the kidneys, and if these are damaged it is safest, in our present state of knowledge, to restrict proteins somewhat.

Such restrictions must never be carried to the extreme limits formerly advocated, and two-thirds of a gram per kilogram of body weight may be regarded as a minimum.

In the nephrotic type of case a high protein diet is usually indicated.

REFERENCES

- ¹ Claude Bernard, quoted by A. M. Fishberg. *Hypertension and Nephritis*. Third edition, p. 163. 1934. London: Baillière, Tindall and Cox.
- ² Watson, Chalmers: Appendix to *Food and Feeding*, November, 1910. (Quoted by Drummond.)
- ³ Newburgh, L. H.: *Arch. Int. Med.*, 1919, xxiv, 359.
- ⁴ Polvogt, L. M., McCollum, E. V., and Simmonds, Nina: *Bull. Johns Hopkins Hosp.*, 1923, xxxiv, 168.
- ⁵ Osborne, T. B., Mendel, L. B., Park, E. A., and Winternitz, M. C.: *Journ. Biol. Chem.*, 1927, lxxi, 317.
- ⁶ Evans, N., and Risley, E. H.: *Californian and Western Med. Journ.*, 1925, xxxiii, 437.
- ⁷ Drummond, J. C., Crowden, G. D., and Hill, E. L. G.: *Journ. Physiol.*, 1922, lvi, 413.
- ⁸ Addis, T., MacKay, E. M., and MacKay, L. L.: *Journ. Biol. Chem.*, 1926, lxxi, 139.
- ⁹ Miller, A. J.: *Journ. Exper. Med.*, 1925, xlii, 897.
- ¹⁰ Jackson, H., jun., and Riggs, M. D.: *Journ. Biol. Chem.*, 1926, lxxvii, 101.
- ¹¹ Reader, V. B., and Drummond, J. C.: *Journ. Physiol.*, 1924-5, lix, 472.
- ¹² Jackson, H., jun., and Moore, O. J.: *Journ. Clin. Investig.*, 1928, v, 415.
- ¹³ Smith, A. H., and Moise, T. S.: *Journ. Exper. Med.*, 1927, xlv, 263.
- ¹⁴ Anderson, H.: *Arch. Int. Med.*, 1926, xxxvii, 297.
- ¹⁵ MacLean, H., Forest Smith, J., and Urquhart, N. L.: *Journ. Exper. Path.*, 1926, vii, 360.
- ¹⁶ Squier, T. L., and Newburgh, L. H.: *Arch. Int. Med.*, 1921, xxviii, 1.
- ¹⁷ Addis, T.: *Journ. Clin. Investig.*, 1926, ii, 417.
- ¹⁸ Keutmann, E. H., and McCann, W. S.: *Ibid.*, 1932, xi, 973.
- ¹⁹ Addis, T.: *Journ. Amer. Med. Assoc.*, 1925, lxxxv, 163.
- ²⁰ Strouse, S., and Kelman, S. R.: *Arch. Int. Med.*, 1923, xxxi, 151.
- ²¹ Rennie, J. B.: *Lancet*, 1935, ii, 658.
- ²² MacAdam, W.: *British Medical Journal*, 1933, i, 452.
- ²³ Callis, H. A.: *Med. Record*, 1935, cxli, 149.
- ²⁴ Aldrich, C. A., and Boyle, H. H.: *Journ. Amer. Med. Assoc.*, 1933, c, 1979.
- ²⁵ Fishberg, A. M.: *Hypertension and Nephritis*. Third edition, p. 162. 1934. London: Baillière, Tindall and Cox.
- ²⁶ Idem: *Ibid.*, p. 59.
- ²⁷ Nuzum, F., Osborne, M., and Sansum, W.: *Arch. Int. Med.*, 1925, xxxv, 492.
- ²⁸ Mosenthal, H. O.: *Amer. Journ. Med. Sci.*, 1920, clx, 808.
- ²⁹ Lieb, C. W.: *Journ. Amer. Med. Assoc.*, 1926, lxxxvii, 25.
- ³⁰ McClennan, W. S., and Du Bois, E. F.: *Journ. Biol. Chem.*, 1930, lxxxvii, 651.
- ³¹ Thomas, W. A.: *Journ. Amer. Med. Assoc.*, 1927, lxxxviii, 1559.
- ³² Harris, I., Aldred, C. N., and Hawthorne English, A. W.: *Lancet*, 1935, i, 1327.
- ³³ Benedict, F. G.: *Human Vitality and Efficiency under Prolonged Restricted Diet*. Carnegie Institute of Washington. Publication No. 180. 1919.
- ³⁴ Volhard, Franz: *The Kidneys in Health and Disease*, p. 393. By Berglund and Medes. London: Henry Kimpton. 1935.
- ³⁵ Lashmet, F. H., and Newburgh, L. H.: *Journ. Amer. Med. Assoc.*, 1930, xciv, 1883.

