case the tumour disappeared completely, leaving an almost normal breast. These results compare very favourably with those obtained by amputation.

In the inoperable cases, where no alternative method of treatment was possible, the results quite exceeded expectation; large fungating masses disappeared, and ulcerating surfaces healed over. As most of the patients were 70 years of age or more, this was really all that one could ask, and in the majority of cases the patient was saved from a distressing condition. It is remarkable, however, that even at the age of 86, extensive generalization can occur. It would, of course, have been impossible if the ulcer had not been treated, since the patient would have died of exhaustion.

It will be seen, then, that in inoperable cases radium can give a relief which cannot be otherwise obtained. In advanced cases the evidence seems to show that radium can give results at least as good as those obtained by amputation, at the cost of far less inconvenience and with no disfigurement. In early cases it may certainly be used with a considerable prospect of success, on condition that the case is most closely watched, and with the stipulation that in the event of a recurrence a complete amputation shall immediately be performed. Most surgeons will agree that the wider their experience of carcinoma the less inclined they feel to dogmatize either as to the treatment to adopt or the result which may be expected. Sometimes they are surprised by a brilliant result in an apparently hopeless case, and have some compensation for the many disappointments they are bound to meet. The use of radon seeds in the treatment of carcinoma of the breast furnishes them with a method which is applicable to almost every case. There is no case so advanced that local relief is impossible, while in the earliest cases I am convinced, from my own experience, that the surgeon is fully justified in offering this alternative to amputation, and that he need have no fears of prejudicing the interests of his patients. We are all only too familiar with patients who refuse to ask for help until the condition is so far advanced that it can no longer be concealed, and I feel that if the possibilities of radium were more widely known patients would be inclined to seek advice at a much earlier date, to their own inestimable advantage.

THE INTRADERMAL TUBERCULIN TEST IN NON-TUBERCULOUS ADULTS

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The investigation here described had for its object the study of the variations in "tuberculin sensitivity" manifested by adults free from clinically recognizable tuberculosis and the comparison of the findings in non-tuberculous with those in clinically tuberculous groups.

One of us (S. L. C.) had already published, with his colleague Dr. S. B. H. Walker, the results of preliminary studies on this subject, and he makes some further use of the material then collected for the purpose of the present inquiry. The other (A. C. E.), as pathologist to the Denbighshire Mental Hospital, was in a position to carry out tuberculin tests on a considerable number of patients suffering from mental symptoms only, but otherwise in average bodily health.

The tests were arranged so as to correspond as closely as possible with those previously carried out in Cardiff. One of us (S. L. C.) prepared the dilutions of tuberculin on standard lines and supplied them as required so that

they should be used fresh. The other (A. C. E.), having worked for some time in the tuberculosis laboratory at Cardiff, was in a position to carry out the tests and read the results on lines similar to those applied in the previous series.

The tuberculin used was selected for us as of standard strength by Dr. R. A. O'Brien, director of the Wellcome Physiological Research Laboratories. Its description is as follows: "P.T. No. B 1648. B. W. and Co." Dilutions in tenths were prepared with 0.5 per cent. carbolic in normal saline solution, ranging from 1 in 10 to 1 in 100,000.

Previous observations having satisfied us that all persons giving a definite positive reaction to any given dilution tend to react still more markedly to the next in order of strength, we decided to start the tests on each individual with the highest dilution and to excuse all positive "reactors" from further tests, applying successively stronger dilutions to the "negatives" only. In this way we gradually narrowed down the "negatives" to those failing to react to a dilution of 1 in 10.

"Control" tests with "glycerin broth" were omitted, previous observations having satisfied us that these are always negative until strong concentrations are reached. The non-specific reactions which tend to occur with very strong concentrations of "glycerin broth" have been shown by D'Arcy Hart to be confined to those persons who also react to tuberculin; so the possibility of non-specific reactions need not be taken into account.

Intradermal tuberculin tests on these lines were applied to three successive series of persons under treatment in the mental hospital: a first male group of 304, a second male group of 141, and a female group of 150 persons. In the tables which follow the two male series have been combined into one group of 445 persons for comparison with the female group.

The following table shows, by sexes, the percentages of persons reacting to the various dilutions of tuberculin used.

