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Observations

ON

THE PRINCIPLE OF REPEATED MEDICATION FOR CURING INFECTIONS.

BY

COLONEL SIR RONALD ROSS, K.C.B., K.C.M.G.,
F.R.S., F.R.C.S.

ENCOURAGING results are now being reported in the treatment of various parasitic infections—spirochaetes, intestinal amoebae, Plasmodia, Leishmaniae, Piroplasmodidae, trypanosomes, skin parasites, and even Bilharziae and Filariae. Some years ago all our efforts seemed to be aimed at finding, if possible, some agent which would extirpate the invaders after a single dose, or, at the most, after a few doses; but we are now observing that the medication must be repeated much more often than we had supposed. Even to-day, however, the number of doses which may be required to produce complete cure remains a very open question, and is discussed only in the light of empirical results, which are often few and not too decisive. It is high time, therefore, to examine the theoretical principles upon which repeated medication may be or should be given.

The best known case is that of malaria. It has been recognized for centuries that cinchona bark or its derivatives will generally reduce an attack or a relapse of malarial fever in a few days, but nothing definite has been laid down as to how long the drug should be continued. When I went to India in 1881 the practice was to give the patient about 30 grains of quinine daily (sometimes much less) while the fever persisted and for three days afterwards, and then to discharge him to duty as "cured." I protested against this custom in the *Indian Medical Gazette* for February, 1896, and advised at least one fortnight's treatment in hospital. Later I increased this period to three weeks, but when I myself was infected in 1897 I thought still better of it and took 10 grains of quinine daily for four months; I did not have a relapse. In my lectures, and in my book, *The Prevention of Malaria* (1910) I recommended four months', and suggested even six months', continuous treatment. Early in the present century the Indian military authorities ordered six weeks' treatment, with good results. During the war practice varied greatly, the duration of treatment being abbreviated by military exigencies on one hand and prolonged by the issue of prophylactic quinine on the other hand. A period of two months was laid down in 1917 by the War Office at my suggestion (see the War Office publication, *Observations on Malaria*, 1919) for men invalided home. When Sir Alfred Keogh established a number of special malaria hospitals in the United Kingdom early in 1917 many experiments were commenced with a view to producing complete and early cure (*Ibid.*), but the results were most disappointing, and relapses occurred in large percentages of the cases after trial of many lines of treatment—intravenous and intramuscular injections of quinine, heroic oral doses, combined methods, quinine with arsenic, etc., kharsivan, and several nostrums which had been commended in medical literature—though, of course, all the lines of quinine medication caused great improvement while they were being given, except perhaps in very rare cases.

Thirty grains of quinine daily for three weeks were followed, after stoppage, by relapses in a large percentage of the cases. Even treatments commencing with 100 grains a day and continued for nearly a month in smaller doses gave no guarantee of permanent cure, though they seemed to yield slightly better results on the average than did the lower scales of dosage. On the other hand, only 8 grains daily in four doses appeared to be as effective in reducing fever and parasites, as estimated by careful countings (T. Gardner). But 5 grains daily failed to prevent relapses—even while being taken; and without any quinine at all the patients remained heavily infected and generally became more and more anaemic. We concluded, therefore, that 8 grains daily or more sufficed almost invariably to improve the cases greatly while being taken, but failed to cure them completely even after six weeks' administration or more. There is much other literature to the same effect. What is the explanation?

