of the vertebrae and a psoas abscess several years ago. He had now evidence of fresh tubercular mischief in the form of evening rise of temperature, night sweating, emaciation, etc., and his opsonic index was examined to see if it cast any light on the diagnosis. At the first three examinations it/

^x Note: The case of "R. B.", however, was one where the tubercular lesion (cervical glands) had been excised one week before the first index was taken, and, as Wright ^① has pointed out and as I had observed independently, a considerable rise in the level of the opsonic index frequently follows operation on a tubercular focus.

it was found to be normal (.98, 1.1 & .84) and it was only at the fourth and fifth examinations that any abnormality in the index was evident.

In Case 16, no abnormality in the index appeared till the fourth examination, and in Case 32, four consecutive examinations yielded a normal index.

- (d) Having stated the results obtained from the investigations in the three classes of cases specified, I now wish to determine whether the data acquired can aid at all in answering the questions already set forth, viz., (1) Whether there are any levels of index which may be said to be pathognomonic of tubercular infection, and (2) If so, whether these levels are found in all cases of Tuberculosis.

In view of the exceptions which have been stated in the case of pneumonia, whooping-cough and diabetes, and also taking into account the incompleteness of our knowledge of the effects of exercise, diet, drugs, etc. on a healthy index, it is quite impossible at present to give an affirmative answer to the former question.

The index in healthy persons ordinarily ranges from 0.80 to 1.20 and, as far as the present observations go, neither "hereditary predisposition", nor injury, nor

disease - other than Tuberculosis and the exceptions just named - has the power of causing it to vary beyond these limits. Therefore, when a case presents an index below 0.80 or above 1.20, it is reasonable to conclude that there is a strong probability of tubercular infection; a more emphatic statement is not yet justifiable.

To the second question - whether an index below 0.80 or above 1.20 is found in all cases of Tuberculosis - the answer is definitely "No". An index within the normal limits has been found in at least twentyfive per cent of the cases of Tuberculosis reported by the different observers, and it is here that the limitation of the value of the opsonic index as a diagnostic agent appears. In my series of ninetyone cases given in Table V, thirtythree yielded a normal index at the first examination. As I have already pointed out, a certain number of these cases proved to have a fluctuating index and were found outside the normal range at a second or subsequent examination and it is highly probable that a larger number would have shewn an abnormal index if repeated examinations had been carried out in all cases. This, however, is obviously tedious and uncertain and some other and simpler test is desirable for those cases

which fail to give an abnormal index on the first examination. Wright⁽¹⁾ has suggested that a phagocytic test with the patient's heated serum may clear up the diagnosis. The experiments of Denys and Leclef⁽¹¹⁾, Mennes⁽¹²⁾, Savtschenko⁽¹³⁾, Neufeld and Rimpau⁽¹⁴⁾, Leishman,⁽¹⁵⁾ and others have shewn that when an animal is immunised by bacterial injections a specific immune substance, capable of inciting active phagocytosis is formed in the blood. This immune substance is thermostable.

Dean⁽¹⁶⁾ has endeavoured to prove that there is in normal serum a substance having a similar action and which also resists a temperature of 60° C. for hours; this substance he believes to be identical with that got in the blood of animals ~~whod~~ have been immunised.

Wright denies the existance of such thermostable "incitor elements" in normal serum and his view is supported by the experiments of Bulloch and Atkin⁽¹⁷⁾. Referring to the effect of heat on the normal serum the latter observers state that "after the serum has been heated in the water-bath at 60° - 65° C., for ten to fifteen minutes, in most cases the opsonic effect is entirely abolished. In a few cases, however, some slight

slight effect can be witnessed but this is mainly, if not entirely, due to traces of serum left attached to the leucocytes where these have been incompletely washed in normal salt solution".

