CLINICAL EVIDENCE FOR A TOXIC FACTOR IN
CERTAIN DISEASES.By JAMES ADAM, M.A., M.D.,
Hamilton.

THAT certain diseases owe part of their etiology—their exciting cause—to endogenous toxins can be shown by a consideration of certain clinical facts which have not been sufficiently noticed, and which may be regarded as clinical experiments proving such a cause.

In a thesis on asthma written in May, 1900,¹ I drew attention to the fact that asthmatic attacks in working men occurred most frequently on Sundays or Mondays. Of 10 men, 8 showed this "week-end" periodicity; and, of the other 2, one was an architect whose condition of life did not vary greatly throughout the seven days of the week; and the second, a miner, consulted me before I knew of this weekly peculiarity. Further, a schoolboy, whose attacks were irregular during his schooldays, developed asthma regularly on Sundays and Mondays after he started work as a bricklayer. This periodicity was obviously connected with the altered life of the "week end," its rest and good feeding, and its frequent want of exercise.

This regularity is rarely manifest in asthmatic women, because their work is rarely periodic, but I have seen it in a young woman who worked a tailor's machine during the week. And I have known an ironworker escape his week-end attack of asthma when he had to work on Sunday. The want of exercise, especially of open-air exercise, without restriction, and indeed often with excess, of diet, resulted in imperfect metabolism, in a toxic condition of the blood setting up the asthmatic spasm; and the conclusion came to was, that asthma was caused by a spasm-producing toxin acting on a diseased respiratory tract—the nose being the most frequent starting point of such disease as it is the starting point of that tract. At the same time uric acid excess, though shown to be more or less constant in asthma, could be regarded as little more than a symptom, an indicator of other poisons present; for, amongst other reasons, the excess was not closely enough related to the spasm to be its cause.

That this "week-end" periodicity is more than an interesting fact, but one of some clinical—and especially of pathological—significance, is evidenced by its presence in other diseases. It occurred in the following striking case of the variety of urticaria called by Quincke "acute circumscribed cutaneous oedema."

CASE I.—A Carter, aged 17, awoke on Sunday, July 20th, 1894, with pronounced brawny, painless swelling of one eyebrow; this disappeared towards evening. The following Sunday morning he found similar swelling of lower part of forehead and of both eyebrows, and towards evening of lower lip. During next day the swelling disappeared. Again the next Sunday, when I first saw him, he had similar swelling of upper lip, as if from a wasp sting, so that tip of lip was on a level with tip of nose. This disappeared during next day; yet the following Sunday a similar recurrence with a similar result. He was treated with purgatives and had no further trouble. Now on Saturday and Sunday this patient had more nitrogenous food and much less work than on other days, and it is to be noted that until seven weeks before his first attack he had been a shepherd, always in the open air, and always on the same diet and work seven days a week.

CASE II.—A grocer, aged 24, came to me one Sunday about 1 p.m. to be examined for life insurance. Albumen in the urine was found; it was also found that he had been working late the night before and had lain in bed until he came to me. The insurance company asked for three more examinations of urine. I asked the patient to come any day but Sunday or Monday, found no albumen, and passed him as a first-class life. Complying with a further request he gave me samples of urine on two subsequent Sundays; albumen was found in one.

CASE III.—Again, my friend Dr. Alex. Morton, of Glasgow, kindly allows mention of a case of epilepsy under his care. A lad who worked as a builder during the week, and who loafed about and fed up on Sunday, usually had a fit during the Sunday night. Dr. Morton cut down his diet and increased his open-air exercise on Sundays, so that no more fits recurred for a month. Then Dr. Morton went on holiday; the patient got lax in his régime, and had fits as before. The lad was then taken by another doctor to a consultant, who ordered rest in bed on Sundays and abundant feeding, with the result that the fits were worse than ever on Sunday nights.