By far the most probable theory to account for relapses in malaria is the one described in my book, and studied by D. Thomson and myself.¹ According to this theory the parasites continue to breed in the blood by the known method from the moment of infection until the last of them has died out; but their numbers are always varying greatly. A normal man of 10 stone (64.7 kilograms) weight contains (by one estimate) about 3,000,000 cubic millimetres of blood, and, allowing 5,000,000 red corpuscles per cubic millimetre, he should have 15,000,000,000,000 red corpuscles. We estimated that the lowest number of asexual mild tertian parasites able to cause fever was about 100 per cubic millimetre, or 300,000,000 altogether, with a much higher figure for malignant tertian (our cases were old infections). When there is considerable or high fever, the numbers range from about 5,000 to 300,000 per cubic millimetre; but in a fatal case in Mauritius, in 1908, I estimated that the parasites must have numbered over a million million. Between the relapses—that is, when there is no fever—the parasites often become too few to be found at all in the small quantity of blood examined (say, 1 c.mm.); but even if there be only one parasite per cubic millimetre, that would mean that there might be 3,000,000 in the body altogether. Thomson often succeeded, however, in finding very small numbers per cubic millimetre even when there was no fever, and these numbers generally increased two or three days before another relapse of fever. Similar variations in numbers of pathogenic organisms are found in other diseases; but, of course, there are certain species of parasites, such as *Ascaris*, *Uncinaria*, *Filaria*, *Bilharzia*, which, according to our present knowledge, are not capable of multiplying inside the body, except by fresh arrivals from without.

What causes variations in the numbers of those parasites which can multiply within the body? Why do they not always maintain a fixed population? I presume either that the host's resistance varies or that an overcrowding of the parasite population produces substances injurious to themselves. Perhaps the latter hypothesis may explain the limitation of the parasite population when it has reached a very high figure; but the resistance-hypothesis seems necessary to explain the entire extirpation of the invaders, which certainly often occurs without treatment in many diseases, such as malaria and relapsing fever, for example. There may also be some biological law which limits the numbers of non-sexual cell divisions. However this may be, there is much evidence to suggest that unfavourable climatic conditions, fatigue, starvation,

excess, or concurrent illness, tend to precipitate relapses—at least in malaria. The picture most of us have formed is that while the infection continues there is a constant struggle, with varying fortunes to either side, between the invaders and the opposing forces of the host; and that in hosts who survive the invaders are finally mastered, though, perhaps, not until years have elapsed. There is, I believe, a general mathematical theory that during any constant struggle between opposing forces (for example, between stream and wind) a wave condition of alternating success or failure for either side is produced. The alternating “rallies and relapses” seen in so many diseases, including malaria, seem to suggest this class of phenomena.

Principles of Treatment.

By our treatment, then, we are called upon to help the patient in his fight. We may attempt this either by trying to assist his natural powers of resistance, or by attacking his enemies by specific medication. Many people write as if the former process is the proper one: but unfortunately we really do not know how to assist natural powers of resistance. Keeping patients at rest, “feeding them up,” giving them tonics, etc., sound very well, but the patients too often continue to relapse just as before. We have little real evidence to show that people who are in the best of health at the moment of infection suffer less severely when they are invaded by some parasitic infection than do people who have previously been in poor health—rather the converse, in fact. Certainly I think that rest and good feeding help patients to overcome the illness due to parasites. But that is another point; we must not confuse the illness caused by parasites with the parasites themselves; and a patient who is better able to resist the effects of the parasitic invasion does not necessarily possess greater natural power of extirpating the invasion. We are too prone to confuse these two issues. Indeed, experience tends to show that the healthy, vigorous, full-blooded young man is more likely to suffer from very acute attacks than are less healthy people. The obstinacy of infections probably depends chiefly upon unknown natural qualities in the blood or tissues, favourable or unfavourable to the invaders.

However this may be, the clinician is always driven to try some parasitocidal drug if one be known. If we class specific serums in this category, and possess them for a given kind of infection, we use them for this purpose; but if not, we have to fall back upon other agents which have been empirically recommended, sometimes after great general experience, such as quinine for malaria or ipecacuanha for amoebic dysentery. But the question at issue is, How exactly are we to use such drugs?

