OBSERVATIONS ON THE SALICYL TREATMENT OF ACUTE RHEUMATISM.

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EVERYONE who attempts to arrive at a definite verdict with regard to the efficacy of a medicinal remedy for a given disease must necessarily find himself confronted with difficulties of many kinds: difficulties in the accumulation of sufficient material; difficulties in securing uniformity of conditions; difficulties in connection with the ever-varying progress and development of the disorder under consideration; difficulties in grasping and appreciating properly a complex assemblage of symptoms; and, last but not least, difficulties in exhibiting that mental serenity, accuracy of perception, and judicial impartiality which alone can guide the observer to a right interpretation of his impressions.

With a full regard for these difficulties, I think that we are now, nevertheless, in a position to speak with very considerable confidence as to the merits of the salicyl compounds in the treatment of acute rheumatism. The method has been before the profession for upwards of ten years, and opportunities of observing its effects are almost of daily occurrence. Moreover, the tests of its action are exceptionally simple and clear, namely, the relief of the pain, the reduction of the fever, and the influence on the duration of the disease. There is almost a universal consensus of opinion that, judged by these tests, the treatment of acute rheumatism by the salicyl compounds is superior to any other method which has been as yet introduced. As to the relief of pain and the reduction of fever there can be no question whatever; but as to the influence of the drug in shortening the duration of the rheumatic process, pure and simple, there is not as yet complete unanimity. For my own part, I hold a very strong opinion in the negative as regards this last point.

At the same time, it is pretty generally admitted that the good effects of the drug are by no means equally manifested in all cases, and in some it appears to fail altogether. Some observers have been so impressed with the instances in which the action has been unsatisfactory that they have at once rashly concluded that the salicyl compounds are very much over-rated drugs as remedies for this disorder, and that they cannot be relied upon. But, bearing in mind the marvellous relief which follows their use in the majority of cases, it would surely be more logical to attribute the disappointing results to the operation of some exceptional modifying condition, the nature of which should be carefully searched out, in the hope that we might be able to distinguish beforehand those cases in which the remedy will succeed from those in which it will fail. Inquiries are repeatedly being made in the columns of our medical journals for guiding indications in the use of the salicyl compounds for this disorder, and the object of this paper is to attempt to define with sharper outlines and greater precision the relation and scope of this method of treatment, so far as my own observations and experience enable me.

In the first place, it is important to frame a good working hypothesis as to the nature of the rheumatic process. I use the term "working hypothesis" advisedly, for the subject is too complex and difficult to admit of absolute demonstration in the present state of our knowledge; and it is thus quite scientific to accept that hypothesis which covers the largest number of known facts with regard to the matter under consideration. The prevailing views of the nature of the rheumatic process are four in number: 1. That it is due to the accumulation in the system of certain products of tissue-change—probably of an acid nature—by interference with their elimination as the result of cold; this is, broadly speaking, the humoral theory. 2. That it is due to cold acting directly or indirectly upon the vaso-motor or trophic nerves of the joints, and so exciting inflammation in them; this is the neural theory. 3. That it is due to the operation of microbes, in a manner closely analogous to what occurs in malarial fevers; this is the miasmatic theory. 4. That, under the influence of cold, operating through the medium of the nervous system, a disturbance occurs in the metabolism of the tissues, leading to the formation and accumulation in the blood of abnormal substances, on which the outward manifestations of the disease depend; this may be termed the neuro-humoral theory, inasmuch as it combines elements of both the humoral and neural teaching. I assume that in all these theories, except perhaps the miasmatic, a special inherited

predisposition would be regarded as a necessary factor in the evolution of the actual disease.

I shall refrain from enumerating the arguments for and against each of these views, and shall merely state that I give my adhesion unhesitatingly to the last, or neuro-humoral theory. I cannot pretend to say whether the incidence of the disturbing influence is general or partial in its distribution; but the important fact to remember, as it seems to me, is that as a result of the nutritive disturbance, abnormal substances are formed and accumulate in the blood, and that to the secondary effects of this offending material most of the striking outward phenomena of rheumatic fever are due. Dr. Latham, in an extremely elaborate and able series of papers published in the JOURNAL in April, 1886, brings forward very cogent evidence to show that glycocine is the most important of these abnormal substances; and I am convinced that, though he may be in error on some points of detail, the principle is correct so far as one can test it by clinical observation.

I propose briefly to consider the bearing of this doctrine upon the joint affection, so far as may be necessary to elucidate the principles of treatment. The synovial sacs are known to be in direct communication with the vessels of the absorbent system, and it is a matter of general clinical experience that the joint cavities tend to become involved in serious toxic conditions of the blood, as in pyæmia, for instance. The liability to joint-inflammation in rheumatic toxæmia is, therefore, by no means surprising. The nature of the mischief which is set up is that of simple inflammation caused by irritation from abnormal chemical ingredients in the synovia or lymph-fluid which bathes the articular surface. It is identical in every respect with such inflammation as would be set up by the presence of any ordinary irritant in the joint-cavity. As a rule it is slight and fleeting, affecting only the more superficial parts, and not extending to the cartilaginous and fibrous structures around. If, on the other hand, the irritation be very severe, frequently recurrent, or of long duration, then greater damage is inflicted upon the joint, which undergoes more or less considerable structural change. We arrive, then, at the following conclusions: 1. That the joint-affection is merely an incident in the rheumatic disorder, which might conceivably be wanting altogether without vitiating the nature and reality of the rheumatic process; 2, that it is secondary in its origin; and (3) that the changes which take place in the joint-structure have no special feature belonging to them which serves to distinguish them from any other kind of simple arthritis.