But this week-end periodicity occurs also in domestic animals under precisely similar conditions to those already mentioned. "Monday-morning disease"² is so called by American ostlers because horses take it on that day. It is also called "black strangury." "Broken-down haemoglobin or haematin" appears in the blood and urine. The change

seems to originate in the cells of the voluntary muscles. Woods Hutchinson says:

"Its onset is marked by sudden stiffness and soreness, rapidly developing into complete loss of power in the muscles of the back and hind quarters, so violent and swift in its course as to have been at one time regarded as a form of paralysis. The disease is well known and greatly dreaded by horse owners, as it is not only frequently fatal—often barely 30 per cent. recovering—but seems specially prone to attack vigorous horses in the prime of life. In spite of the most careful examination of the affected muscles, no causal organism has yet been discovered, and we are completely in the dark as to the etiology of this strange degenerative myositis. The only predisposing condition known is overfeeding and idleness after work, as it seems to attack city work horses in high condition and stallions just after the breeding season. Indeed, in many of our large American carriage and express stables it is known as 'Monday morning disease,' as it is most apt to appear on that day of the week after thirty-six hours' rest and high feeding. It does not appear to be infectious, although it will often attack three or four horses in the same stable within a few days."

Now, the more obvious exciting cause of this remarkable disease of horses (which I have italicized) is just what during the last ten years has been forced on my attention as regards asthma in working men. Only, from a consideration of all the diseases mentioned this further explanation seems obvious. There is an error of metabolism, probably also of elimination.

Oxidation of nitrogenous food is most active in the muscles. When these are exerted much below their usual activity, and yet get their usual, or more than their usual, share of food, oxidation will be imperfect, and especially will this be so if the owners of those muscles, be they men or horses, keep indoors as in the cases adduced. Consequently the blood gets loaded with poisons. These toxins may be of various constitution and action according to the degree of oxidation, the nature of the food, and the chemical factor involved in the constitutional peculiarities of the individual. As a result, partly of this diversity of toxins and their affinity for special tissue cells, partly of other morbid conditions in the tissues, we get various disease manifestations. The tendency to such manifestations is probably increased by defective elimination accompanying the excess of food and the want of open-air exercise. The uric acid excess, which is more or less constant in asthma, and probably in some of the other conditions referred to, besides telling of imperfect oxidation, is less diuretic than urea. But except as thus hindering elimination, it is a symptom not a cause.

Now, it seems impossible to explain these diverse periodic manifestations in any other way than as the result of toxins. The Fourth Commandment was not made for microbes, and yet to credit them with the cause, as Hutchinson seems inclined to do, is to credit them with more than a human remembrance for Sunday. In any case, to look for microbes in the muscles of the horse in "black strangury," as he mentions having been done, is hopeless.

If they are to be found it will be in the alimentary canal, and in this regard it is to be noted (1) that digestive disorder is an extremely likely and very frequent concomitant of the diseases mentioned and of their predisposing conditions; and (2) that eosinophile leucocytosis occurs in asthma and urticaria, and accompanies the presence of interesting parasites. Gulland,³ speaking of it in connexion with filariasis, says it protects the body from the toxin of parasites. But microbioc agency is not needed to explain the production of toxins in the circumstances here referred to, any more than it is needed for the production of peptones or of snake venom, and until the connexion can be proved need only be kept in mind as a possibility.

Many writers have pointed out the toxic origin of urticaria, but in connexion with the "week-end" asthma and the "Monday morning disease" of horses, Bouchard's observations on the toxicity of urine are important. After pointing out that the urines of sleep are of a markedly convulsive character, he says: "The toxicity of the urine of sleep being only half of the toxicity of the urine secreted during an equal period of the day, we might think that the urine of repose ought to be less toxic than the urine of muscular effort. But it is the contrary that is true. One day of great muscular activity spent in the open air in the country diminishes the toxicity of the twenty-four hours by one-third, and on that day the toxicity does not diminish only during the time devoted to muscular exercise. The toxicity which diminishes

during work remains less during the repose which follows this work and during the sleep which succeeds this day of muscular activity."

