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RÉSUMÉ

Un des dérivés organiques des composés quaternaires d'ammonium est le bitartrate de pentaméthylène:1:5-bis-(1-méthylpyrrolidinium) connu sous le nom commercial de Ansolysen. Comme l'hexaméthonium, il agit par bloquage de la transmission nerveuse au niveau des ganglions autonomes. Les effets secondaires sont les mêmes. Ce médicament fut employé par les auteurs dans une série de 30 hypertendus, dont 8 avaient une hypertension maligne. L'observation s'étendit sur une période variant de 4 à 56 semaines.

Une chute de tension artérielle, quelquefois marquée, fut observée dans chaque cas. L'effet fut encore plus considérable lorsque le médicament avait été employé en combinaison avec la rauwolfia. On observa une régression importante des lésions oculaires. L'hypertrophie ventriculaire gauche ne fut cependant pas améliorée.

La dose initiale du traitement était de 20 à 40 mg. administrée entre 15 et 20 minutes avant chaque repas et au coucher. Chaque dose fut augmentée de 20 à 40 mg., quatre fois par jour, à des intervalles de 5 à 7 jours jusqu'à ce que l'effet hypotensif fut obtenu. La dose habituelle varie entre 160 et 800 mg. par jour. Les mêmes précautions vis-à-vis l'hypotension orthostatique doivent être observées comme dans l'emploi des autres hypotenseurs. Il en va de même pour les contre-indications.

Quand un abaissement rapide de la tension artérielle s'impose, Ansolysen peut être administré par voie intramusculaire ou sous-cutanée à raison de 5 à 15 mg. Il est toujours prudent de commencer avec 2 ou 3 mg. afin d'évaluer la sensibilité individuelle du malade au médicament.

M.R.D.

THE CHANGING PATTERN OF NEUROSYPHILIS*

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IT IS FIFTY YEARS since Schaudinn and Hoffmann recognized that the *Spirochæta pallida* was the causative agent of syphilis. During this half century, the picture of neurosyphilis has undergone dramatic change. The first important trend occurred 46 years ago with the introduction by Ehrlich in 1910 of specific therapy in the form of the arsenical compound "606". This was followed by a succession of new arsenicals and bismuth. Fever therapy, although known and tried for many years, was not in common use until about 1917. The climax occurred with the introduction of penicillin in the therapy of syphilis, just about 10 years ago.

Proof that syphilis in general and neurosyphilis are being successfully combated can be readily obtained by reviewing the incidence of these cases in the special treatment clinic of the Toronto General Hospital. In 1940, 1,088 cases were under treatment for syphilis, of which 373 were newly diagnosed during the year. In 1949 there were 598 cases under treatment, and only 158 newly diagnosed; in 1954 there were 341 cases, 72 newly diagnosed. Among these, there were 13 new patients with neurosyphilis. Although previous annual figures relating to neurosyphilis are not available, it has generally been considered that 5% to 10% of all patients with syphilis show neurological involvement if they are not treated or are inadequately treated.

In the past four years, 180 cases of syphilis with some form of neurological involvement have been reviewed. This figure represents the sum total of all patients with neurosyphilis who have attended the special treatment clinic of the Toronto General Hospital during that period. This group does not include all the cases of neurosyphilis treated or recognized throughout the hospital in recent years, but it does represent a large proportion of them. Many were treated both as inpatients and outpatients. This study includes 177 cases personally reviewed. Most patients were observed on several occasions. The three not included were eliminated primarily because of insufficient data.

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Canad. M. A. J.
May 15, 1956, vol. 74

It is not my purpose to review the well-known classical forms of neurosyphilis, for it is apparent that the day for this variety of original observation of advanced forms of neurosyphilis is long since past, in view of the apparent changes following upon the introduction of specific therapy. The detailed and vivid descriptions of authors such as Kinnier Wilson[1] will likely never be surpassed. In effect, for the most part we are seeing abortive or relatively incomplete forms of neurolues. We still occasionally encounter some far-advanced and classical patterns, but these represent relics of a previous phase in therapy, still within our midst.