TABLE I.—*Tuberculin-sensitivity Variations in Terms of "End-point" of Reactivity in Healthy Persons*

	Dilutions					
	1 in 100,000	1 in 10,000	1 in 1,000	1 in 100	1 in 10	Negative to 1 in 10
Males (445): Positive per cent.	14.1	45.8	88.3	96.6	99.1	0.9
Females (150): Positive per cent.	21.3	58.0	88.0	93.3	97.3	2.7

The female group, while including a larger number of negatives than the male, showed a decidedly higher percentage of "positive" reactors with the higher dilutions. It will be noted, too, that while 85.9 per cent. of the males and 78.7 per cent. of the females were "negative" to a dilution of 1 in 100,000, only 11.7 per cent. of males and 12 per cent. of females were negative to 1 in 1,000. This point is stressed as a reminder of the fact that, while "positive" is an absolute term, the expression "tuberculin negative" is relative only, and depends on the technique employed and the dilution of tuberculin used. The von Pirquet scarification method, for instance, when carried out with undiluted old tuberculin, has been shown to be not quite so stringent a test as the intradermal inoculation of a 1 in 1,000 dilution of the same tuberculin. "Negatives" to the von Pirquet test, therefore, may be taken to include at least 10 per cent. of persons who would prove to be "positive" if tested intradermally with 1 in 100 and 1 in 10.

For comparison with the above the results of intradermal tuberculin tests in 100 persons, forty-five males and fifty-five females, suffering from active pulmonary tuberculosis are set forth in Table 1A.

It was not thought safe to give intradermally of 1 in 100 and 1 in 10 to actively tuberculous persons, so a final concentration of 1 in 500 was used instead. Here again the females included a larger percentage of "negatives" than the males, but, in the higher dilutions, the findings

were reversed, and the males showed greater reactivity than the females.

It is clear that, in the groups tested, the tuberculous patients showed a much higher percentage of "reactors"

TABLE IA.—*Tuberculin-sensitivity Variations in 100 Persons with Active Pulmonary Tuberculosis*

	Dilutions				
	1 in 100,000	1 in 10,000	1 in 1,000	1 in 500	Negative to 1 in 500
Males (45): Positive per cent.	46.6	73.3	93.3	97.8	2.2
Females (5): Positive per cent.	30.9	63.6	87.2	92.7	7.2
Both sexes: Positive per cent.	38.0	68.0	90.0	95.0	5.0

to the higher dilutions of tuberculin than did the "healthy" persons referred to in Table I: over three times as many in the case of males to a dilution of 1 in 100,000.

The percentages of "negatives" are not comparable, as in the healthy group the non-reactors were negative to 1 in 10, while in the tuberculous group the non-reactors were negative to 1 in 500 only. It is probable that all the tuberculous group would have been found positive if tested with 1 in 10 tuberculin.

The recording of the "end-point" reactivity is not, however, the only method of evaluating tuberculin sensitivity. There is also the size of reaction area, the measurement of which affords a rough index of intensity.

In Table II are set forth for the healthy persons of Table I the average sizes of the reaction areas noted in each dilution. Only those who had failed to

TABLE II.—*Tuberculin-sensitivity Variations in Terms of Average Size of Reaction (Healthy Persons)*

	Dilutions				
	1 in 100,000	1 in 10,000	1 in 1,000	1 in 100	1 in 10
Males (average size in millimetres)	7.7	10.5	14.15	18.5	13.7
Females (average size in millimetres)	12.8	12.8	20.0	16.1	11.7

react to the next highest dilution are included in each average. Had the sizes of the reactions in those who had also been "positive" to a higher end-point been included, the averages would, of course, have been greater. Only the "raised" area, not the red flush, was included in the measurement.

Here again it is to be noted that with the three higher dilutions the reactivity of the females was greater than that of the males, although with the stronger concentrations it was rather less. It looks as if, in these Welsh females at least, the threshold of reactivity were higher, both in "end-point" and in "reaction size," than in the corresponding male groups—a circumstance which may, perhaps, be connected in some way with the fact that they are liable to show a particularly severe type of the disease. The reaction size in the actively tuberculous groups corresponded to the above, though there was a tendency to rather smaller reaction zones.

This problem is approached from a different angle in Table III, where the numbers and percentages of different sizes of reaction for each dilution are given under four headings. These figures are based on the male groups only, and concern the measurements of the reactions in 445 persons.

Here the tendency to a weaker and less extensive type of reaction with the higher dilutions is well seen.

It is to be noted, however, that of those found positive even with such a high dilution as 1 in 100,000 of tuberculin, two-thirds showed a well-marked reactivity, and only one-third gave weak reactions of a diameter of 5 mm. or under.