But if we admit the presence of toxins in the periodic cases of these diseases—asthma, urticaria, epilepsy, "black strangury"—we must go further, and say that such toxins are probably an essential factor in all cases of these diseases. Periodicity is less marked in other cases, because the variations in the predisposing conditions are less regular or more complex; hygienic errors may be less marked, yet active. If this be so, the endogenous formation of toxins is of interest in view of recent theories as to immunity against microbes. In autointoxication certain organs or tissues deal with certain foods imperfectly; in immunity the production of cytotoxins, haemolysins, etc., is regarded as resulting from an alteration of the normal food-assimilating powers of the tissues. Whether the toxins originate directly in the intestine or in the muscles future investigation must show. In favour of the latter view are two points:

1. The diseased condition of the muscles in "black strangury" of horses.
2. A markedly predisposing condition is defective muscular exercise.

It is to be noted that this deficient use of voluntary muscle is accompanied by perverted contraction of involuntary muscle in asthma, urticaria, and possibly epilepsy. In asthma there is spasm of the smaller bronchial tubes, and probably of the arterioles; in urticaria, spasm of the arterioles. (N.B.—Urticaria and asthma are often concurrent or intercurrent.)

In epilepsy there is, of course, spasm of the voluntary muscles; but the idea of sudden cerebral anaemia in epilepsy is one that dies hard, and will take a good deal of dislodging from the mind of any one who has observed, as I have several times, the initial groan and epileptiform movements which sometimes accompany simple syncope. For example, these symptoms occurred in an attack of syncope brought on in an asthmatic man, aged 54, by slight intranasal interference; and again in a cabdriver, aged 26, while having an abscess opened. In neither case has there been any question of epilepsy before or since. And I have to suggest that just as the poison causes spasm of the involuntary muscles of tubes or vessels in asthma and urticaria, so it may in those of the cerebral vessels in epilepsy. This would not preclude it acting on the cerebral cortex directly, or, indeed, on the nervous system generally, both in epilepsy and asthma. The cumulative effect of such toxin acting over a period of time might not only result in an epileptic fit, but might also do much toward inducing the excitable condition of the cortex which is supposed to exist in epilepsy, or the condition of the central nervous system which Dr. Sidney Martin⁵ thinks exists in asthma, "a condition which cannot be defined categorically, but only expressed vaguely as that which is present in the individual predisposed to asthma."

In the "Monday-morning disease" of horses the poison, as might be expected in animals with such muscular power and exercise suddenly immured and overfed for thirty-six hours in dark stables, is much more powerful than those in the human being, and often is fatal. But it may well be of kindred nature; here also the blood vessels seem to be attacked. The difference between the stimulating effect of the poisons in the human diseases and the paralytic effect in that of horses suggests comparison with stimulating and paralyzing doses of alcohol and other drugs. While haemolysis is pronounced in the horses, it is to be remembered that blood extravasations are frequent in the human diseases. I have records of several cases of petechiae and blood-stained sputum in asthma; haemorrhagic varieties of erythema are well known, and the last case of epilepsy I saw showed, twenty-four hours after the fit, a diffuse venous duskiness of the skin of the forehead as if from capillary extravasation. This, however, might be fairly regarded as asphyxial.

While such toxins are an efficient cause of the diseases mentioned, in no case can they be a sufficient cause; there must be other factors. These must also demand treatment, but the importance of preventing toxin formation by suitable hygiene and of procuring rapid elimination of such when formed is obvious. For example, in asthma, after intranasal treatment, a teacher took fortnightly doses of blue pill and salines, and has been able to work for the last four years, though previously off work seven years. I think I have also seen benefit in epilepsy from a weekly blue pill, but of this I cannot be sure.

As a final proof of the position here stated, I should like to

mention one undoubted case of toxic disease (toxic amblyopia) which is remarkable because it was induced by the same conditions as in "week-end" asthma, because it was pronounced in its effect, and because it was cured by proper open-air exercise.