Some of the problems or questions that might be solved or answered by a current study of neurosyphilis include the following:

1. The relative incidence and varieties of neurosyphilis.
2. The general pattern and course of neurosyphilis in the pre-penicillin and post-penicillin eras. This would include the clinical picture as well as serological and spinal fluid changes.
3. The question whether neurosyphilis may progress in a clinical form in spite of inactivity of the cerebrospinal fluid following therapy.
4. The relationship of previous therapy to the development of neurosyphilis.
5. The problem of resistant forms or cases difficult to control, including the problem of relapse, as determined by either the clinical pattern or by spinal fluid examination.
6. The necessity for other forms of specific therapy in addition to penicillin.
7. The occurrence of the so-called Herxheimer reaction with commencement of therapy.
8. The effect of penicillin on some of the particular manifestations of neurosyphilis, including lightning pains, gastric crises, and the development of Charcot joints.
9. General observation of interesting and unusual cases of neurosyphilis, as well as the association of several other features, such as syphilitic cardiac disease or peptic ulcer.
10. The effect of treatment on the pathological changes associated with syphilis.

Some of these questions can be answered directly from our study. Others have already been the subject of intensive review, and have brought forth substantial conclusions, some of which are still controversial.

Of the 177 cases of neurosyphilis in this review, many were of long duration, and still under observation because of some evidence of clinical progression or activity in the cerebrospinal fluid within recent years. However, a large percentage had only recently been recognized as having neurological complications of syphilis, found either upon routine examination of the cerebrospinal fluid in the course of treatment, or by the various clinical manifestations. This group included 150 males and 27 females.

Classification of all cases was not always clear-cut, for it is well recognized that there is a considerable amount of overlapping in the clinical as well as in the pathological picture. However, in attempting to assess each case as accurately as possible, the following distribution was arrived at:

Tabes dorsalis—56.

Asymptomatic—43. This includes patients with spinal fluid changes only, and no symptoms or signs of syphilis.

General paresis of the insane—32.

Meningovascular (cerebrospinal)—17. This group includes primary involvement of the meninges or blood vessels, of either the brain or spinal cord.

Pupillary involvement only—14.

Taboparesis—a combination of tabes dorsalis and general paresis—4.

Absence of ankle jerks only—4.

Optic atrophy only—4.

Congenital neurosyphilis—3. Two of these were primarily paretics, and one patient had epilepsy with mental retardation.

The monosymptomatic groups have been purposely left separate, in preference to attempting to force them into any of the above specific classifications. This was done primarily because of the conflicting opinions regarding the outcome of these cases. In general, in patients with pupillary changes only, the condition may remain essentially stationary or they may develop tabes dorsalis, or general paresis, or even meningovascular neurosyphilis. Similarly in the group with optic nerve involvement exclusively, the condition may remain stationary, or the full syndrome of tabes dorsalis may develop. Some examples of patients with pupillary changes bearing resemblance to Argyll-Robertson pupils in conjunction with absent ankle jerks have been found, and these are included in the group of tabes dorsalis. They appear to represent a *forme fruste* of tabes dorsalis, which was recognized even before penicillin therapy.

There were several particularly interesting clinical patterns, including two examples of neurosyphilis in association with Parkinsonism. One of these occurred in a patient now known to have had carbon monoxide poisoning. It is likely that the Parkinsonism is best accounted for on this basis. The other was an example of a well-developed Parkinsonism in a 55-year-old man who had tabes dorsalis of many years' duration, with inactive cerebrospinal fluid, before the actual development of the features of basal ganglia involvement. The patient had previously received penicillin. The question in this case is whether the Parkinsonism is of syphilitic origin or whether its occurrence is purely coincidental. We are inclined to favour the latter view.

There was one example of tabes dorsalis with early luetic amyotrophy of the shoulder girdles. One other patient had neurosyphilis and associated motor neurone disease which was rapidly progressing. The relationship to the luetic process here is not definitely determined.

In seven patients neurosyphilis was associated with cardiac involvement and evidence of aortic insufficiency. There were three examples of peptic ulcer occurring in tabetics. Each of these had presented with a picture resembling gastric crises. This is a well-recognized association, and suggests some neurogenic influence in the production of gastric ulcer in such cases. The lesion has been attributed to a vagus nerve disturbance. In one of our patients a vagotomy was performed, and on later examination although the ulcer was healed the pattern of persistent gastric crises remained essentially unchanged. Two of these patients appeared to have true gastric crises as well as the peptic ulcer. From the evidence of the operative case, one would conclude that the so-called vagus neuritis suggested as one of the many theories to account for gastric crises is not the only causative factor.

