of five years, attacks of constitutional disturbance followed x-ray exposures of diminishing strength. The symptoms—intense nausea, copious vomiting, general malaise, vertigo, and dyspnoea, with a fall in the leucocyte count and of the blood pressure—were regarded as anaphylactic and due to sensitization to the products of the disintegrated leucocytes. I have seen a similar sequence in a case of chronic lymphoid leukaemia which was fatal. According to M. and G. Giraud and Parès, after a holiday radiologists may become supersensitive from accumulation of antibodies and die, but no statistical proof of this startling statement is given. De Courmelles, after mentioning an x-ray mechanic who eventually became so sensitive to radiations that he had to give up his occupation, compares this experience with that of chemists who, after twenty or thirty years' exposure to ipecacuanha, become subject to asthma. Fortunately examples of acquired sensitiveness to radiations are so rare that the explanation of anaphylaxis, which has met with considerable opposition, cannot be pressed; for if this were the reason, the occurrence of allergic manifestations should be much commoner.

The Future of Radiology.

The great future of radiology is generally agreed to lie in the direction of its biological applications, and it may be safely prophesied that the science of biological physics, which presents physiological phenomena purely from a physical standpoint, and thus is the complement of biochemistry, though the partition may be thin, will thus be greatly facilitated. Just as the structure of the atom has

been revealed by the use of x rays, so, it may be hoped, may the activities of the living cell be elucidated.

A few examples of further research already begun, which may in the future be of practical utility in medicine, may be mentioned. Thus the production by x rays of bactericidal fluorescence from the mineral fluorite (Newcomer) and from calcium phospho-tungstate (Peacock and Whitby) opens up a possible method of treating bacterial infections by injecting solutions of such inorganic bodies followed by radiations. Protection of the skin against the destructive action of x rays in cases in which deep radiotherapy is employed would be most desirable, provided the tumours or pathological conditions to be acted upon are not simultaneously made more resistant. Auer and Witherbee found experimentally that rabbits previously sensitized by injection of horse serum acquire in the majority of instances a remarkable resistance to doses of x rays that destroy the skin of normal control rabbits. In man this method might be of the greatest use in inoperable malignant disease by enabling much larger doses of x rays to be given than the skin can ordinarily stand, provided that the cells of the growth are not similarly rendered more resistant, a question which it would not be difficult to determine. A problem already mentioned is the sensitization of the cells of malignant tumours by artificial means so that they may be the more readily destroyed by radiations. Just as medicine is gaining by the cultivation of comparative pathology and medicine, so it is desirable that veterinarians should, as far as possible, work at comparative radiology and thus help human radiology.

DISSEMINATED SCLEROSIS:

ETIOLOGY, SYMPTOMATOLOGY, AND OCCUPATIONAL INCIDENCE.*

BY

DOUGLAS K. ADAMS, M.A., B.Sc., M.D., M.R.C.P.,
F.R.F.P.S.,

ASSISTANT TO THE REGIUS PROFESSOR OF MEDICINE, GLASGOW UNIVERSITY;
ASSISTANT PHYSICIAN, WESTERN INFIRMARY, GLASGOW.

THE problems presented by a study of disseminated sclerosis are so varied and intricate that I would prefer to direct attention to some aspects of the disease which, in view of recent work, appear to be specially important.

Etiology.

Though the disease was first described in 1832 by Cruveilhier¹ and extensively studied from the clinical standpoint by Frerichs,² Vulpian, Charcot,³ Marie,⁴ and other workers, it is only in very recent years that advances in the sciences of bacteriology and serology have rendered possible an experimental investigation into its etiology. In 1913 Bullock (Gye),⁵ by injecting spinal fluid from a case of disseminated sclerosis, produced paralysis in rabbits. These results were confirmed and extended by Kuhn and Steiner in 1917.⁶ They claimed to have passed the disease through a series of four guinea-pigs and two rabbits, and to have demonstrated spirochaetes in the heart blood and in the vessels of the liver. In 1919 Marinesco⁷ confirmed these results, and found spirochaetes in the ventricular fluid of the inoculated animals. About the same time Siemerling,⁸ Schuster,⁹ and Speer¹⁰ independently described spirochaetes in the brains of human subjects dead of the disease. In 1921 Blacklock and I¹¹ published a series of experiments in which paralysis had been produced in rabbits inoculated with material from seven cases, and in several instances transmitted from one rabbit to another. On two occasions the virus had been inoculated in Smith-Noguchi medium for fourteen days in the course of passage. At the same time Gye reported similar results.¹² In seven out of forty-two of our inoculated animals spirochaetes were found in the internal organs, and our subsequent endeavours have been to discover what part, if any, these spirochaetes play in the etiology of the disease. It was found that the ventricular fluid of a large series of normal

control animals of various species contained spirochaete-like structures, which might constitute a serious source of fallacy. These were investigated and described, and it was shown that they differed morphologically from the organisms found in the internal organs of inoculated animals described above.¹³ The possibility of a generalized spontaneous infection with spirochaetes had to be considered. In this connexion a large amount of work has since been done on the cutaneous spirochaetosis of rabbits due to *Treponema cuniculi*. In a paper shortly to be published in conjunction with McCluskie and Cappell evidence is advanced which goes to prove that this infection is purely local and cutaneous, and that *T. cuniculi* does not infect the deep organs. We are therefore of opinion that *T. cuniculi* can be excluded as a source of fallacy.