Apparently most people have usually thought that a few very large doses may be able to destroy all the invaders at a blow—hence heroic doses both of quinine and of ipecacuanha. But are we so sure of this? There are reasons for thinking that the patient's body is so affronted by the massive dose that it endeavours to cast it forth at once. The studies “On Quinine in Animal Tissues,” by W. Ramsden, I. J. Lipkin, and E. Whitley, published some years ago,² certainly do seem to suggest that a heroic dose of quinine put straight into the blood is cast out by it almost at once, while a much more moderate dose is likely to remain there longer and to do its work on the Plasmodia. Several biologists to whom I have mooted the matter are inclined to agree with me in this. The patient's blood and tissues are obliged, so to speak, to protect themselves against any foreign chemical agents as much as against invading parasites. When suddenly subjected to a great dose of something, they adopt the usual course and get rid of it as soon as they can, not being aware that the dose was intended to help them—to speak metaphorically. According to this hypothesis, then, a large dose may possibly be cast out so rapidly that in the end actually a smaller amount of it may reach the parasites to poison them than if a small and more easily tolerated dose had been given to begin with. Probably this accounts for the little difference between the effects of small and of large doses which we observed during the war in the home hospitals. Where we find little difference between the results of, say, 10 grains a day and 100 grains a day, we suspect that there has been some fallacy in the arguments which led to the adoption of the larger medication.

But another point must now be remembered. Whatever dose be given, are we sure that it will reach all the parasites in the body simultaneously? Perhaps so in certain

cases, as in those of parasites which live in open sites, such as the skin and intestines, and are easily attacked by drugs—though even these cannot always be destroyed at once. But how can we expect to obtain such a decisive result in the case of millions of organisms capable of constant reproduction and occupying more recondite positions in the body? We must disabuse ourselves of the notion that the parasites in a host are like fish in a bowl, which can be destroyed all together by mixing a single dose of poison with the water. They must be much more like the enemy on a battlefield many of whom will escape in their trenches and dug-outs the most violent barrage; and, as I for one have always thought and taught, there must be many recesses and backwaters of the circulation which, possibly, no medication bearable by the host can reach. This has been ably suggested and perhaps* proved by the chemical work just mentioned—especially by I. J. Lipkin's paper. According to it, quinine is concentrated in the suprarenals, kidneys, and spleen; cast out quickly from the lymphatic glands and the blood; and destroyed by the liver and the muscles. If so, even in the quickly moving circulation, large numbers of the Plasmodia are likely to escape any dose that we can give—especially in view of the fact that a stasis of them often occurs in certain capillaries. Lastly, if we lift the quinine-barrage for a long enough interval the enemy will immediately begin to bring up reinforcements in the form of fresh generations of spores and make good what reduction we had previously succeeded in effecting.

Single-Dose Reduction Rate.

Put in this way, these considerations appear simple enough, but many fail to realize them in practice. Suppose, for example, that 30 grains of quinine reduce the Plasmodia to one-half; then, in order to reduce 1,000 million of them to one we must probably repeat this dose, not twice nor thrice, but thirty times; and even after this we must continue to repeat it, say, four times in order to make nearly sure of destroying the last remaining Plasmodium and its spores. For if P be the original number of a parasite population, and p the number remaining after a course of treatment, and if $\frac{a}{b}$ be a fraction which represents what I call the “single-dose reduction rate”—so that after this single dose $p = \frac{a}{b}P$; then, if we can reduce p still further by giving a succession of n similar doses, all of which have the same effect, we should expect that ultimately

$$p = \left(\frac{a}{b}\right)^n P.$$

Hence, taking logarithms of both sides, we have

$$n = \frac{\log. P - \log. p}{\log. b - \log. a},$$

where, of course, P is greater than p and b greater than a .

The following table will help the reader to compute without logarithms the number of doses which should be required on this hypothesis to reduce P to p , when both are expressed as powers of 10. Suppose that also $b = 10$ and $a = 9, 8, 7, \dots$ in succession; so that Row A of the table gives single-dose reduction rates varying from 0.9 to 0.1. Next let $P = 10$ and $p = 1$; then Row B will be the corresponding values of n calculated from the equation $n = \frac{1}{1 - \log. a}$, where n is the number of doses required to reduce 10 parasites to 1.