In proposing the heat test for diagnostic purposes, Wright says:

"When a serum is found to retain in any considerable measure, after it has been heated to 60° C for ten minutes, its power of inciting phagocytosis, we may conclude that 'incitor elements' have been elaborated in the organism, either in response to auto-inoculations occurring spontaneously in the course of tubercular infection, or, as the case may be, under the artificial stimulus supplied by the inoculation of tubercle vaccine".

The points which are of interest, so far as the present research is concerned, are:-

I Whether ^{Removable} "incitor elements" are formed in the blood of tuberculous patients in response to auto-inoculations;

II Whether these elements, if formed, are in sufficient quantity to be of diagnostic value, and

III/

III Whether normal serum ever contains a similar thermostable substance in any appreciable quantity.

Until these questions are placed beyond the region of controversy, it is impossible to claim any definite value for the heat test in the diagnosis of Tuberculosis.

In connection with the present experiments there has been a further difficulty in applying this test, as proposed by Wright, in so much as the indices yielded by my tuberculous cases did not enable me to arrange them according to Wright's two classes into (1) those with a strictly localised infection and an index which is uniformly low, and (2) those where there is general constitutional disturbance and evidence of systemic infection where the index is variable - now high, now low, now normal.

As has already been shewn, the cases in which there is any necessity for a diagnostic test, beyond the simple examination of the opsonic index, are those in which the index at a first examination falls between the limits of 0.80 and 1.20. Now, according to the above classification, these are cases where the infection is no longer strictly localised, where, therefore, auto-inoculations have taken place and where the index is

at one stage of its fluctuation between a high and a low level. If, therefore, "incitor elements" are formed after auto-inoculation in any considerable quantity, the cases of Tuberculosis which shew a normal opsonic index will be the very instances in which their presence may be demonstrated and used for diagnostic purposes.

But, as I have pointed out, my tuberculous cases ~~ix~~ did not all fit into the above classification. Many of the cases of strictly localised Tuberculosis shewed an index within the normal limits; e.g., "J. K.", Case 8, was a patient with advanced tubercular laryngitis having abundant T. B. in the sputum but giving no evidence of systemic infection and no signs that the lungs were involved; he could not, however, be put into Wright's class of "strictly localised infections" as his index was 1.00 and 1.08 on the two occasions on which it was examined.

"A. S.", Case 5, was a similar - though more recent and less severe - case of tubercular laryngitis and had an opsonic index of 0.90 and 1.080 on two successive examinations.

The heat test has not been claimed as having any diagnostic

diagnostic value in cases where the tubercular infection is strictly localised, therefore, even if it does prove capable of clearing up the diagnosis in a certain proportion of the cases under consideration - those, namely, where there is systemic infection and where the index is normal - there will still remain ~~ix~~ a number of cases which have resisted our attempts at diagnosis.

Table VI gives the results got with this test in the case of fifteen patients who were definitely tuberculous but whose unheated serum had yielded a normal index; these are contrasted with the results obtained in the case of three normal men. The test in my hands has not been satisfactory; I have found no constant difference between the index in the case of the healthy individuals and that in the case of those whom I knew to be tuberculous and who shewed definite signs of systemic infection.

In cases 8 to 21, a phagocytic mixture containing over one per cent NaCl was used in order to avoid the fallacies associated with "spontaneous phagocytosis" which have been pointed out by Wright¹⁸; in cases 1 to 7, the salt content of the mixture was less than one per cent.

Table VI. Tuberculo-opsonic power of blood which has been subjected to a temperature of 60° C. for fifteen minutes.