CASE IV.—A teacher, aged 24, who took little exercise, and spent most of his spare time in study, consulted me in July, 1899. Vision: left barely counts fingers; right, 3; no marked fundal change. Dr. Maitland Ramsay, of Glasgow, to whom I sent the case, and to whom is due the credit of the cure, emphasizing the fact that the defect in the visual field was central, not peripheral, and that there was persistent oxaluria, gave a hopeful prognosis. The patient was at first made to rest in bed in a dark room, and got pilocarpin injections and other eliminants. Later he was allowed to get out with dark protection glasses, and medicinal treatment (hyd. perchlor., ammon. chlor., pot. iod.) was continued. During the winter vision became worse, so that he could not see the chairs in my consulting room, and stumbled against them. About a year after I first saw him there was no improvement, and a well-known ophthalmologist in Edinburgh gave a very black prognosis, and said patient would never be able to read again. Shortly after this, strychnine having been added to the medicine, the patient thought he began to notice slight improvement; he could just see the largest test types. Dr. Ramsay had pressed for a sea voyage. To this patient was reluctant, but in July, 1900, he went for a trip to Shetland. By the time he reached Kirkwall he could see the town clock. On his return a few weeks later distant vision was 2. A trip to Canada completed the cure, and he could read the smallest print.

Here the toxin hit the organ most strained, but while its effects were most manifest in the eyes they were doubtless widespread, as seems likely from the oxaluria. The importance of a sea voyage in quickening metabolism is obvious.

REFERENCES.

- ¹ The Nature and Treatment of Asthma, *Glasgow Hospital Reports*, 1901, p. 151. ² Woods Hutchinson, *Studies in Human and Comparative Pathology*, p. 166. ³ BRITISH MEDICAL JOURNAL, April 5th, 1902, p. 832. ⁴ Bouchard, *Autointoxication in Disease*, Olliver's translation, p. 41. ⁵ BRITISH MEDICAL JOURNAL, 1898, vol. ii, p. 1862.

CASE OF GENERAL PNEUMOCOCCAL INFECTION, WITH FEW SYMPTOMS.

By GEORGE PARKER, M.A., M.D. CANTAB.,
Physician to the General Hospital, Bristol.

This case seems worth recording, not because generalized pneumococcal infection is at all rare, but because it shows how few of the recognized symptoms may be present in children, even in fatal cases. Here was a child whose blood and pericardial fluid gave a pure culture of the pneumococcus, who had peritoneal and pulmonary lesions, and whose mediastinum and pleurae were obstructed with effused lymph. His illness, too, had probably lasted six months, and yet for the last month, when under my care, there were hardly any symptoms of acute illness except a few rales and dullness at the base of one lung, and at times a slight rise of temperature, which was entirely normal for the last nine days of life.

History.—G. B., a male child of 17 months, was admitted into the Bristol General Hospital on January 21st, 1903, with a history of broncho-pneumonia, which had been recognized for a fortnight. He had been breast-fed, and was always healthy till August, 1902, when he suffered from measles, followed by an attack of diarrhoea. For the next two or three months he was feverish and ailing, but there was no cough. The mother remarked that during that time he was ravenous, and seemed to be always hungry.

State on Admission.—His temperature was normal; the bowels were regular, and there was a faint trace of albumen in the urine. In both lungs there were a few scattered rales, most numerous at the right base, where there was some dullness on percussion and diminished respiratory murmurs. There was little or no cough. Two days later the temperature rose to 101°, but fell to normal in two days, and afterwards showed only smaller oscillations before it became permanently normal. The lungs cleared up, and frequent examinations failed to show anything except slight dullness and a few rales at the right base. The abdomen, the heart, and the other organs were normal, and the patient slept and took liquid food well. However, at times the breathing was very rapid—50 to 60 per minute—the skin was remarkably white and pallid, though the palpebral conjunctivae were not blanched, and there was also very slight oedema of the legs. As there seemed little or no evidence of kidney disease or heart failure to account for this, the blood was examined carefully. The red cells were nearly 5,000,000, while the white numbered 54,500. The differential count made by Mr. F. Leighton, the clerk, gave polymorphous cells 61 per cent., eosinophile 1.6 per cent., small lymphocytes 31.6 per cent., large hyaline 4.6 per cent., neutrophile myelocytes 0.6 per cent., eosin ditto 0.2 per cent., and basophiles 0.2. The haemoglobin was 50 per cent. and a few nucleated red cells were present. There was no enlargement of the liver, spleen, or other glands or evidence of any haemorrhage. The optic discs were normal. In order to avoid the possibility of overlooking any fluid in the pleura from the uncertainty of pulmonary signs in children, a needle was twice inserted into the right pleura, but with no result,