Sir H. Lindo Ferguson, C.M.G., M.D., F.R.C.S.I., has retired from the active staff of Dunedin Hospital and Medical School, following his withdrawal from the chair of ophthalmology in the University of Otago. He was associated with the hospital for fifty-two years as ophthalmic surgeon and had been dean of the Medical Faculty of the University for the last twenty-two years. He qualified at Dublin in 1880, and he is believed to have been the first trained ophthalmic surgeon to settle in New Zealand, and his fame drew patients from as far as Australia. At the official opening of the new administration block of Dunedin Hospital on March 23rd a warm tribute was paid by Professor J. B. Dawson, chairman of the honorary visiting staff and professor of obstetrics, to Sir Lindo Ferguson's period of service to the institution, which was a record of hospital service that had been seldom, if ever, equalled. In this new century of amazing advances in medical science, he said, Sir Lindo had retained a clearness of vision, an acuity of mind, and a capacity to select and assimilate the best of the new doctrines which many of his younger colleagues might well emulate. Sir Lindo is an honorary Fellow of the American College of Surgeons and a Fellow of the Royal Australian College of Surgeons.

THE RENAL FUNCTION IN DISEASE*

BY

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About a hundred years ago Richard Bright¹ gave us clinical descriptions of kidney disease which in many respects are difficult to surpass to-day. Physiology has since supplied by Cushny² hypothesis of renal function, which, though probably not acceptable in its entirety, is still considered to be the basis of what we know of the secretion of urine. Nearly forty years ago Rose Bradford³ made some experiments on the kidney which have since become classical, and Verney⁴ and Winton⁵ have recently added a great deal to our knowledge of the behaviour of the kidney under varying conditions. The present paper is an attempt to bring the findings of the physiologists into line with the observations that can be made at the bedside.

Physiology of Renal Secretion

The arrangement of the glomerulus and its tubule and their blood supply is represented schematically in the diagram.

The afferent arteriole enters at A, and breaks up into capillaries which form the glomerulus. Through these capillaries and the membrane lining Bowman's capsule, water and substances in solution pass from the blood stream into the tubule, but the membranes are (normally) impermeable to protein and, of course, to the blood cells. The capillaries reunite to form the efferent vessel, E, which again breaks up into capillaries over the cells of the renal tubule. These again unite into venules, V, which eventually join to form the renal vein.

According to the Cushny theory a simple process of filtration occurs in the capsule, and from this filtrate the cells of the tubule secrete back into the blood stream a fluid of constant composition, a saline solution containing the water and salts necessary to the blood in their correct proportions. The most attractive feature of this hypothesis is that it relieves one of the necessity for supposing that the renal cells themselves have some unique power of varying their secretion according to the needs of the body at the moment. Special mechanisms probably exist for the excretion of excess of water and for the synthesis of ammonia and hippuric acid.

The urine may therefore be looked upon as the waste material from the blood filtrate; its composition depends primarily upon the composition of the blood.

Reserve Forces of the Kidney

Nevertheless the kidney is capable of increasing its normal rate of activity in two distinct ways, and each of these brings about changes in the composition of the urine. In the first place the number of nephrons in the normal kidney is far more than is necessary under ordinary circumstances, and we know that they undergo alternating periods of rest and activity, the blood supply to the resting glomeruli being practically shut off or possibly shunted through the artery of Ludwig. The ability to

*An address delivered to the Dewsbury Division of the British Medical Association, March 20th, 1936.

call out an increased number of nephrons has been called by Verney *the structural reserve of the kidney*.

In the second place the effective filtration pressure in the glomerulus, commonly known as the glomerular pressure, can be increased independently of the systemic blood pressure. Reference to the diagram shows that the glomerular pressure can be altered by changes at four distinct points. It can be increased by increasing the arterial pressure, or, more correctly, the pressure in the afferent arteriole, A; it can also be increased by contraction of the efferent arteriole, E; increase of the ureter pressure, U, on the other hand, will reduce the filtration pressure in the glomerulus, and increase of the venous pressure, V, has the combined effect of increasing the pressure in the efferent arteriole and at the same time causing compression of the tubule by dilatation of its surrounding venules. The result of these effects has been shown by Verney and Winton to reduce the filtration pressure.