Table.

A =	0.90,	0.80,	0.70,	0.60,	0.50,	0.40,	0.30,	0.20,	0.10.
B =	21.85,	10.32,	6.46,	4.52,	3.32,	2.51,	1.91,	1.43,	1.00.

In order to obtain from this table the number of doses needed to reduce P to p (given in powers of 10), we have only to multiply the figures in Row B by the difference between the numbers of zeros in P and p respectively. For example, if a single dose reduces the parasite population from 1,000,000,000 to 800,000,000, then 10.32 doses should reduce it to 100,000,000, or one-tenth, and 9×10.32 , or 93 doses say, should reduce it to 1. But this will not extirpate the infection entirely, for we must still destroy the last Plasmodium. The chances against doing so by a

* H. W. Acton and H. King (*Biochemical Journal*, xv, 1, 1921) have recently criticized the method of Ramsden and Lipkin and find that it fails to yield 30 to 40 per cent. of the quinine added to samples; but this should not greatly impair their comparative results mentioned above.

single additional dose will be 5 to 1, for a reduction-rate of 0.8 ($= 4/5$), because in such case only 1 out of 5 parasites is destroyed by the single dose. Hence I suggest reduction to another one-tenth at least, which means another ten or eleven doses; but even this by no means quite exhausts the chances of survival which the last of the invaders may possess.

Such calculations are useful, because they help to define and classify our ideas; but no one imagines that the same dose will always have exactly the same effect. Many causes of which we have little knowledge, such as indigestion, fatigue, etc., may diminish the effect from day to day; others, especially the parasitocidal bodies generated by the patient himself, are likely to increase the effect. On studying again the work of D. Thomson and myself already referred to, together with some additional statistics which he obtained, I think that in malaria cases (mostly *P. falciparum*) in England, daily doses of 30 grains of quinine give each a reduction rate of 0.8 or a little less (say 0.75). The fall in the number of parasites was, however, often much greater immediately after a smart attack of fever associated with many parasites, which I attribute to the stimulation of the patients' own antibodies by the attack and not to any change in the dosage of quinine (since we usually gave the same dose throughout). I presume that as cases advance into the second year of infection and longer, these antibodies become more and more powerful—which, as mentioned above, is one possible explanation of ultimate spontaneous cure; so that the same dose of quinine may apparently have a more marked reduction rate in old than in new cases.

On the other hand, newly inoculated Plasmodia may possibly be able themselves to resist the drug more effectively than their descendants in the same host. Certainly, in Salonica many cases became infected while they were actually taking 30 grains of quinine a day for months—a dose more than sufficient to produce, say, an 0.8 reduction rate now, when the same cases have become chronic. Considerable light is thrown on this subject in a recent paper by Etienne and Edmond Sergeant,³ who have experimented on over 1,000 canaries, which they inoculated with *Plasmodium relictum* and then treated with subcutaneous injections of quinine. Contrary to previous Italian reports, the drug acted upon this Plasmodium just as it acts on the human species; but large doses, equivalent to 30 grains or more for men, given before inoculation, during it, or after it, failed to exclude infection; though, if given during the incubation period, they reduced the numbers of the invaders and the illness caused by them (the true value of "prophylactic quinine"). Personally I am inclined to think that the more marked reduction rates apparently obtained in older cases are probably due rather to the combined effects of the quinine and the antibodies than to any diminished resistance in the parasites themselves.

