six strychnine injections. Gained 1 lb., and sputum and cough nearly disappeared.

7. Scottish apprentice, aged 19. After admission for trivial injury of wrist developed symptoms of acute general tuberculosis. Pyrexia, rales at left apex, obstinate constipation, abdominal pain and retraction and vomiting; dry cough and night sweats. Von Pirquet's reaction strongly positive, but very slow in developing. Had one tuberculin and ten strychnine injections. When he left felt well, but there was dullness over left apex.

8. English A.B., aged 31. Cavity left apex. Tubercle bacilli in sputum $\frac{0}{1}$ to $\frac{5}{1}$. Von Pirquet's reaction feebly positive. Ill some months. In thirty-two days had three tuberculin and twenty-four strychnine injections. Sahli's inoculations over site of trouble seemed to ease cough and sputum. Patient left practically free from cough with scant sputum. No night sweats, and with a good appetite.

9. Greek stoker, aged 34. Ill six months. Both apices affected. Excavation. Anorexia and night sweats. Severe pain over right apex relieved by Sahli's inoculations. Three tuberculin and twenty-five strychnine injections in thirty-one days. Gained 2 lb., lost cough and night sweats. Regained appetite.

10. Swedish carpenter, aged 37. Ill fifteen months (?). Evident fibrosis. Three attacks of pleurisy with effusion. Rapidly losing flesh lately. Intense loathing for food. Severe pleuritic pains (which were relieved by inoculations). Von Pirquet's reaction positive. Fingers and nose congested and clubbed. In thirty-one days had three tuberculin and fifteen strychnine injections, and left with a good appetite, feeling fit, but still occasionally sweated at night. Physical signs *statu quo*.

11. Irish A.B., aged 36. Acute dry tuberculous pleurisy and lung fibrosis. Great anorexia; made what seemed to be a good recovery in forty-six days. Had five tuberculin and thirty-four strychnine injections. Sahli's inoculations relieved chest and shoulder pains. Each scarification developed an erythema bump larger than a five-shilling piece. There was a history of plumbism.

12. Australian seaman, aged 32. Ill over eighteen months. Expelled from workman's home on account of cough keeping the inmates awake at night. Both apices excavated. Five tuberculin, thirty-four strychnine injections, and three inoculations in thirty-eight days. Gained 4 lb., and practically lost cough. Tubercle bacilli fewer in sputum.

REFERENCE.

¹ BRITISH MEDICAL JOURNAL, September 28th, 1912.

THE CUTANEOUS TUBERCULIN REACTION OF VON PIRQUET.

By A. J. BRUCE LECKIE, M.D. EDIN.,

LATE RESIDENT MEDICAL OFFICER, ROYAL MINERAL WATER HOSPITAL,
BATH.

The cutaneous reaction was introduced by von Pirquet, who described the test in the *Berliner medizinische Gesellschaft* in 1907. It consists of vaccination with Koch's old tuberculin, said to be followed in tuberculous subjects by inflammatory phenomena.

The Tuberculin Employed.

I employed two solutions of tuberculin of different dilutions, making a series of observations with each. The weaker solution consisted of 25 per cent. solution of Koch's old tuberculin, the diluting medium consisting of 0.3 to 0.5 per cent. of carbolic acid in normal saline solution drawn up in fine sealed glass capillary tubes supplied by the Clinical Research Association. The stronger solution consisted of undiluted Koch's old tuberculin, issued in similar form to the previous by Parke, Davis and Co. Small rubber bulbs are supplied to facilitate expression of the fluid.

Application of the Test.

The method which I employed in applying the test may be shortly stated as follows:

The flexor surface of the forearm was cleaned with ether a sterilized large surgical needle was taken and the skin gently scarified in two places about 2 in. apart, sufficiently to remove the surface epithelium, leaving a reddish area, care being taken to avoid too much effusion of blood. Slight presence of blood is an advantage, as it denotes a small lesion which will render absorption more certain. To one area tuberculin was applied, to the other glycerine as a control. No dressings were applied, but instructions were given for the arm to be kept uncovered until the areas had dried. In children the attentions of the nurse are necessary. Sometimes scarification was performed through the tuberculin, at other times the application was made after scarification.

Most methods are the same in essentials but differ in minor details. Von Pirquet makes three scarifications; to

two of them he applies tuberculin, and the third is left free, forming the control. He also applies a few fibres of cotton for five minutes to prevent flowing. This, however, can be avoided by a little care on the part of the patient. McNeil rubs in tuberculin by boring into the skin with a blunt-pointed instrument, others employ a special chisel-shaped scarifier.