Penicillin therapy appears to have altered the general picture of neurosyphilis. The incidence of monosymptomatic cases and so-called *formes frustes* of the various clinical patterns seems to be increasing. Many of these cases appeared before the penicillin era, but even during therapy, which frequently extended over several years, new signs and symptoms seemed to develop. With penicillin, the condition appears to remain fairly stationary in most cases and upon occasion it showed improvement, which continued for many months. There are several examples of patients treated extensively in the pre-penicillin era, in whom arsenicals, bismuth, mercury and fever, often in combination, failed to avert the progression of the clinical picture. Some of these showed either continued activity or reactivity in the cerebrospinal fluid. This was particularly indicated by a high cell count, as well as a high protein level, very strongly positive Wassermann or Kahn reaction, and abnormal colloidal gold curves.

There are some striking examples in this series, where after years of continued activity in the cerebrospinal fluid in spite of the persistent use of the early forms of therapy, a course of penicillin sometimes returned the active contents to normal within a few months. Following Dattner's[2] observations we have also been inclined to regard the cerebrospinal fluid changes as the most reliable indication of activity in the nervous system. In this connection it is well known that neurosyphilis may continue to progress clinically in spite of inactivity of the cerebrospinal fluid, either spontaneously or after therapy. This may be accounted for on the basis of continuation of the reactive or destructive process set up in the nerve tissue or supporting tissues, in spite of inactivation of the spirochæte itself. One can readily conceive of the continuation of the end results of nerve degeneration which has passed beyond a stage of recovery before treatment. This is well demonstrated in certain cases of general paresis of the insane which may continue to progress clinically in spite of treatment.

Tabes dorsalis may also show clinical progression in the form of development of Charcot joints, and by the persistence or increased severity of gastric crises or lightning pains. Further examples are those of progressive deafness and sometimes progressive amyotrophy.

From this it would appear that precise evaluation of the effects of therapy are linked with the sensitive components of the cerebrospinal fluid. These in particular are the cell count and to some extent the total protein estimation. These elements rapidly return to normal after penicillin therapy. The process usually takes several weeks for the cell count, and generally there is a considerable variation with regard to the protein. A continued high cell count indicates a resistant case. A high protein level is sometimes indicative of this, but not so definitely, for upon

Canad. M. A. J.
May 15, 1956, vol. 74

occasion the level may remain high for several years without further evidence of activity. The colloidal gold and Wassermann tests of the spinal fluid are unreliable indices of activity. Persistently high titres and grossly abnormal curves have been seen for years in spite of clinical improvement after treatment. A change from a normal to an abnormal curve, or a weakly positive to a persistent strongly positive cerebrospinal Wassermann reaction is of significance, but this is generally accompanied by a change in the cell count and protein level as well. After penicillin therapy, the general trend is for the various elements of the cerebrospinal fluid to return to normal. This reversal may never be complete, however. The evidence tends to suggest that arsenicals, bismuth, and fever quite frequently inactivate the cerebrospinal fluid, but there were many exceptions and, as mentioned above, there were several examples of relapsing or resistant cases after years of continued therapy. These cases all seemed to be permanently controlled by penicillin.

In addition, there were frequent examples of persistently positive spinal fluid Wassermann reactions and abnormal colloidal gold curves, which had not been affected by earlier therapy, and soon showed a trend of either partial or complete return to normal after penicillin.

In a few cases treated with penicillin, relapses occurred. One patient showed a relapse as evidenced by cerebrospinal fluid activity and headache, two years after penicillin therapy. Another patient relapsed after three years. In each case one or two additional courses of penicillin were necessary to inactivate the cerebrospinal fluid completely, and no further recurrence was apparent. One patient had 16,000,000 units of penicillin initially, but required 30,000,000 before activity subsided. Dattner[3] had previously concluded that, if cerebrospinal fluid was inactive two years after penicillin therapy, there was no chance of a relapse. Our results bear this out in all but one instance, when the interval was three years. However, we have no precise information on the cerebrospinal fluid picture between the first and third years. Further penicillin was given to this patient, and four years afterwards the pattern was that of complete arrest, both from the clinical standpoint and from the cerebrospinal fluid examination. In no case did penicillin in either single or multiple courses fail to inactivate the cerebrospinal fluid. There is only one example in our series of a patient's receiving close to adequate amounts of penicillin in the early stages of syphilis and subsequently developing evidence of neurological involvement. This was a 26-year-old man treated in 1946 for a primary sore. At that time he received 3,000,000 units of penicillin in addition to arsenicals and bismuth in small quantities. Six months later the cerebrospinal fluid was entirely negative. A rising titre in the Kahn reaction in the blood was noted, and the patient received further arsenicals and bismuth for two years. In 1950 the cerebrospinal fluid was very active and all elements returned to normal in six months after 15,000,000 units of penicillin had been given. No clinical signs were present at any time. This patient has been well and spinal fluid has been inactive for four years. It appears that the initial treatment with 3,000,000 units of penicillin was inadequate. Actually, our earlier syphilis cases are treated with a minimum of 3,500,000-4,000,000 units of penicillin initially. The infrequency of such a relapse is in striking contrast to the former situation in which, even after 150 or more injections of arsenic and bismuth over three years or longer, in addition to fever in some cases, cerebrospinal fluid activity would occur, often in conjunction with clinical features of active neurosyphilis.