We decided, therefore, to carry our dilutions further, and to test the first male group, of 304 patients, with dilutions of 1 in 1 million and 1 in 10 million. These

TABLE III.—*Tuberculin Reaction Size according to Dilution Used*

Dilution	Reaction Size			
	3-5 mm.	6-10 mm.	11-20 mm.	Over 20 mm.
	Per cent.	Per cent.	Per cent.	Per cent.
1 in 100,000 (63 persons)...	33	44	21	1
1 in 10,000 (141 persons)...	14	40	45	1
1 in 1,000 (189 persons) ...	6	21	50	23
1 in 100 (34 persons) ...	6	12	32	50
1 in 10 (12 persons) ...	8	25	59	8

tests, carried out some two months later, showed seventeen reactors to 1 in 1 million, and seven reactors to 1 in 10 million dilution.

The combined results for the whole of this group of 304 males are given in Table IV below.

TABLE IV.—*Results of Serial Intradermal Tuberculin Tests in 304 Male Adults*

	Dilutions							
	1 in 10,000,000	1 in 1,000,000	1 in 100,000	1 in 10,000	1 in 1,000	1 in 100	1 in 10	Neg.
Positives (per cent.)	2.3	5.5	12.4	43.9	85.5	95.4	99.6	0.4
Reaction size (mm.)	4.9	5.9	7.7	10.0	14.3	20.7	14.0	—

It is of interest to note, in passing, that the tuberculin reactivity of this group of male adults is far less marked, especially in the higher dilutions, than that of South African native mine recruits, as set forth in the recently published Report No. XXX (vol. v, 1932) of the Publications of the South African Institute for Medical Research, in which the percentages giving a positive reaction to varying dilutions are as follows:

TABLE V.—*Results of Serial Intradermal Tuberculin Tests in South African Native Mine Recruits (for Comparison with Table IV)*

	Dilutions			
	1 in 10,000,000	1 in 1,000,000	1 in 100,000	1 in 10,000
Positives (per cent.)	48.6	51.5	55.0	72.5

This marked excess of "end-point" reactivity shown by these highly susceptible South African natives over that of European males, as represented by the population of a mental hospital in Wales, is a most interesting phenomenon; more especially in view of the fact that those natives showing marked tuberculin reactions proved, on further observation during their "contract" periods in the gold mines, to be more likely to develop tuberculosis than those reacting weakly or failing to react to the dilutions used.

It will require some years of "follow-up" to ascertain whether there is any similar tendency to an association of marked "reactivity" with liability to develop disease in the Welsh group under observation.

In this connexion a close scrutiny of the "previous histories" and present condition of the 304 mental cases of the first male series was now undertaken; and it was discovered that a history pointing to the occurrence, or possible occurrence, of previous tuberculous disease was present in eighteen of the total. In only two of these was there evidence of present activity. Both these men had reacted to 1 in 1,000 tuberculin, but not to higher

dilutions. It may be added that the distribution of these eighteen cases throughout the group, in terms of "end-point" and "reaction size," was not of a nature appreciably to alter the findings already tabulated. The group as a whole, though made up of mentally defective persons, consisted of individuals in good average health; nor did those persons manifesting high reactivity to tuberculin differ appreciably in health from those giving slight or negative reactions. This latter point is established by a comparison of the average rate of blood sedimentation in fifty of these mental patients reacting to 1 in 100,000, and fifty selected as negative or giving a weak reaction only when tested with the strongest concentrations of tuberculin.

TABLE VI.—Blood Sedimentation Rate in "Strong" and "Weak" Reactors to the Intradermal Tuberculin Test (Healthy Persons)

Time	"Strong" Reactors. Average "Clear Per Cent."	"Weak" Reactors. Average "Clear Per Cent."
After 1 hour	15.0	14.3
After 5 hours	39.7	36.6
After 24 hours	52.0	53.3

N.B.—"Clear per cent." refers to the height of the clear space of fluid remaining above the sedimented red blood corpuscles in a column of fluid 100 mm. high.

It will be seen that there is no appreciable difference in the sedimentation rate in the two groups. In both the average rate of sedimentation, though perhaps rather rapid, is within normal limits.

In order to emphasize the value of the sedimentation test as an index of normal bodily health, the average sedimentation rates of 100 persons with active pulmonary tuberculosis are tabulated for comparison with the above findings.