The Reaction.

Scarification rapidly produces fleshy-looking wheals surrounded by slight hyperaemia; these phenomena are traumatic, and disappear in twenty to thirty minutes. In an hour or so a faint erythematous ring gradually appears round the inoculated area, which slowly increases in intensity and breadth. It occurs in most cases whether they are going to react or not, but is not seen round the control. It, and it only, may be the only sign of activity at the end of fourteen to fifteen hours, when it will either disappear or increase, forming a red zone $\frac{1}{4}$ in. to $\frac{1}{2}$ in. in breadth, varying in different individuals. This zone is the first phenomenon of a positive reaction showing definitely in fifteen to sixteen hours. From fifteen to twenty-four hours we find slight swelling of the area and its surroundings, reaching its maximum in forty-eight or fifty hours, when a reddish or brownish papule presents itself, the brown hue being produced by coagulated serum and pigment in the tuberculin. This may not be the final stage. In some cases the papule edge separates into small discrete papules sometimes surmounted by vesicles; meanwhile the summit of the original papule subsides, so that a ring of elevations surrounds a depression, the whole encircled by an erythematous zone. The edge of the papule may be raised without subdivision. The subsidiary papules appear on the second or third day. In some cases a papule is not produced, but simply a persistent injected area which may subside at the end of the second day. A well-formed papule begins to subside at the end of the third day, and in a week or ten days a scaly, brown, quiescent area remains, which daily decreases until at the end of three to four weeks a small brown pigmented area alone remains. The pigmentation persists for weeks or months, and is due to pigment in the tuberculin, not to pigment derived from the blood, as it is never observed in the control. No reaction was observed in the controls, except an occasional evanescent hyperaemic ring. Von Pirquet observed several reactions in controls, probably due to contamination. The test is painless, unaccompanied by constitutional symptoms or inconvenience. I regard cases as positive which, after twenty-four hours, show even slight elevation or a persistent hyperaemic zone.

Abnormal Reactions.

Sometimes the inoculated area may have an irregular outline sharply delineated; in one case it resembled a "port wine stain," and appeared on the sixth day in a non-tuberculous subject; scattered over it were petechial haemorrhages. In several other cases haemorrhages appeared on the edges of the papules in four to five days. Never have I observed these on the controls; hence they are not due to trauma. One case showed a papule surmounted by a crop of vesicles, which subsided in twelve hours. The only excessive reaction which I have seen occurred in a case clinically free from tuberculosis. In forty-eight hours the test area was converted into a red oedematous swelling, 5 by 8½ cm. in breadth, the centre occupied by the papule; from this area a red lymphatic could be traced to the axilla. Pain was present, but there was no pyrexia or other constitutional symptoms. No enlarged glands were detected. Under treatment by fomentations, all except the papule had disappeared in twelve hours. Pyogenic infection, of course, cannot be absolutely excluded, but susceptibility to tuberculin must also be considered. These abnormal results occurred where a positive reaction was obtained. Four out of six cases showed no evidence of tuberculosis; two of them occurred with the 25 per cent. solution, including the excessive reaction. Atypical reactions may be exhibited by the reaction time, a pronounced latent period, or rapidity of onset. An early reaction may appear as a well-formed papule in a few hours, maintained for two or three days; papulation within twelve to fourteen hours may be regarded as early. Three of my cases exemplified this, one showing a papule in three hours,

maintained for five days, the other two maturing in seven and twelve hours respectively. Conversely delay in reaction may occur. Four of my cases exhibited this; one of these, in sixty hours, formed a papule, preceded by erythema. Another showed no activity until the lapse of ninety hours, when papulation occurred. Neither of these cases was tuberculous. McNeil observed two delayed reactions of ninety and one hundred and twenty hours. Raw has published cases in which there were violent reactions accompanied by marked pyrexia and brawny cellulitis; one of his cases became purulent. Wolff-Eisner and Kronig saw lymphangitis following inoculation. Furunculosis has been noticed by Bandelier and Roepke; ulceration by von Pirquet, Pfaunder, and Oppenheim; phlyctenules and lichen scrofulosorum by Doganoff and Moro. Such phenomena require notice as evidence against the complete safety of the test. According to von Pirquet, a second application may produce a late reaction on the abortive primary site in children clinically free from tuberculosis.