The primary chemical change in the blood to which I have referred as the necessary etiological antecedent of the joint-affection also leads to secondary changes in the blood itself, of which, perhaps, the most important is a rapid destruction of the red-corpuscles. By careful hæmacytometric observations, I have found that the proportion is often reduced to nearly a half of the normal amount, that the destruction continues until the temperature begins to fall, and then, after a variable interval, the number begins to increase again. No one can fail to have noted the rapid development of anæmia in acute rheumatism, and the marked pallor which, as a rule, accompanies the chronic variety. The fact, however, is scarcely mentioned in most text-books, and yet it has an important bearing in many directions.

Apart from the anæmia and the various troubles directly dependent upon it, there are at least two phenomena on which this corpuscular destruction throws much light. First, the highly pigmented condition of the urine, which is due to the liberation of a large amount of hæmoglobin; and, secondly, the excessive coagulability of the blood, which is due to the liberation of certain fibrin-factors. Moreover, such a destructive change as this must of necessity load the blood with extractive matters, and in many other ways, impossible exactly to identify in detail, greatly disturb its chemical composition—facts which, taken together with the primary toxæmia, go far, in my opinion, to account for the occurrence of endocarditis, and possibly also the phenomena of hyperpyrexia. Interesting and suggestive as these pathological conditions are, I cannot now follow them further, but hasten again to take up the therapeutic thread which has been temporarily dropped.

The first question to be answered is this: On what principle do the salicyl compounds produce their effect? If it be true that there is nothing of a specific nature in the joint inflammation; if it be true that acute rheumatism is at bottom a metabolic disturbance attended with chemical alteration of the blood; and if it be true that the joint affection is but the direct outcome of chemical irritation, then it appears to me that there are only three possible hypotheses which can be suggested as to the way in which the remedy acts: (1) That the drug directly allays the joint inflammation; (2) that it strikes at the root of the morbid process as such; and (3) that it in some way neutralises and prevents the chemical irritation of the joint.

Now we do not find that the salicyl compounds have any influence on arthritis which is unconnected with rheumatism or the disorders allied to it, so I cannot accept the first view. Then, against the next alternative, we see that, however much the drug relieves the pain and reduces the fever, the rheumatic condition returns immediately the remedy is suspended, a fact which irresistibly suggests the conclusion that the drug operates by checking the outward manifestations rather than by curing it at its seat of origin. We are thus driven by a process of exclusion to the third hypothesis, namely, that the salicylates act by neutralising and preventing the chemical irritation of the joint. This, too, is the view which, as we shall find, covers known clinical facts best.

Dr. Latham, in the lectures already referred to, not only brings forward a mass of strong evidence in support of this doctrine, but is further able to suggest the probable nature of the chemical action of the salicyl compounds. Without entering into the clinical details with which his paper abounds, his view is that whatever salicyl compound is given, salicylic acid is set free in the system, which combines in the blood with glycocine and uric acid or their immediate antecedents, and so prevents all secondary manifestations traceable to this source.

We are now in a position to consider the circumstances under which these remedies are alleged to fail. Probably the most common source of failure consists in a faulty mode of administration. Either the drug is not given in sufficiently large doses nor at sufficiently short intervals. For a young adult, in a case of average severity, the dose should not be less than 20 grains, nor should the intervals between them exceed three hours. In cases of unusual severity, the dose should be repeated every two hours. Of course, it is not necessary to maintain this high dosage. As soon as the symptoms begin to yield, the quantity should be gradually diminished. If the drug be pure we need not fear its toxic effects. When they occur they are seldom alarming, and in any case quickly disappear on reducing the dose or temporarily suspending the drug. There seems good reason for believing that toxic symptoms are less liable to occur when these compounds are derived from willow-bark than when (as is most usual) they are prepared synthetically.

Failure in many cases may be explained by the fact that inflammatory changes have been set up in the joint which are too severe and deep-seated to subside immediately on the removal of the primary irritation. The salicylates remove the latter, but have no direct influence over the inflammatory change in the joint. Thus, we find that the salicyl compounds always answer best in the early stages of the disease, before the joint mischief has had time to make any headway. The longer the treatment is deferred after the invasion of the disease, the more disappointing are its results, other things being equal. Then, again, the treatment is always more satisfactory in first attacks than in subsequent ones, and this in direct proportion to the frequency of recurrence and the shortness of the intervals between consecutive attacks. Precisely similar arguments apply to cases of sub-acute and chronic rheumatism. In these instances it is not that the salicylates act otherwise than in early acute attacks; but, while in the latter the joint-inflammation, though sharp, is short, and quickly subsides on removal of the primary source of irritation, in the former, structural changes of an inflammatory origin have taken place which give rise to persistent pain, beyond the reach of salicyl influence, requiring time and careful local treatment to regain their normal condition.