TABLE VII.—Blood Sedimentation Rate in "Strong" and "Weak" Reactors to the Intradermal Tuberculin Test (Persons with Active Tuberculosis)

Time	"Strong" Reactors. Average "Clear Per Cent."	"Weak" Reactors. Average "Clear Per Cent."
After 1 hour	43.0	56.5
After 5 hours	55.6	65.6
After 24 hours	60.6	68.7

Here it is seen that, especially in the first hour, the rate of sedimentation is much more rapid in the tuberculous than in the "normal" groups shown in Table VI. It will be noticed, too, that the "weak reactors" show a much more rapid sedimentation than the "strong reactors," indicating that, in this tuberculous group, the weak and negative results of tuberculin tests are the expression of the "anergic" state characteristic of the terminal phases of the disease.

DISCUSSION

It is easy to suggest an explanation of the individual differences in tuberculin sensitivity manifested by persons suffering from active tuberculosis, since we know that the progress of the disease first stimulates and finally damps down the allergic function—a fact which implies marked variation of reactivity in the individuals of a clinically "active" group. When, however, we attempt to explain the equally marked variation in reactivity shown by individuals free from active disease, the problem becomes more complicated, as "anergy," or at least "negative energy," cannot be cited as a factor.

All the reactions, whether manifest to high-dilution "end-points" or to the stronger concentrations of tuberculin, must be taken to prove antecedent infection with the tubercle bacillus. Animal experiments show that the

tuberculo-allergy evoked by infection with strains of low virulence gradually dies out as the lesions undergo spontaneous healing. From this it might seem reasonable to conclude that the variations in tuberculin sensitivity in "healthy" persons depend on individual differences in the degree of spontaneous healing of minute lesions due to early or recent subinfections.

It is probable that we all encounter minute doses of tubercle bacillary infection in our daily life, and, thanks to our resistance to reinfection, partly natural and partly acquired through previous contact with Koch's bacillus, we kill off these minor invasions at or near the threshold and remain in health.

The community under discussion, consisting of the inmates of a mental hospital, is clearly one in which the handing round of respiratory infections is liable to occur; and the well-known fact that tuberculosis mortality tends to be high in mental hospitals supports the suggestion that reinfections are common in such institutions, and often eventuate in disease.

Such reinfection must vary greatly in frequency and extent, according to the number of unrecognized "open" cases in the community and according to accidental factors depending on contact with infected room-mates, table companions, and work associates, and accentuated by the prevalence of the spitting habit, the breathing in of contaminated dust, and so forth.

It is probable that these variations in intensity of subinfection suffice to explain the differences in reactivity noted, if taken in conjunction with the differences in resistance efficiency possessed by the individuals concerned. In this latter connexion the differences observed between males and females are of interest, and deserve further investigation.

CONCLUSIONS

1. In the groups investigated, marked individual variations in cutaneous tuberculin sensitivity were noted.

2. These variations were apparent both in regard to "end-point" reactivity with serial dilutions and to the intensity of reaction as evaluated through measurement of the size of the reaction area.

3. In the non-tuberculous groups—that is to say, the groups of persons free from clinically apparent tuberculosis—the variations were not associated with differences in general health, as tested by the rate of blood sedimentation in contrasted groups. In these healthy groups the females showed a more marked reactivity than the males; but both the males and the females of European race showed less reactivity than that recorded for South African native mine recruits in the report of the South African Tuberculosis Research Committee (1932). It is to be noted in this connexion that young adult females in Wales are liable to a more acute and severe type of tuberculosis than corresponding male groups, and that South African mine natives exhibit a still more marked liability to fatal acute tuberculosis. In other words, pronounced cutaneous tuberculin sensitivity in a group appears to be associated with liability to severe tuberculosis.

4. In actively tuberculous groups the reactivity of florid cases of the disease is greater than the reactivity of non-tuberculous persons; and the reactivity of tuberculous males appears to be greater than that of tuberculous females in the small groups tested. Here, however, the findings are complicated by the gradual onset of "anergy," as the cases progress in severity and as the systemic disturbance increases—a progression which, in Wales, tends to be more rapid in young females. This perhaps explains their lower sensitivity in the tuberculous group.

5. The "anergic" state in tuberculous persons is associated not only with loss of tuberculin reactivity, but with marked increase in the rate of sedimentation of the red blood corpuscles.

Our thanks are due to the medical superintendent of the Denbighshire Mental Hospital, through whose kind co-operation the observations here recorded were rendered possible.