Nature of Test.

The reaction is regarded as specific in the sense of the production of antibodies stimulated by the extra toxin. Daels has examined the papules histologically, demonstrating giant cells of Langhans type surrounded by epithelioid cells produced either by the toxin or bacillary fragments. Is it not, however, possible that these papules were tuberculous, produced by living bacilli, as such have been found in tuberculin preparations?

Results Obtained with the Cutaneous Reaction.

Von Pirquet obtained 88 per cent. of positive reactions in tuberculous adults, and 10 per cent. in non-tuberculous cases; 97 per cent. reactions appeared among tuberculous children; 200 of the cases were confirmed by autopsy. Mills found reactions in 95 per cent. of cases, and failed to get results in non-tuberculous subjects. Among 155 patients McNeil saw 65 reactions, but only 10 out of 20 tuberculous cases gave results. In tuberculosis Bride observed 70 per cent. of reactions, but 20 per cent. of non-tuberculous individuals were positive. In my series of nearly 200 cases, almost half the tuberculous cases reacted, but 36 per cent. of positive results appeared among the non-tuberculous. Feer states that he never saw a failure in scrofula, whereas Impallomeni had no reactions in cases clinically free from the disease. My tuberculous cases may be tabulated as follows:

Disease.	No. of Cases.	Positive.	Negative.
Pulmonary tuberculosis ...	53	24	29
Tuberculous disease of bone	22	12	10
Tuberculous glands ...	2	2	0
Ltupus ...	1	1	0
? Tuberculous laryngitis ...	4	3	1
Tuberculous empyema ...	1	1	0

Value of Test.

The cutaneous reaction is an ingenious attempt to solve the difficult problem of early recognition of tuberculosis. Like the ocular test it is simple and devoid of discomfort; though not entirely free from untoward results, it is void of those tragic manifestations which condemn the conjunctival reaction. What is its value as a diagnostic aid? The results of observers are greatly at variance, and before an adequate reply can be given some points require consideration. The terms "advanced" and "old-standing" have been employed synonymously, and misleadingly so; advanced lesions frequently react, old-standing ones seldom. Von Pirquet failed to get results in advanced and cachectic cases. McNeil claims good reactions in chronic cases. Mills found persistent reactions in old healed lesions. Old-standing and moribund cases fail, no doubt, owing to toxin saturation and exhaustion of resistive power. I find that the older the patient the less is the probability of a positive result, as shown by the following table:

Tuberculous Cases giving a Positive Reaction with Age-Periods.

4-6 Years.	7-10 Years.	11-15 Years.	16-20 Years.	21-30 Years.	31-40 Years.	41-50 Years.	51-60 Years.	61-70 Years.
7+	11+	7+	5+	7+	2+	4+	0+	1+
0-	2-	0-	4-	13-	9-	7-	8-	3-

The table shows a decrease in positive results as age advances. I suggest that the skin in a young individual is more liable to react than in more mature years, as partly shown in the following table:

Non-Tuberculous Cases with Age-Periods.

4-6 Years.	7-10 Years.	11-15 Years.	16-20 Years.	21-30 Years.	31-40 Years.	41-50 Years.	51-60 Years.
0+	1+	6+	10+	13+	3+	1+	1+
1-	7-	11-	10-	12-	14-	8-	1-

In this table a considerable number between the ages of 11 and 30 react. Above 30 there is a rapid fall. Many tuberculous individuals from a few years of age up to 60 years fail while many cases clinically free respond. That a patient is apparently free from the disease is not proof of its absence, but as obviously tuberculous cases very often give no result, many cases which respond are probably healthy—a deduction which is legitimate. Von Pirquet obtained positive reactions in one-fourth of all children aged 1 to 2 years, one-third in those aged 3 to 4 years, one-half of those between 5 and 6 years, and two-thirds of those aged 11 to 14 years—a gradual increase with advancing years in early life similar to what is shown above.

Hamburger made 848 autopsies on children to ascertain the correspondence between reactions and tuberculous lesions as follows:

Hamburger's Post-mortem Results.