In addition to the above investigations, control work has been done on other pathogenic spirochaetes, including *T. pallidum*. We were fortunate also in securing the brains of seven patients who died of disseminated sclerosis, four of these being supplied by the courtesy of Dr. James Dawson of Edinburgh. A very large number of sections from various parts of these brains were stained by Jahnke's method, and no spirochaetes were found. The question, therefore, would appear to us to be an open one. There is at present no scientific proof that a spirochaete plays any definite part in the etiology of the disease. On the other hand, various facts have to be considered in regard to the hypothesis that the causal agent is a spirochaete. In the first place, there is the large mass of experimental evidence of numerous workers on the Continent, who state that they have demonstrated their presence in human tissues and those of animals experimentally infected. In the second place, there are the admittedly very great difficulties in demonstrating spirochaetes in the lesions of known spirochaetal diseases—as, for example, tabes dorsalis. A third consideration is one which should not be overlooked, and appears to me personally to be of great importance. What might be termed the natural history of disseminated sclerosis is suggestive of an infection with a spirochaete or some closely allied organism. I refer, of course, especially to the phenomena of onset with mild pyrexia, and the course characterized by exacerbations and remissions. In this connexion it should be noted that the first suggestion that a spirochaete might be the infective agent in the disease was made by Buzzard in 1911 on general considerations.¹⁴

* A communication to the Association of Physicians of Great Britain and Ireland.

In even a brief discussion the serological aspect cannot be omitted. The spinal fluid picture which we have found to be almost constant is a normal or slightly increased cell count, a normal protein content, a negative Wassermann reaction, and a positive reaction to colloidal gold.¹⁵ This latter test, in conjunction with a negative Wassermann reaction, is, in my opinion, of undoubted value in the recognition of early cases of the disease.

Symptomatology.

As regards the symptomatology of disseminated sclerosis, I would like to emphasize one of the earlier manifestations. Retrobulbar neuritis is specially worthy of investigation and experimental research. In one of my cases of frank disseminated sclerosis in a woman aged 37 I obtained the following history. Fifteen years prior to the onset of gross symptoms she had suffered for a short time from bilateral retrobulbar neuritis, but in the interval had appeared to be in good health. Here we would appear to have a latency of infection comparable with syphilis. The occurrence of so-called idiopathic retrobulbar neuritis in a young and otherwise healthy adult should always be carefully investigated as a potential early manifestation of disseminated sclerosis.

Occupational Incidence.

So far I have referred chiefly to laboratory methods in the investigation of this disease. There are other channels into which inquiry may be profitably directed. It is of great importance not merely to study the natural history of a disease, but especially to investigate the circumstances under which the earliest manifestations appeared. The following observations are based on my personal experience of cases in the West of Scotland, and may be governed by conditions peculiar to the district. The majority of the patients I have seen with disseminated sclerosis come from the country, as opposed to the town. The incidence of the disease in this respect would appear to be in direct contrast to that of neuro-syphilis. The typical picture is that of a young adult, usually of good physique and with a healthy family history. It is excessively rare to find two cases occurring in the same family or in the same household—a fact which would point either to special personal susceptibility or to special exposure to infection. In this connexion the theory of insect transmission is worthy of investigation. Such a view has already received the support of Dreyfus¹⁶ in a published paper and Kuhn in a personal conversation. The occupations which seem to me to render the individual most liable to infection are farming, woodworking, game-keeping, gardening, byre-keeping, etc. Persons so employed are essentially earning their living in the open air in country districts. It is not only in these individuals that the disease seems specially liable to occur, but also in various members of their families. Recently McAlpine¹⁷ has referred to the desirability of investigating this occupational incidence of the disease.

Admittedly such a history cannot be obtained in a proportion of cases, but when one realizes the apparent latency of infection, to which reference has already been made, the difficulties of ascertaining when and where the infection occurred will be immediately apparent.

REFERENCES.