The authors give the case of a bird in which the Plasmodia appeared to become quinine-resistant after nine months' quinine treatment and remained very virulent in two passages through two other canaries; and they think it is a case of a genuine quinine-resistant strain. We have had a few similar cases in our malaria camps, and also in the Tropical Diseases Clinic (Chelsea) of the Ministry of Pensions out of very many thousands of cases; and I now have two cases who have resisted 20 grains or more for a month. But, in spite of what evidence has been shown for it, I feel very doubtful regarding the whole theory that strains may become drug-resistant. We do not know how quinine acts, whether as quinine or as a metabolite. The blood of some persons may perhaps throw out either the quinine or its metabolite so quickly that these have no time to affect the parasites, or can affect only a very few of them; while in other persons who have been long and irregularly dosed the blood may possibly gradually acquire this power in self-protection. Probably both kinds of cases exist; and I remember one patient at least on whose Plasmodia quinine had from the first no apparent effect at all, and who died in consequence—several cases of the same kind were reported during the war. But I think that such are cases of idiosyncrasy in the host, and not in the parasite.

The term "single-dose reduction rate" used above refers to the total reduction of the parasites actually obtained even when the proliferation of such parasites as escape destruction is taken into account. Obviously, if the treatment is interrupted long enough to allow large numbers of

organisms to proliferate in the interval, then the final result will receive a set-back. Calculating on the basis of the incubation period, I judge that *P. vivax* multiplies roughly at the rate of ten to one every two days, and *P. falciparum* still more quickly. Hence, perhaps, we may infer that any intermission of continuous treatment for one or two days may allow the invaders to multiply ten times in the interval, thus undoing all the good work effected by the whole number of doses given according to Row B in one column of the table. I am quite sure that the reason why most returned patients in this country continue to relapse is that they stop their quinine (often on medical advice) a few days or weeks after an attack of fever. The histories which they almost invariably tell us at our clinic are that they have been instructed to continue quinine only for a short period. Suppose that during this period they have reduced the invaders to 1,000, then ten or twelve days afterwards the numbers will return again to the fever point, the patient will take more quinine, will stop it again too soon, and so on indefinitely, allowing relapse to follow relapse for months or years. The whole object of continuous medication is frustrated by such interruptions, especially when comparatively small doses are given; and success will be attained only if the clinician warns the patient strongly that the remission of quinine for one or two days will cost him all the fruits of seven to ten days' previous treatment. It may be a different matter if large doses, such as 30 grains, are given, say, twice a week, because then the drug may remain at sufficient strength in the blood during the intervals; but out-patients will seldom submit to such dosage, and the daily dose of 10 or 15 grains is better. Anything under 60 grains a week appears to be almost useless in the large majority of cases; and anything over 15 grains daily seems only to be required when there is fever, and say for a week or fortnight afterwards, followed, of course, by the 10 or 15 grains daily for months.

Exhaustion Period.

The period of treatment required to exhaust the infection entirely on this hypothesis may be called the exhaustion period. For malaria, in order to reduce say 1,000,000,000 Plasmodia to 0.1, we must multiply the figures in Row B of the table by 10. Then, if the single-dose reduction rate for 10 grains of quinine averages 0.8, the exhaustion period for a series of daily doses should be 104 days; but if the average reduction rate is 0.7 the exhaustion period should be only 65 days. Anything approaching decisive scientific statistics on the subject are, I think, not to be obtained; because, to obtain them, we should have to keep the same patients under strict supervision, not only for the whole period of treatment but for months or years afterwards, unless we were free to test the blood of treated cases by experimental inoculations into healthy human beings. But from clinical results extending over forty years I think that a 10-grain daily dosage carried out rigorously for three months (eighty-four days) is sufficient in the large majority of cases. This means an average single-dose reduction rate of 0.7602. In early infections perhaps four months would be safer; and in all cases, of course, reinfections must be excluded from our calculations. The two divisions which were brought from Salonica to France in 1918 were treated by Colonel J. Dalrymple on the three-months' principle (see the War Office publication mentioned), and we have had very few of these men in our clinic since then. In that clinic we have now treated 24,000 cases of real or alleged malaria infection on the same principle since October, 1919, and all I can say is that the large majority of those who take their quinine properly seem to be finally cured; but that those who are excused the third month of the course, or who do not take their medicine, or who are given doses below 10 grains daily, or for whom "tonics," etc., are substituted for quinine, generally continue to relapse as before. And I venture to speak still more definitely in the same sense with regard to cases in my private practice, who have no interest in pretending to have relapses when they are cured, or in pretending to be cured when they are not.