A third important source of alleged failure is to be found in the association with the rheumatic condition, of more or less grave deterioration of the general health, with nervous debility and depression. It will be more convenient, however, to defer the consideration of this matter until the question of relapse has been discussed. No more frequent charge is brought against the value of the salicylates as a remedy for rheumatism than the indubitable tendency for the symptoms to return as soon as the drug is suspended.

I would explain the relation of the salicyl treatment to relapses in the following way: The cases treated by the expectant method show clearly that acute rheumatism tends to subside spontaneously after an average duration of about three weeks. As a rule, the more frequently the attacks recur, the longer their average duration, until they merge into chronic rheumatism. Now, it has already been shown that the salicylate treatment has no direct effect on the rheumatic process, but produces its influence by chemically repressing or preventing some of its earliest secondary manipulations.

Accordingly, if the drug be suspended during the early days of the fever, relapse is practically certain; later on, relapse is less likely to occur, until at last, when the metabolic disorder which constitutes the essence of the rheumatic process has naturally subsided, relapses

do not occur at all. Applying these facts to actual practice, it is necessary to continue the use of the drug, in reduced doses, for at least three weeks from the date of onset, and even then, on the slightest return of symptoms, to recommence its administration, and to continue it at least for another week or ten days. In this light, so far from the occurrence of relapses depreciating the practical value of the drug, they show up the specificity and certainty of its operation, within its own limits of activity, in a most striking manner.

To return to the influence of debility as accounting for failure of the salicylates in certain cases. It is well known that a common cold lasts longer, and is thrown off with greater difficulty in proportion to the want of vigour and robustness in the person affected, other things being equal. It is precisely the same in acute rheumatism. In proportion as the patient is debilitated and in feeble general health at the onset of a rheumatic attack, the greater the difficulty in reacting from the disturbance which has been set up, the more tedious its progress, and the less complete the recovery. The rheumatic process once started in a weakly subject is certain to be much more protracted than usual, and sometimes exceedingly so. Hence it follows that, under these circumstances, the salicyl treatment would have to be continued much longer than usual, in order to prevent relapse. But there are practical difficulties in carrying this out owing to the toxic and debilitating effect of the drug when given in full doses, at short intervals, and for a long period. Thus, it can readily be seen why the results of salicyl treatment in such cases are so unsatisfactory. The dilemma is this: either the drug is suspended before the rheumatic process is over, in which cases relapses will certainly occur, or it is continued so long as to depress the vitality of the patient, and make it almost impossible for him to throw off the disorder.

With reference to heart-complications, I believe that they occupy exactly the same secondary relation to the chemical changes in the blood as does the joint-affection. Consequently, in the same manner as the joint-inflammation can be prevented by early and vigorous salicyl treatment, so I believe that cardiac inflammation may be prevented. I have never yet seen cardiac complications occur after the first twenty-four hours of salicyl treatment in a case which was known to be uncomplicated at the outset, and in which it was clear, from the rapid diminution of the joint-pains and fever, that the patient was properly under the influence of the drug. When such complications occur during the first day of treatment, it is probable that the inflammation had already begun when the patient first came under observation; and, as with the joint-inflammation, the salicylates have no direct influence of any kind on the inflammatory mischief *per se*.

I venture to hope that these observations, if carefully followed up, will do some little to place one of the most valuable therapeutic discoveries of modern times on a more rational and solid foundation, and enable us to employ the method more intelligently and with greater promise of success.

THE ETIOLOGY OF RHEUMATISM CONSIDERED FROM A BACTERIAL POINT OF VIEW.

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AFTER demonstrating the bacteria which he had found present during the rheumatic process, Dr. Mantle remarked that although great advances had been made regarding the etiology of disease generally during the last decade, very little had been done to elucidate the causation of rheumatism.

The most common explanation given was that the disease originated from exposure to cold; this, indeed, might be a factor in the production of rheumatism and many other diseases; but until more was known of what this meant, why it was that one particular exposure, probably after many, brought about a certain train of symptoms, the cause assigned did not greatly help us. Pneumonia was frequently spoken of as being produced by cold, but it was now well known that certain micro-organisms were present during the course of the disease, which had (experimentally) caused the disease in the lower animals.

He had investigated, for bacteria, a number of cases of so-called "cold" or catarrh, which had usually been ushered in with chilliness or shivering, sometimes amounting to a rigor, and with a slight rise of temperature; lassitude and more or less aching of the body had been complained of, with or without increase in the lachrymal and nasal secretions. In all of these cases bacteria had been found to be present in the acute stage. This fact was mentioned to suggest that probably the commonly related story of having "caught cold," given as the cause of so many diseases, meant after all not merely a chilling of the body as generally understood, but in many cases the reception of some morbid germ which had found an environment