- ¹ Cruveilhier: *Anatomie pathologique*, two vols. fol., Paris, 1835-42.
- ² Frerichs: *Arch. f. ges. Med.*, Jena, 1849, x, 334.
- ³ Charcot: *Lectures on Diseases of the Nervous System*, New Sydenham Society, 1877.
- ⁴ Marie, P.: *Lectures on Diseases of the Spinal Cord*, New Sydenham Society, 1895.
- ⁵ Bullock, W. E. (now Gye): *Lancet*, 1913, ii, 1185.
- ⁶ Kuhn und Steiner: *Med. Klinik*, 1917, xiii, 1007.
- ⁷ Marinesco: *Rev. Neurol.*, 1919, xxxv, 481.
- ⁸ Siemerling: *Berl. klin. Woch.*, 1918, vol. li, p. 273.
- ⁹ Schuster, J.: *Zeit. f. d. ges. Neurol. u. Psychiat.*, 1921, vol. lxxiii, p. 433.
- ¹⁰ Speer, Ernst: *Munch. med. Woch.*, vol. lxviii, p. 425.
- ¹¹ Adams, D. K.: The early diagnosis and treatment of disseminated sclerosis, *BRITISH MEDICAL JOURNAL*, November 19th, 1921, p. 841.
- ¹² Gye, W. E.: *Brain*, July, 1921, vol. xlv, p. 213.
- ¹³ Adams, D. K., Blacklock, J. W. S., and McCluskie, J. A. W.: *Journ. Path. and Bact.*, vol. xxviii, 1925.
- ¹⁴ Buzzard, E. Farquhar: *Lancet*, January 14th, 1911.
- ¹⁵ Adams, D. K.: *Lancet*, February 26th, 1921, vol. i, p. 420.
- ¹⁶ Dreyfus, H.: *Zeit. f. d. ges. Neurol. u. Psychiat.*, 1921, vol. lxxii, p. 479.
- ¹⁷ McAlpine, D.: *BRITISH MEDICAL JOURNAL*, February 12th, 1927.

ON CERTAIN ADRENALINE EFFECTS AT THE MENOPAUSE AND THEIR SIGNIFICANCE.

(Preliminary Communication.)

BY

JOHN H. HANNAN, M.A., M.D., B.CHIR.CANTAB.,
LONDON.

In two theses read by myself at Cambridge dealing with the causation and treatment of "flushing" at the menopause, and in a recently published monograph on the same subject (1), I have drawn attention to certain adrenaline effects observed during my researches.

Flushing Produced by Adrenaline.

Intravenous injections of 10 minims of a 1 in 1,000 solution of adrenaline chloride, in women complaining of flushing at the menopause, gave rise, in all cases, to an immediate attack of flushing which was in all respects identical with the attacks which occurred spontaneously.

In order to exclude the possibility of this experimental flushing being caused by an increase in blood pressure, or the painful stimulus of an injection, control injections were made of pituitrin and normal saline; in no instance did the control injections give rise to an attack of flushing. It would appear, therefore, that the production of flushing at the menopause by the intravenous injection of adrenaline is due to the specific action of this substance.

A consideration of the results obtained by observers, such as Petzetakis, on the effects of intravenous injections of adrenaline in normal individuals yields no evidence of the production of flushing by adrenaline in such individuals.

Increased Tonus at the Menopause.

Loewi's reaction—namely, dilatation of the pupil following instillation of adrenaline into the conjunctival sac—occurred in 40 per cent. of those women at the menopause upon whom the experiment was tried; the reaction was constant on eight consecutive days; only women who complained of flushing were selected for this experiment.

If adrenaline be instilled into the conjunctival sac of a normal individual no dilatation of the pupil occurs, owing to the destruction of the adrenaline (Dixon). In some diseases of the pancreas, however, where there is impairment of the secretory cells, certain adrenaline effects become more pronounced and dilatation of the pupil occurs; this phenomenon being caused, according to Loewi, by the absence of the restraining influence of the pancreas on the suprarenal glands, these glands being physiological antagonists. Bearing in mind, therefore, that pancreatic disease might be present in some of my cases, an examination of the urine was undertaken in those cases where the pupil reaction was positive; in no instance was evidence of glycosuria obtainable.

From my experiments it would appear that the sympathetic nervous system of women, who at the menopause complain of flushing, is in a condition of increased tonus. The menopause is, we know, associated with ovarian atrophy and loss of the Graafian follicles; furthermore, removal of both ovaries will produce a syndrome closely resembling the natural process: my research, therefore, would seem to indicate that the internal secretion of the ovaries and that of the suprarenal glands (medullary portion) are physiological antagonists.

The ovarian extracts which are available at the present time are unsatisfactory, but I have had some success in the treatment of flushing at the menopause by the subcutaneous administration of an extract of the whole ovary in combination with a dry extract of the corpus luteum, orally (2). In two of my cases, Loewi's pupil reaction has disappeared under ovarian substitution therapy.

The Significance of Adrenal Sensitiveness at the Menopause.

It would appear from my research that the flushings of the menopause are due to an increase in the tonus of the sympathetic nervous system at this time, this increase being caused by the absence of or deficiency in the restraining influence of the internal secretion of the ovaries on the