I do not say that no one can be cured of malaria under three months' continuous quinine course. That will probably depend upon two factors—the patient's own parasitocidal bodies and the receptivity of his blood for the drug. Certainly numerous persons have recovered entirely, either spontaneously or after only short courses. But we never

know when this is going to happen; and it is therefore seldom safe to order less than the three months' course from the date of the last relapse.

The comparative virtues of the various cinchona alkaloids and their salts and of different modes of administration cannot be dealt with here; and discussion of the best means of treating the rare intractable cases would also be out of place, though I must repeat that in my opinion such are due to natural or acquired quinine resistance in the host and not in the parasite. It is a misfortune for the whole Empire that, in spite of the loss of millions of pounds over the Salonica malaria, more investigation on such points is not now being carried on. But our Governments are incorrigible on the subject of research.

With regard to continuous medication in other infections, it appears to me probable that the quick cures which are often reported (especially in spirochaete infections) are really due chiefly to the patient's parasitocidal bodies, to which the curative drug only adds the finishing touch. We may possibly, however, find drugs which possess more marked reduction rates (for multiplying parasites) than those shown in the table. At our clinic many of us have had very encouraging results as regards intestinal amoebae from a form of continuous medication with ipecacuanha suggested by Colonel Drake-Brockman, and similar to that which we employ in malaria. I give from 3 to 10 grains of powdered ipecacuanha in pill, without any adjuvant, on an empty stomach at bedtime every night for months without fail. Others give the drug in powder or cachet, or add small doses of Dover's powder. The principle involved seems to be the same as that which I have endeavoured to indicate, as briefly as possible, in this paper.

REFERENCES.

- ¹ See also *Proc. Roy. Soc.*, B, 1910; *Ann. Trop. Med. and Parasitol.*, 1910, vol. iv, p. 267; and *Journ. Roy. Army Med. Corps*, June, 1917.
² *Ann. Trop. Med. and Parasitol.*, vol. xii; and Lipkin, *Ibid.*, vol. xiii.
³ *Arch. des Instituts Pasteur de l'Afrique du Nord*, I, 1, March, 1921.

ON CHRONIC NASOPHARYNGEAL INFECTION, CHRONIC TOXAEMIA, AND DISTRESSED HEART IN CHILDREN.*

BY

C. PAGET LAPAGE, M.D., M.R.C.P.,

LECTURER IN DISEASES OF CHILDREN, MANCHESTER UNIVERSITY;
PHYSICIAN TO THE MANCHESTER CHILDREN'S HOSPITAL,
PENDLEBURY; AND TO ST. MARY'S HOSPITAL,
MANCHESTER.

Nobody will dispute the statement that nasopharyngeal infection is a very common trouble, especially in manufacturing districts; and that, though it is often acute and obstructive in nature, it is also very often present as a chronic infection with catarrhal rather than obstructive signs. The points which I wish to bring to notice are:

1. That this chronic infection of the nasopharynx serves as one of the most important foci from which organisms may generate toxins which cause a chronic lowered state of health in the child.
2. That the nasopharyngeal infection may be due to different kinds of organisms, the influenza bacillus being an especially potent factor and often acting as the initial infecting agent, though it may not remain in the nasopharynx.
3. That this toxæmia often gives rise to heart lesions, and that, though these heart lesions may be valvular, they are often of quite a different nature from valvular lesions—that is, they are more in the nature of nervous irritation than of inflammatory troubles affecting the heart.
4. That these special forms of heart trouble need methods for diagnosis which are not usually employed, while they also need different treatment from that usually prescribed.