No.	Initials.	Healthy or Diseased.	Patient's Phagocytic Index. serum heated	Pool Phagocytic Index. serum unheated	Opsonic Index. (got by dividing the phagocytic index of the patient's heated serum by the phagocytic index of unheated healthy pool.
1	R. W.	Tubercular Pleurisy	0.60	1.52	0.39
2	A. C.	Tubercular Peritonitis.	0.52	1.52	0.33
3	P. F.	Tubercular glands in neck and axillae	0.63	1.52	0.41
4	J. S.	Tubercular ulceration of Bowel	0.77	1.52	0.50
5	A. S.	Tubercular Laryngitis	0.47	1.52	0.30
6	J. A. C.	Normal	0.58	1.52	0.38
7	D. M.	Normal	0.30	1.52	0.20
8	J. K.	Tubercular Laryngitis	0.56	4.20	0.13
9	J. S.	Tubercular Ulceration of Bowel	0.42	4.20	0.10
10	D. C.	Tubercular Glands in Abdomen	0.72	4.20	0.17
11	L. F.	Lupus Vulgaris	0.60	4.20	0.140
12	M. S.	Tubercular Pleurisy	0.88	4.20	0.20
13	W. G.	Phthisis	0.82	4.20	0.19
14	M. A.	Tubercular Peritonitis	0.90	4.20	0.21
15	J. McC.	Normal	0.43	4.20	0.11
16	R. K.	Normal	0.55	4.20	0.13
17	J. A. C.	Normal	1.20	4.20	0.28
18	M. P.	Advanced Phthisis	0.85	4.57	0.18
19	B. D.	Early Phthisis	0.85	4.57	0.12
20	J. H.	Multiple Tuberculosis	0.70	4.57	0.15
21	D. C.	Normal	1.77	4.57	0.38

Note: Case 11, a patient with lupus vulgaris and an opsonic index of 0.70 is inserted only for the sake of comparison.

"M. P.", Case 18, was a case of advanced Phthisis with considerable "constitutional disturbance", and "J. H.", Case 20, was a patient with Multiple Tuberculosis who had had a course of Tuberculin (TR) treatment completed about six weeks before this examination. In these cases the index was 0.18 in the former and 0.12 in the latter, while in the case of the normal man, "D. C", Case 21, it was 0.38.

These experiments are quite insufficient to enable one to form an opinion as to the value of the heat test; as far as they go, however, they yield no evidence of the presence of thermostable substance in the blood of tuberculous patients in sufficient quantity to be of diagnostic importance.

In a few of the cases under consideration, the diagnosis has been aided by the differential test applied to the blood serum and the fluid obtained from a pleural or peritoneal exudate or from an abscess of the same patient. This test also has been suggested by Wright^① and he reports several very striking cases of diagnosis arrived at by this method.

This experiment is founded on the fact noted by

Wright and Lamb⁽¹⁹⁾ and, later, by Wright and Douglas⁽²⁰⁾, that in the actual focus of infection there is a lowered "bacteriotropic pressure". The fluid obtained from pus by centrifugalisation or the fluid taken from a pleural or peritoneal effusion is examined and its opsonic power is compared with the opsonic power of the blood serum of the case under investigation. If the index is found to be appreciably less in the former case than in the latter, this fact is taken as evidence of infection with the particular germ used in the experiment.

Table VII. Tuberculo-opsonic power of fluid from the focus of infection compared with tuberculo-opsonic power of the blood serum in tuberculous cases.

No.	Initials.	Disease.	Tuberculo-opsonic power of blood serum.	Tuberculo-opsonic power of fluid obtained from pleural exudate or from abscess.
1	M. B.	Tubercular Pleurisy & effusion	1.54	1.30 (pleural exudate)
2	F. C.	Tubercular Pleurisy & effusion	1.20	1.07 (pleural exudate)
3	P. McL.	Tubercular Periostitis	0.80	0.40 (pus from abscess)

Additional observation may prove that this is a very valuable diagnostic test in those cases where fluid for examination can be obtained from a definite focus of/

of infection.

However, in spite of the exploitation of all the methods which have been detailed in this paper, there still remains a class of tuberculous patients in which an examination of the tuberculo-opsonic index affords no clue to the diagnosis. These are cases where the index is found within the normal limits, where the heat test fails to shew the presence of any considerable amount of thermostable substance and where there is no possibility of obtaining fluid from a focus of infection. Is the opsonic index, then, of no value in these cases? On the contrary, I believe that, if used in conjunction with small doses of Tuberculin (TR), it may be of the greatest value.