Age.	No. of Individuals with Tuberculous Lesions.
1 to 3 months ...	4 per cent.
3 to 6 months ...	18 "
6 to 12 months ...	23 "
2nd year ...	40 "
3 to 4 years ...	60 "
Puberty ...	70 "

These valuable statistics agree to some extent with von Pirquet's results. Naegeli goes further, and states that 72 per cent. of all individuals show evidence of tuberculosis. The majority of children clinically tuberculous between 4 and 15 years of age react, but failures are not uncommon. According to von Pirquet, 20 per cent. of children clinically free from tuberculosis give positive results. No results are obtained under six months, but between 10 and 14 years of age 55 per cent. react as compared with my results, where 60 per cent. reacted up to 14 years and 40 per cent. between 11 and 15 years. Calmette only relies on the cutaneous test under 3 years of age, although he admits an error of 4 per cent. among infants. He holds that this test reveals latent and healed cases as contrasted with the conjunctival reaction, for which he claims the demonstration of an active focus. Stern agrees with him. It is unreasonable to suppose that the minor differences of introduction of the tuberculin in the two tests are going to portray such important states. Blümler points out how rare tuberculosis is under 2 years. Radcliffe attended von Pirquet's clinic, and reports that the cutaneous method is relied upon under 2 years of age; also that tuberculin treatment is continued until the test becomes negative. The advantage of this is not evident. If the test fails owing to saturation with toxin it does not signify cure; if it is considered to become negative as a result of cure, this completely destroys the idea that the test reveals latent or healed lesions. Blümler relies upon it up to 2 years of age, but he weakens his position by the assertion of its greater value if negative. Bandelier and Roepke's suggestion that reaction implies a previous infection with tubercle bacilli has nothing to support it. Among my cases, 66 per cent. tuberculous females reacted as compared with 35 per cent. of tuberculous males. Among cases clinically free the ratio was 35 per cent.

females to 30 per cent. males. Thus as many non-tuberculosis women give positive results as tuberculous men.

The female liability to react supports the suggestion of delicacy of skin being a factor which cannot be ignored. I cannot agree with McNeil that a hard skin will explain some late reactions if the scarification was adequate; the abrasion should, of course, be regulated according to the quality of the skin. Bride regards the test as valuable in early pulmonary tuberculosis; the reverse is the attitude adopted by Roepke and Bandelier. I had only one case of lupus which gave a good result. One would expect a skin already the site of tuberculous disease locally to react readily to inoculation with the same toxin. Kreibich and Bandler refer to severe reactions in skin lesions; they found 22 results out of 26 cases. Two out of my 3 cases of pleural effusion reacted; the failure exhibited definite signs of pulmonary tuberculosis. Impallomeni comments on good results obtained in osseous lesions, especially in cases cured or improving; he had the unique experience of never having seen a reaction in a case clinically free from the disease. Only about half of my osseous lesions responded. Curschmann notes 10 reactions out of 11 patients, the failure being in a cachectic case. Bandelier and Roepke note good results and severe reaction in surgical tuberculosis which my records do not bear out. They issue a warning that cases with tuberculous glands and simple effusion into a joint are apt to be misleading, as a good reaction may be obtained and tuberculous joint trouble as a consequence diagnosed. McNeil places reliance on the test in obscure traumatic joints. Among my series rheumatic cases gave good reactions; 8 out of 13 cases responded. Cases of chorea without exception failed. Among my cases cardiac lesions, plumbism, carcinoma, etc., gave results. Three syphilitic patients failed; these are of interest, as Favre and Nicholas claim as good results in such cases as in tuberculosis. Out of 12 cases of enteric fever 1 reacted. Von Pirquet affirms that enteric complicated with tuberculosis does not react. Any superimposed toxæmia, according to Holt, interferes with the reaction. In tuberculous peritonitis 3 out of my 5 cases failed. McNeil found good response in such lesions, but they proved unsatisfactory in the hands of Bandelier and Roepke, though Bride claims value for it in early diagnosis from enteric. Bandelier, Bride and Roepke report bad results in tuberculous meningitis. There is no doubt that the reaction is most marked in vigorous individuals, irrespective of the intensity of the infection, and no prognostic value can be applied to it. Early and late reactions have no significance, though Wolff-Eisner regards early reactions as indicative of an unfavourable termination, and delayed results as suggestive of healed or latent lesions. Some of my cases were tested with 25 per cent. solutions, but the results were very similar to those obtained with the undiluted tuberculin.

Conclusions.

From the preceding observations I have arrived at the following conclusions:

1. That the cutaneous reaction is of no prognostic or diagnostic value.
2. That results are more frequently obtained in women and children than in men.
3. That the older the individual the less likely is the reaction to be obtained; old-standing lesions, as distinguished from advanced cases, usually fail.
4. That cases of rheumatism give more positive results than tuberculous individuals.
5. That late and early reactions have no clinical significance.