It has been repeatedly shown that if the cerebrospinal fluid is inactive in cases of general paresis as well as other examples of neurosyphilis, no further benefit can be gained by giving repeated courses of penicillin to prevent clinical progression. There are several examples in our series of progression of paresis with inactive cerebrospinal fluid. Some eventually were committed to Ontario Hospitals in spite of repeated courses of penicillin during the period of clinical progression. The reason for this has been discussed earlier in the paper; it is related to the irreversible change involving the nerve tissue. We no longer find it necessary to use mercury, bismuth or arsenicals in the treatment of syphilis in the early or tertiary stages. Penicillin alone seems to be adequate, as indicated in our series of patients as well as by several comprehensive reports in the literature.[4-6] Fever therapy has not been used in our clinic for the past four years. Convincing controlled studies have tended to eliminate this form of therapy, and it is rapidly being abandoned in widespread

fashion, although some centres still use fever as a last resort in severe and progressive cases of general paresis of the insane.

The Herxheimer reaction has scarcely been a problem in our patients. At one time it was felt that bismuth therapy should precede penicillin therapy. It was also considered best to give penicillin in small quantities initially, and gradually increase the dosage to therapeutic levels in order to avoid a Herxheimer reaction. This precaution was followed initially in our cases but was later abandoned. Serious Herxheimer reactions have not occurred in spite of the fact that large quantities of penicillin were given initially to very active cases in our series. Other studies[7] have shown that small amounts of penicillin, gradually increased, do not in any event prevent the Herxheimer response.

Although occasional deaths have been reported,[8] which have been attributed to Herxheimer reactions even after small quantities of penicillin, we have not found this to be a problem in therapy, and few significant untoward results have been observed. There has been an occasional mild and transient increase in mental deterioration, and slight febrile reaction. Some reactions undoubtedly have been overlooked because the patients were treated as outpatients. We know of two severe Herxheimer reactions that occurred during penicillin treatment in hospital recently, but these patients were not in the series reviewed. One other patient with severe paresis continued to deteriorate rapidly and followed a downward course for three weeks which eventually led to death. This occurred before and during the course of penicillin therapy. It is considered unlikely that there was any relationship to a Herxheimer pattern, for this febrile reaction did not commence until one week after penicillin therapy began, and rapid deterioration was apparent even before the first treatment. This case could rightly be classified as a rapidly developing destructive variety of general paresis, beyond the stage responsive to therapy. There have been several minor reactions, and one severe reaction attributable to penicillin sensitivity itself.

The problem of lightning pains still remains unsolved. They have generally been attributed to the process of destruction and irritation of the posterior root near the root entry zone of the spinal cord. There is essentially a radicular perineuritis. These pains have been notorious for persisting after all forms of therapy, in spite of successful control of the course of the disease, as well as inactivation of the cerebrospinal fluid. We observed six patients in whom penicillin seemed to have a definite and beneficial effect on lightning pains. Some of these cases relapsed after a period of several months, however. One patient stated that for the first time in 25 years he had relief from pain, and this occurred immediately after the first injection of penicillin. There was no recurrence in the six months that he remained under our observation. On the other hand, there was a larger group of patients in whom lightning pains were in no way affected by penicillin therapy. In two cases lightning pains developed for the first time during the actual course of penicillin treatment. Another patient complained of these pains one year after penicillin therapy had been given. In general, there is a variable pattern of response, and the evidence would suggest that in possibly 40% of the cases some improvement does occur with relief of lightning pains after penicillin therapy, although the improvement is often short-lived.

Similarly, gastric crises are not generally affected by penicillin, although an occasional example suggested that there was some definite effect. In general one could not be impressed with the results, as close scrutiny indicated that there had been spontaneous remissions previously, and this pattern could readily have accounted for the improvement in the cases in question. Actually, two out of four patients seemed temporarily improved.