Verney terms the ability of the kidney to vary its glomerular pressure in this way *the functional reserve of the kidney*. This author has also shown by animal experiment that, no matter by what means the glomerular pressure is altered, the composition of the urine depends upon the rate of its secretion. If in a pair of kidneys the ureter pressure of one is increased while the arterial pressure of the other is reduced to such an extent that the rate of secretion of the two kidneys is the same, then the composition of the urine is also found to be the same.

It is also found that if the glomerular pressure is increased the composition of the urine approximates more and more closely to that of the blood plasma minus its proteins, and has therefore a specific gravity approaching more and more nearly to 1009. This is because when filtration is rapid there is less opportunity for activity on the part of the tubule cells, and the fluid leaving the distal end of the tubule has undergone little change in composition since its filtration at the glomerulus. Conversely, if the glomerular pressure is lowered the composition of the urine is more variable and highly differentiated, because during its relatively slow passage through the tubule the renal cells have had increased opportunity for the reabsorption of water and salts. The resulting urine will be dilute or concentrated according to the state of the blood at the moment. Unless much water has been ingested the specific gravity will be considerably more than that of the blood plasma, and the urea percentage will be high.

We may therefore summarize the physiological findings which are important for our present purpose as follows. The kidney responds to the varying demands of the body in two chief ways: (1) by increasing (or reducing) the number of nephrons actually in use; and (2) by varying the glomerular pressure. A high glomerular pressure gives rise to a copious dilute urine, which differs little from a simple filtrate of the blood plasma. The specific gravity of such a urine is approximately 1009. A low glomerular pressure gives rise to a highly differentiated urine, which under normal circumstances is concentrated and of high specific gravity. The total amount of waste products (low-threshold bodies) excreted depends upon the volume of the *glomerular filtrate* and not upon the volume of the urine.

Syndromes of Renal Disease

Let us now leave the physiological laboratory for the time being, and consider the clinical appearances of renal disease as we see them in practice and in the hospital wards. Whatever classification of kidney disease may be adopted it will be agreed that in general two main syndromes can be recognized. The first we may briefly

call *oedematous nephritis*, the features of which are oedema, oliguria, concentrated urine, and no nitrogen retention (no tendency to uraemia). This syndrome is typically seen in acute and subacute nephritis and in the albuminuria of pregnancy. The second may be called the *uraemic syndrome*, the main features of which are dry skin (no oedema) and thirst, polyuria, dilute urine (fixed specific gravity), and tendency to nitrogen retention. This is typically seen in the late stages of chronic nephritis, and may occur as a terminal stage in any disease of the kidney. It is usually associated with a permanently high blood pressure, and may be seen in patients who have previously passed through the syndrome of oedematous nephritis.

Considering these two syndromes in this way, and bearing in mind the changes in the composition of the urine which we have seen to correspond with variations in the glomerular pressure, it seems rational to suggest that the oedematous syndrome results from a low glomerular pressure and the uraemic syndrome from a high glomerular pressure. Let us therefore examine these syndromes a little more closely from this point of view.

Renal Oedema

Normally, as we have seen, only a portion of the total number of the glomeruli of the kidney are in action; their glomerular pressure is adapted to the needs of the body at the moment, and they produce an amount of filtrate which is sufficient for the necessary removal of waste products. Suppose that the glomerular pressure is now pathologically lowered by some disease process. The amount of filtrate produced in each glomerulus will be less than before, but by calling out the structural reserve, and using a larger number of glomeruli, the total filtrate can be brought up to a normal level, and the nitrogenous substances be satisfactorily excreted. The slow secretion will, however, lead to increased tubular reabsorption of salt and water, and this saline fluid will be retained in the body as oedema unless it can be excreted by other channels than the kidney. The total amount of urine will be less than normal, but it will contain more than its usual percentage of urea and similar substances. Thus the four outstanding features of oedematous nephritis can be simply explained by the supposition that the glomerular pressure of the kidney has been reduced.