BIBLIOGRAPHY.

- McNeil: *BRITISH MEDICAL JOURNAL*, 1909, vol. ii.
 Bandelier and Roepke: *Tuberculin in Diagnosis and Treatment*, 1909.
 Doganoff: *Wien. klin. Woch.*, 1907, No. 31.
 Moro: *New York and Philadelphia Medical Journal*, 1908.
 Daels: *Medizinische Klinik*, 1908, No. 3.
 Feer: *Beiträge zur klin. tuberkulose*, xviii, No. 1.
 Radcliffe: *Fifth Annual Report, King Edward VII Sanatorium*, Midsbury, 1910-11.
 Bride: *BRITISH MEDICAL JOURNAL*, 1910, vol. i.
 Favre: *Bulletin Société Médicale des Hôpitaux*, 1910.

Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

THE INTENSIVE METALLIC IODINE TREATMENT FOR CHRONIC ARTHRITIC AFFECTIONS.

Preliminary Note.

IODINE seems to be unique in combining relative harmlessness with a range of beneficent action, the extent of which had not been realized until the intensive method, for which it is well suited, had been successfully resorted to in phthisis and in tuberculosis by Boudreau and by Curle and Reeve, simultaneously with its universal adoption by surgeons as the best local antiseptic. It is to the iodine that the iodides owe their efficacy in pneumonia, in syphilis, in adenopathies, etc. They, too, are capable of intensive administration, as for instance in the special treatment of aortic aneurysm, which I instituted many years ago by long-continued heroic doses of potassium iodide, in association with the suppression of fluids in the dietary. But they lack some of its virtues; and they have toxic tendencies of their own (particularly potassium iodide) which depress the nervous system instead of stimulating it, that stimulation being a leading feature of iodine, and its only obvious effect upon the nervous structures and functions. For that reason, and for dread of their greater hydrating effect upon the mucous membrane, we have systematically shunned them in phthisis. Above all they lack its volatility, which explains so much.

Hitherto iodine had practically not been tried internally. Therefore, in spite of its extensive use as an inhalant, we had missed the greater opportunity of its continuous volatilization all the way down the alimentary tract, which seems to me to be the practical feature in Boudreau's "intensive iodine method" by means of the strong 10 per cent., iodide free, French tincture (the same as our Indian tincture). This I may now venture to identify more closely as the "metallic iodine method," as the iodine is almost entirely precipitated in the glass by the water or other beverages which have to be added to the dose. Whilst perusing the account, published only last January,¹ of his remarkably successful experience of ten years in phthisis and in tuberculosis, I concluded that it might apply at least equally well for my own ailment, as the iodides have been for so long, not shunned as in phthisis, but steadily trusted and prescribed in all arthritic affections—even for rheumatoid arthritis (which is the main objective of this note), although so like phthisis in its record of depression as a cause and a result. Not having been disappointed, I have no diffidence in inviting its wide trial in all of them, above all in the early rheumatoid stage, without needlessly delaying for many sufferers a probable benefit (allowing, of course, for exceptional idiosyncrasies) in the direction of a general or "hormonic" stimulation, whatever the arthritic advantage may ultimately amount to in individual cases.

Of upwards of three years' progress, my symptoms, which had been denied any thorough treatment beyond a long course of large doses of aspirin, or any rest, were those of a severe spastic coxalgia with marked vasomotor and blood pressure depression, and considerable muscular weakness, and eventual atrophy. Last September, at Dax, they had their first instalment of rest and of strenuous as well as effective treatment, under Dr. Delmas, whose diagnosis was early dry arthritis of the hip (although the x rays had recently given no structural evidence of it), and slightly too of the opposite shoulder. The winter brought back much of the trouble. Seven weeks ago, on reading Boudreau, I started a thorough course of his treatment, and I have now settled down, after taking more, to a daily total of 100 drops of the tincture, containing 10 grains of iodine, with no other treatment except, quite recently, a large morning dose of aspirin, which now seems to be more active, and to alleviate the symptoms slowest to yield and presumably nervous, those of recurring severe barometric reactions. The most rapid result was an initial and lasting constitutional rebound; and this has been followed by an arrest, as I hope, but at any rate by a steady improvement in all the coxalgic symptoms and in

¹ *Journ. de méd. de Bordeaux*, January 4th, 1914.