The fact that lightning pains and gastric crises may develop in patients who have received apparently adequate treatment, and in whom the cerebrospinal fluid has shown no evidence of activity, is well shown in some of our patients, and has been mentioned earlier. Another interesting example of progression of syphilis in spite of negative spinal fluid is illustrated by a patient who began to have evidence of multiple Charcot joints and spontaneous fractures six years after the cerebrospinal fluid had been inactivated. The fractures occurred spontaneously in several different locations. There was only minimal evidence of demineralization of the bones and no indication of change in the significant biochemical studies. Spontaneous fractures in tabetics have been previously recognized, but are generally considered extremely rare. They have been attributed to trophic changes resulting from involvement of the lateral horn of grey

Canad. M. A. J.
May 15, 1956, vol. 74

matter in the spinal cord. The patient in question had not been treated with penicillin in the past.

From the pathological standpoint, we have previously seen examples of arrested general paresis and other forms of neurosyphilis after treatment with arsenicals and fever. In these cases there is essentially evidence of a healed and inactive process. This pattern seems to be becoming more frequent since the introduction of penicillin. The earlier the treatment is given, the more normal the tissue appears to be. This is particularly striking in cases of general paresis, and fairly dramatic examples of clinical improvement with penicillin would seem to fit well with the pathological evidence of an essentially healed process. Our own observations on some of the pathological material available have not actually included examples in which penicillin alone has been given, hence no conclusion can be drawn from that standpoint.

In general, it may be stated that no treatment known is designed to restore degenerate or narcotic parenchyma, nor can therapy attempt to overcome the advanced processes of tissue reaction. Hence treatment is primarily aimed at preventing further damage. There may be some restoration in function in tissue only partially damaged. On the other hand, as we have already implied, some form of destructive or irritative lesion may persist as a result of a process that had begun long before therapy itself had been effective.

The general routine for penicillin treatment has been that of intramuscular injections of 600,000 units of procaine penicillin G in oil (aluminium monostearate) three times weekly for about four to six weeks. In cases of neurosyphilis there is no absolute rule, but generally 7,000,000-11,000,000 units of penicillin have effectively controlled the large majority of cases, and active spinal fluid has returned to normal. When repeated courses are necessary, about 15,000,000 units are given with treatment extended over a period of eight weeks.

In addition to the pattern of cerebrospinal fluid changes, the general quantitative titres of the blood reaction are also carefully observed. No patient treated for early syphilis is discharged even after adequate therapy, unless blood titres have remained low for a minimum of three years, and a spinal fluid examination three years after therapy has shown no evidence of activity. In this way, it should be possible to recognize and control effectively with penicillin all cases of early syphilis, and to prevent the late complications, including neurosyphilis.

SUMMARY AND CONCLUSIONS

1. A review of 177 patients with neurosyphilis has been given. Penicillin alone was the chief therapeutic measure used, although other forms of therapy had been given to many of the patients in the past.

2. Some interesting examples of neurosyphilis have been described.

3. The general trends in the clinical pattern and cerebrospinal fluid pattern after therapy before and during the penicillin era have been discussed.

4. The effectiveness of penicillin alone in the treatment of neurosyphilis has been emphasized.

5. The relative effect of penicillin therapy on gastric crises, lightning pains, and Charcot joints, as well as on advanced paresis, has also been discussed.

6. Penicillin alone has been effective in controlling all groups of neurosyphilis. In general it has been least effective in altering the course of advanced paresis, or moderately advanced tabes, when fixed and irreversible reactions have already occurred.

7. A general program for the effective control and elimination of neurosyphilis has been briefly outlined.

Dr. R. Smith and Dr. H. H. Hyland have offered some valuable suggestions in the preparation of this paper.

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WHY DIDN'T THEY ASK?

"I was once asked to see a girl with dermatitis artefacts with the idea of hypnotizing her and finding out what she was doing to her skin, and why she was doing it. Before considering hypnosis I said to her: 'Tell me; are you putting something on your skin which makes all those sore places?' She replied: 'Well, yes; I do it with hydrochloric acid from my brother's laboratory; you see, if my Dad thinks I'm ill he treats me much more nice.' The consultant, when I told him the solution, was most impressed until I explained the method of obtaining it. He admitted that it had not occurred to him."—Richard Asher, *Brit. M. J.*, 1: 313, 1956.