This, I hold, is the only satisfactory explanation of the oedema of kidney disease, and the only theory which will account for the anomaly of salt and water retention together with adequate nitrogen excretion. But note that uraemia *can* occur if the glomerular pressure falls so low that even the whole reserve of nephrons cannot produce an adequate amount of filtrate. Such a condition occurs in cases bordering on anuria.

Let us look for further evidence in support of the theory. While it was being elaborated from the work of Verney and Winton, Shaw Dunn⁸ concluded from a consideration of the diffuse nature of the glomerular lesions in oedematous nephritis that if the blood supply were distributed equally through a greater number of nephrons than usual the opportunities for reabsorption would be increased, and that this might be an explanation of the oedema.

Histological evidence can also be held to support the theory that in oedematous nephritis the glomerular pressure is reduced. In *acute nephritis* there is swelling of the capillary loops, with endothelial proliferation and infiltration with leucocytes, so that the blood supply is much impeded, many of the vessels containing few, or no, red corpuscles. In *subacute nephritis* more chronic changes of the same nature are seen.

The type of oedematous kidney disease often known as *nephrosis* has been long considered to be a disease primarily affecting the tubules, but Shaw Dunn⁹ has recently demonstrated that the glomerular capillaries show a condition of abnormal patency, and that this condition again is diffuse throughout the kidney. Verney⁵ has already suggested that "a fall in the tone of the glomerular vessels with a consequent rise in the inter-tubular capillary pressure may conceivably be a factor in initiating the oliguria and proteinuria of nephrosis," and it is just such a condition that Shaw Dunn seems to have found.

I cannot here go fully into all the other theories of renal oedema, but Epstein's theory must be mentioned, since it is the only one which seems to be withstanding the test of time. Epstein showed that in all cases of chronic and severe renal oedema the plasma protein had been depleted by the prolonged loss of albumin in the urine, and he also demonstrated that this lack of plasma protein, by lowering the colloid osmotic pressure, would encourage the transudation of fluid from the blood stream into the tissues. Observations made since Epstein advanced his theory have left no doubt that the lack of protein in the blood plasma is an important factor in the production of renal oedema, but it cannot be the only factor, since this loss of protein does not occur in acute nephritis or pregnancy albuminuria, although we know that oedema may accumulate rapidly in those diseases. We may therefore look upon lowered glomerular pressure as the probable initial cause of renal oedema, supplemented by loss of plasma protein in the more protracted cases.

Chronic Nephritis

When we turn to the uraemic syndrome there is no difficulty whatever in accepting a high glomerular pressure, together with loss of nephrons (destroyed by disease) as an explanation of the peculiarities of renal function in this stage of kidney disease. This has already been fully argued by Verney. Increase of glomerular pressure will account for the production of a copious urine with a specific gravity constantly about 1009, and this will, in turn, account for the absence of oedema and the presence of its clinical opposite—the dry skin and thirst of chronic nephritis. It has been shown by experiment that pathological reduction of the number of nephrons results in a compensatory polyuria. Thus many years ago Rose Bradford showed that if part of the kidney were destroyed the remainder would often secrete more urine than had previously been produced by the whole kidney. But although the urine might thus be increased in volume it was relatively dilute, and the amount of urea excreted was less than before. Verney has more recently confirmed these findings by producing a sudden obstruction to the blood supply through half the kidney, and showing that the remainder of the kidney immediately increased its glomerular pressure and excreted a copious urine which resembled in its composition a simple filtrate of the blood plasma.

The raised glomerular pressure will increase the amount of filtrate produced by each nephron, and thus compensate for a time for the destruction of part of the kidney; we know that, clinically, polyuria antedates uraemia often by months or years. But eventually there are too few nephrons remaining to produce an adequate filtrate, even though they work under the highest possible pressure, supplemented by a high systemic blood pressure. Nitrogen retention then ensues, followed by the symptoms of uraemia.

We see this syndrome clinically in cases of chronic nephritis and nephrosclerosis, though it may also occur in the end stages of any destructive disease of the kidney, such as tuberculosis or polycystic disease. After death

we find areas in which the glomeruli are fibrous and presumably functionless, their tubules being atrophied, and other areas in which there is hypertrophy with dilatation. In general, the more chronic the course of the disease the more patchy do we find its distribution, for patients with the more intense and diffuse involvement have died in the subacute stage, there being presumably no nephrons sufficiently normal to develop the compensatory increase of glomerular pressure.