In treating tuberculous patients with inoculations of new Tuberculin (TR) Wright ⁽¹⁰⁾ had found that the opsonic index invariably fell after the inoculation and remained low for a certain number of hours or days; this he called the "negative phase" of the index. He noted also that the "negative phase" supervened upon much smaller doses and persisted much longer in the case where the patient was the subject of extensive infection than in the contrary case".

Lawson and Stewart (Op. cit) followed up these investigations and, by examination of the blood in a large number of cases of pulmonary tuberculosis after therapeutic inoculations of new Tuberculin (TR), they confirmed Wright's statement as to the constancy of a negative phase in tuberculous patients. They then endeavoured to find out whether a negative phase occurred after the inoculation of a similar dose into a healthy individual. The difficulty encountered was in finding a sufficient number of healthy individuals who were willing to be inoculated with Tuberculin. They examined four such cases after inoculation and found the negative phase absent in all. They therefore suggested that in cases of doubtful diagnosis where Tuberculosis was suspected, the doubt might be dispelled by giving the patient an inoculation of a small dose of Tuberculin (TR).

To make this suggestion of value it is necessary that the observations made in cases of pulmonary tuberculosis should be repeated in cases of surgical tuberculosis in order to determine whether in these also a negative phase invariably supervenes on the inoculation of small doses of TR. It is necessary also that a much more/

more extended series of observations of the effect of such inoculation should be made in the case of non-tuberculous persons.

I have had the opportunity of examining the blood in a considerable number of cases of Tuberculosis undergoing treatment by TR in the surgical wards of the Glasgow Royal Infirmary and, in every case where the examination was made within twentyfour hours of the inoculation, I have found a negative phase to be present.

I have also had the opportunity of examining the blood after inoculation of TR in ten cases of non-tuberculous persons, and in no case have I found evidence of a negative phase. The opsonic index examination was in all cases made within twentyfour hours of the inoculation. These results are given below in Table VIII.

Table VIII Shewing the effects on the opsonic index of the inoculation of $\frac{1}{1000}$ milligram of Tuberculin (TR) in the case of ten tuberculous patients and of ten non-tuberculous persons.

No.	Initials.	Disease. (if any)	(a) Tuberculous Cases.	
			Tuberculo-opsonic index before injection.	Tuberculo-opsonic index within 24 hours after injection.
1.	J. B.	Tubercular Osteomyelitis	0.95	0.46
2	S. L.	Tubercular disease of knee	1.28	0.40
3	W. B.	Tubercular sinuses in thigh	0.70	0.53

Table VIII continued.

No.	Initials.	Disease. (if any)	Tuberculo-opsonic index before in- jection.	Tuberculo-opsonic index within 24 hours after in- jection.
4	J. F.	Tubercular di- sease of Wrist	0.90	0.57
5	A. D.	Tubercular ul- ceration of Bowel.	1.40	0.59
6	M. P.	Tubercular Peri- tonitis	1.60	0.70
7	L. W.	Tubercular di- sease of meta- carpals.	1.10	0.83
8	M. H.	Tubercular Py- onephrosis	0.70	0.40
9	R. B.	Tubercular cer- vical glands	1.50	0.90
10	R. M.	Tubercular di- sease of Elbow	1.60	0.48
(b) <u>Non-Tuberculous Cases.</u>				
1	B. G.	-----	0.81	1.20
2	J. Y.	-----	0.92	1.20
3	J. I.	-----	(count lost)	0.82
4	O. S.	-----	1.10	1.20
5	J. G.	-----	0.85	1.08
6	J. McF.	-----	1.09	1.28
7	W. A.	-----	0.84	1.17
8	M. McC.	-----	1.00	1.80
9	A. K.	-----	1.15	1.16
10	J. S.	-----	0.80	0.80

These experiments seem to point strongly to the conclusion that by the inoculation of a thousandth part of a milligram of new Tuberculin and the subsequent examination of the blood, a diagnosis of the presence or absence of tubercular infection may be definitely made.