Chronic Nasopharyngeal Infection.

Such cases may be either obstructive or merely catarrhal. The obstructive ones are easy to recognize. The catarrhal cases are, however, often overlooked if a careful history is not taken from the parents. The child has not necessarily adenoid facies, but has a history of chronic catarrh, of frequent colds and of a running nose, while on making an

examination mucus may be seen dropping from the nasopharynx. The tonsils may not be enlarged. Another point is that the glands behind the ear are often enlarged; these are the highest of the posterior cervical glands and less commonly the posterior auricular glands. It is an interesting point because it shows which glands drain the nasopharynx.

Chronic Toxaemia.

It is a commonplace that a septic focus may give rise to chronic toxæmia; dental caries and chronic gastrointestinal infection are the two examples which occur at once. The nasopharynx is another situation from which infective trouble may cause a very definite toxæmia. The symptoms are: pallor, which may often be very marked indeed; darkness under the eyes, especially on getting up in the morning; pains may occur which can best be described as those usually known as "growing pains." These are said to be especially associated with rheumatism, but they are to my mind quite as often met with in the chronic toxæmia of nasopharyngeal infection due to various organisms.

Amongst other general signs we meet with slackness of the ligaments, especially those which are subjected to strain in a growing child, the spine, and the arch of the foot; in this way scoliosis, or general round-shouldered carriage, may occur, or flat-foot may make its appearance. The extremities easily become cold; the pulse becomes rapid and very easily disturbed in rhythm. There may be anaemia in addition to pallor. The heart signs and symptoms I shall describe later. The thyroid gland is not uncommonly a little enlarged. Enuresis is sometimes a symptom.

The nervous system, next to the heart, shows the most important symptoms and signs. The child often has bad headaches and is irritable and nervous. The mother says that the child's disposition has changed, and that he or she has become peevish, moody, or lackadaisical, and in some instances very depressed. Disturbed sleep is also common. If the child has a vivid imagination, all sorts of morbid ideas may occur. And of course, as one would expect, children of the neurasthenic type, who are those who have been endowed with a nervous system which feels the stress and strain of life, are the first to give out the above signals of distress when any lowering agent such as toxæmia makes its appearance.

Tic or habit spasm is common. It is necessary to make a clear distinction between this and chorea. Chorea is generalized and indiscriminate in that sudden and diverse movements of practically any part are provoked. In tic, on the other hand, there is a peripheral stimulus which acts on the excitable nervous system, and finds expression in a constant repetition of one particular movement. The spasm may affect one group of muscles, or, later on, change to another group.

The common forms of tic are: (1) blinking the eyes; (2) contorting the mouth (I have known cases punished in school for pulling faces where in reality they have had tic); (3) drawing the head round to the shoulder; and (4) constant clearing of the throat. This last may, of course, be present in a child who really has mucus at the back of the throat.

Chorea is a rheumatic manifestation, and is not a common accompaniment of nasopharyngeal toxæmia; on the other hand, tic or habit spasm is. In association with this I should mention the differential diagnosis between rheumatism and toxæmia. The term "rheumatism" has come to be used too loosely in relation to disease in children; it has often been used to give a name to cover a variety of symptoms, just as influenza is a convenient diagnosis when there are no clear indications as to the cause and nature of acute illness. To my mind the term rheumatism should at present be limited either to (1) the acute cases with hyperpyrexia, with joint inflammation; or to (2) those with throat trouble and chorea and morbus cordis; or to (3) those with subcutaneous nodules and, as often happens with these nodules, very acute and rapid valvular disease and heart failure.

The organism which causes acute rheumatism may cause chronic toxæmia, and no doubt it often does; but there is no doubt that other organisms may give rise to the signs and symptoms of chronic toxæmia, therefore these signs and symptoms should not be labelled as rheumatic.

* An address, the substance of which was delivered to the Bolton Medical Society on December 7th, 1920.