Treatment and Prognosis

Time does not permit me to deal with some other aspects of my subject such as the nature of albuminuria and high blood pressure, but I may conclude by considering some of the clinical implications to which we are led by a study of the renal function in disease. If we accept the views I have put forward we see that in the oedematous syndrome the blood supply to the glomeruli has become altered in such a way that their filtration pressure is reduced. As yet we know of no way of restoring that blood supply to normal, but we know that prolonged rest in bed and warmth has a favourable influence on the course of the disease. It has been shown that chilling of the body surface, on the other hand, produces a contraction of the renal vessels, which will therefore impede the blood supply still more.

We can also try to adjust the excretory needs of the body so far as possible to the type of function which the damaged kidney can perform. Thus the intake of both salt and water can be limited. Restriction of protein in the diet is probably of less importance at this stage, but it may be advantageous in further resting the kidney, as we know that the normal kidney has to call upon its reserves of function when a large amount of nitrogen requires to be excreted.

In the uraemic syndrome, on the other hand, the patient may have a liberal amount of water, corresponding roughly with the amount of urine he is excreting. Salt may be given in moderate quantities, but protein food should be restricted to the minimum. It is better for such persons to live on an almost exclusively vegetarian diet. May I remind you here that in a diet restricted in protein fish is *not* to be given as a substitute for meat, and that half a pint of milk contains more protein than an ounce of beef.

It is extraordinary to what extent really strict limitation of protein will often improve the symptoms in cases of chronic nephritis which have reached the stage of nausea, anorexia, and vomiting. Although the disease in the long run is progressive and incurable, it is quite as rational to do all we possibly can to slow down its course as it is to insist upon rest in cases of heart failure.

With regard to tests of renal function, I am gradually eliminating most of them and relying more and more upon two simple methods. First we must have a test for the amount of accumulation of waste products in the blood. Here I use the blood non-protein nitrogen investigation, though the blood urea estimation gives almost equally good results. Such a test will estimate the efficiency of the kidney as an excretory organ and the distance the patient has already travelled towards uraemia, but it is chiefly of use in the late stages of the disease, and is not a delicate test of renal function. We need, therefore, a test which will show us to what extent the reserve forces of the kidney are already used up. In the oedematous case the degree of oedema, checked if possible by frequent weighing of the patient, is a sufficient guide to progress. In the non-oedematous case the dilution and concentration test of Volhard, modified by Rosenberg,¹⁰ furnishes exactly the information we require, and informs us, supposing that the blood test is satisfactory, whether excretion is being

performed normally or only by the aid of a permanent increase of glomerular pressure.

The test is as follows. On the first day the patient, after passing urine, drinks 1,500 c.cm. of water within half an hour. Urine is passed at half-hourly intervals for the next four hours, each specimen being saved separately and tested for volume and specific gravity. Normally the whole 1,500 c.cm., often more, is excreted within the four hours, and the specific gravity falls to 1002 or less. The second day ordinary meals are given, but the amount of fluid is limited to 500 c.cm. for the whole twenty-four hours, taken in four roughly equal portions. Fruit should not be given, or should be reckoned as fluid. Urine is passed as and when the patient wishes, and each specimen is again collected separately and tested for volume and specific gravity. The total urine for the day should not exceed 750 c.cm., and the specific gravity should rise to at least 1027.

In cases of renal insufficiency the volume of urine on the first day is too little, while that on the second day

is too much, as excretion tends to continue at the same rate irrespective of variations in the requirements of the body. The limits of variation in specific gravity become more and more narrowed as the disease progresses, until at length a fixed point of about 1009 is reached. Often the dilution test will show a minimum of about 1005 and the concentration test a maximum of about 1015 long before the patient complains of any symptoms or the blood shows any evidence of uraemia.

REFERENCES

- ¹ Bright, Richard: *Guy's Hospital Reports*, 1836.
- ² Cushman, A. R.: *The Secretion of the Urine*, second edition. London, 1926.
- ³ Bradford, J. Rose: *Lancet*, 1898, i, 765.
- ⁴ Verney, E. B.: *Ibid.*, 1929, i, 751.
- ⁵ *Idem*: *Ibid.*, 1930, ii, 53.
- ⁶ Winton, F. R.: *Journ. Physiol.*, 1931, lxxii, 49.
- ⁷ Platt, R.: *Nephritis and Allied Diseases*, London, 1934.
- ⁸ Dunn, J. Shaw: *British Medical Journal*, 1933, ii, 477.
- ⁹ *Idem*: *Journ. Path. and Bact.*, 1934, xxxix, 1.
- ¹⁰ Rosenberg, M.: *Die Klinik der Nierenkrankheiten*, Berlin, 1927.