The uniformity of the results leads one to hope that this will prove a delicate and reliable test.

As regards the objection to the use of Tuberculin (TR) for diagnostic purposes, I may say that I have watched the results of the therapeutic inoculation of doses varying from $\frac{1}{1000}$ to $\frac{1}{500}$ m.g. in a considerable number of cases and have never seen the slightest evidence of ill-effects - even of headache or nausea.

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C O N C L U S I O N S .

1. The tuberculo-opsonic index in healthy persons ranges from 0.80 to 1.20, and at present there is no reliable evidence that it ever reaches beyond these limits.
2. The level of the tuberculo-opsonic index is not altered, so far as we know, by either of the following factors:-
 - (a) Non-tubercular disease (except some instances of pneumonia, diabetes and whooping-cough).
 - (b) "Hereditary Predisposition" to Tuberculosis.
3. The opsonic index in cases of tubercular disease

may vary from as low as 0.20 or 0.30 to as high as 2.40 or over.

In about seventyfive per cent of the cases the index is found above or below the normal limits (taken as from 0.80 to 1.20) at a first examination. In the remaining twentyfive per cent of the cases, a first examination will yield an index within these limits.

4. These facts enable one to state that, when an index of over 1.20 or under 0.80 is recorded in any case, there is a strong probability of the presence of tubercular infection.

5. The statistics in Table V of this paper go to shew that the twentyfive per cent of cases of Tuberculosis, presenting a normal index at the first examination, consist of cases in which the disease appears to be strictly localised as well as of cases in which the disease is much more advanced and where there is obvious constitutional disturbance. Furthermore, many cases in which the tubercular disease appears to be strictly localised yield an index considerably over 1.20

6. For the diagnosis of those cases in which the index is within normal limits, Wright's differential test, applied to the patient's blood serum and to fluid from a pleural effusion, an abscess, etc., may be very useful in those cases where there is the possibility of obtaining fluid from a local focus of infection.
7. The phagocytic test with heated serum may prove ^{p. 31} to be of value in those cases of tuberculosis where auto-inoculations have taken place and where the opsonic index (which is fluctuating) has been found within the normal limits at the first examination.
8. There still remains, however, a considerable number of cases in which the opsonic index fails to give conclusive evidence of the presence of tubercular ~~inf~~ infection. In these a definite diagnosis may be arrived at by the estimation of the patient's opsonic index before and after the inoculation of a small dose of Tuberculin (TR).) This inoculation causes very little inconvenience to the patient and is followed by no ill effects.
9. An examination of the tuberculo-opsonic index, therefore/

therefore, may be made the ultimate appeal in all cases where a diagnosis of the presence or absence of tubercular infection is required.

Note: Theoretically the diagnostic value of the opsonic index is as above stated; practically it is considerably less. With the present methods the testing of an opsonic index is a tedious process, requiring a large amount of time and patience. In inexperienced hands the results got are worse than useless - they are usually entirely fallacious and misleading. It is only after one has done a considerable amount of "apprentice" work and discarded the results, that one surmounts the endless technical difficulties and sources of error and begins to obtain reliable information. Its value, therefore, as far as the general practitioner is concerned, is, under present conditions, very limited, and unless a simplification of technique is discovered, whereby the time necessary for each experiment is considerably reduced, its sphere of usefulness will be practically restricted to Hospital/

Hospital practice and to cases where the patients are able to pay what must necessarily be a large fee to a Research Laboratory.

In conclusion, I desire to express my great indebtedness to Dr. McCrorie and Dr. Campbell of the Bacteriological Laboratory of the Glasgow Royal Infirmary for assisting me, in every way possible, to pursue these investigations.

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