VALUE OF THE NEGATIVE SUBCUTANEOUS TUBERCULIN TEST

B7

ROBERT CARSWELL, M.A., M.B.

In the Epitome of Current Medical Literature published with the *British Medical Journal* of March 17th, 1934, (p. 44, para. 227), there occurs the heading "Limited Diagnostic Value of Subcutaneous Injections of Tuberculin." This refers to two articles by N. Lindborg in the Swedish journal *Hygiea*,¹ in which the author reports that on following up sixty-six subcutaneous negatives* obtained in doubtful cases of active pulmonary or hilar tuberculosis in a Swedish sanatorium eleven instances were found in which tuberculosis subsequently developed. Five of these cases developed the disease within a year, one of them within three months, with pleurisy, and one, a boy of 8, died after an illness of two weeks' duration of tuberculous meningitis three months after the negative test. These five cases Lindborg considers to be "indisputable" evidence that a negative test does not always agree with the clinical event or exclude the possibility of the development of tuberculous disease within a short time.

Lindborg finds support for his conclusion in the figures of Kettelkamp² (the Robert Koch Hospital, St. Louis, Missouri) and Steidl and Heise³ (the Trudeau Sanatorium, New York), 13 per cent. and 6.6 per cent. respectively of clinical tuberculosis found to have occurred in a follow-up of their similarly tested negative cases. The results of Berg⁴ (Wiipuri, Finland)—namely, no subsequent tuberculosis in his small group of ten negative cases†—are thought by Lindborg to be "perhaps due to differences in the material, conditions, infection possibilities, or treatment."

Veterinary Reports

Lindborg's conclusion also finds support in certain veterinary reports. "During the year 1922," writes Parker⁵ (Newcastle-upon-Tyne), "while examining a number of carcasses and internal organs of dairy cows which, immediately prior to slaughter, had been subjected to the subcutaneous tuberculin test, the writer was

surprised to find lesions of tuberculosis in a considerable proportion of those which had given no reaction whatever." In a special research on the subject Parker found that among fifty subcutaneously tested animals eleven of the nineteen negatives showed post-mortem evidence of tuberculosis. In only one of these were the post-mortem findings confirmed by the microscope or by guinea-pig inoculation. Three of the failures were classed as "ceased reactors." One failure to all tests was an attractive-looking animal that had never been known to suffer from illness of any description. She was tested on four occasions by the subcutaneous method, at intervals of not less than one year, also by the ophthalmic and intradermal methods. The result of the test on every occasion was completely negative. Yet on post-mortem examination, within seventy-two hours of the final test, lesions of tuberculosis were found in the bronchial, mediastinal, portal, and mesenteric lymphatic glands. Jowett⁶ (Capetown) made a comparative study of subcutaneous and intradermal tests, checked by post-mortem examination, in 225 cattle. In his table of results he gives nine cases that were subcutaneously negative, post-mortem tuberculous, and intradermally positive. One of his negative cases (positive three and a half years previously) showed at post-mortem three fibro-caseo-calcareous tuberculous lesions in the left bronchial lymphatic gland, each the size of a pea, which were proved by guinea-pig inoculation to contain living virulent tubercle bacilli. Rutherford (Ottawa), in an article on "Open-air Experiments with Tuberculous Cattle,"⁷ gives the interesting post-mortem records of six cases that became "ceased reactors" and of sixteen cases that became "ceased reactors" but subsequently reverted to the positive state. One of his negative cases, a healthy and thrifty 2-year-old heifer, showed that an animal "while still retaining externally the appearance of health may within a comparatively short period become infected to such an extent as to nullify the action of tuberculin." She passed the subcutaneous test successfully on four occasions, yet the post-mortem record is: "Right lung contained six purulent cavities each as large as an egg; tuberculous process involving visceral, diaphragmatic, and costal pleural surfaces, right side of thorax; anterior and posterior mediastinal glands also tuberculous." His experiences led him to conclude that open-air treatment was "not likely to exercise any marked curative influence on animals already tuberculous, especially when reinfection is possible through cohabitation with clinical cases."

* Number of cases tested, 260; of followed-up cases alone (139), 66 negative—that is, over 25 per cent.

† Number of cases tested, 120, of which 10 were negative—that is, 8.3 per cent.