Papers and Originals

The Obstetrician Bids, and the Uterus Contracts*

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We are in a century of change. Nowhere is this more true than in medical, and especially obstetrical, practice. I myself remember the constant fear of puerperal sepsis which made my teachers reluctant to resort to even simple interference with the natural course of childbirth. Rachitic deformities were still distressingly prevalent, and the older men could recall the days when, in the Glasgow Maternity Hospital, for example, no less than one in every 30 deliveries was effected by craniotomy.

Let me put this change into figures. For every 15 women who, even 30 years ago, died in childbirth, to-day only one is numbered. Turning to post-partum haemorrhage—the subject toward which this lecture will be specially directed—for every 10 women who then died in childbirth only one dies to-day. The mortality of post-partum haemorrhage has thus decreased tenfold. What answer can we give to the obvious questions: Why ? and How ?

It would be easy—it would also be misleading—to give a single, simple answer. Many factors have collectively brought about the change. Let me enumerate some of them: better general health of the parturient woman ; better obstetrical technique ; better means of combating infection which so often follows haemorrhage ; better means of replacing lost blood—and here let me remind you that it was one of the major advances of the century when, under the stimulus of the second world war, blood banks were established throughout the length and breadth of the country, and simplified methods devised of effecting safe and adequate transfusion.

Collectively, these are the ways in which obstetric practice has advanced. And yet there is another factor which has probably contributed as much as any to a reduction of the mortality from haemorrhage. This is the introduction and general availability of reliable drugs which cause the uterus to contract and which check post-partum haemorrhage or even prevent it before it has appeared. Chief among these is ergot.

Introduction of Ergometrine

It is not my purpose to trace the long history of ergot, although, with a story so remarkable, the temptation to do so is very great. Nor shall I particularize on some of the unexpected consequences of ergot research which provided the keys to many hitherto guarded secrets of physiology and pharmacology. Those who feel prompted to turn to the history of ergot will find in Barger's *Ergot and Ergotism* a wealth of information.

Somewhat hesitatingly, and at the risk of incurring an anti-climax, I venture to mention in this connexion an address which I myself gave in 1955 on the occasion of the Centenary Celebrations of Queen's University, Ontario. If I now refer to that paper and paraphrase some of its contents it is because it deals, amongst other matters, with events that took place within this hospital—the University College Hospital of London.

To understand the present-day use of ergot we must go back nearly 150 years, to 1808, when Dr. John Stearns, a practitioner in the State of New York, U.S.A., sent to a colleague a letter which was subsequently published in a medical journal. It seems that Dr. Stearns had long been importuned by a local midwife to search in the granaries for diseased heads of rye—the small black spurs which we now know to be the result of a fungous infection by ergot spores—and to administer them as a decoction to women whose labours were abnormally slow. This letter clearly described the remarkable effect of ergot ; and with its publication the drug became widely known to the medical profession. For our present purpose one sentence is of particular importance. It reads: "You will be surprised by the suddenness of its operation ; it is therefore necessary to be completely ready before you give the medicine."

I shall return to this statement later.

With the development of chemical technology ergot was soon subjected to intensive investigation. Interesting discoveries were made, but these related mostly to side-issues ; and for long years ergot retained its secret. By 1906, however, Barger and Carr in this country isolated a crystalline alkaloid to which the name ergotoxine was given. In 1918 another alkaloid, ergotamine, was isolated by Stoll working in the Sandoz Laboratories in Switzerland. Both these substances were extremely complex, and with the chemical methods then available some doubt was expressed whether the two were not identical. Later research, much of it in the Sandoz Laboratories in Switzerland, has shown, however, that in ergot there is a group of large-moleculed alkaloids which have a peculiar property of forming complexes, one with another, and the early product, ergotoxine, appears to be the result of such a union.

In the earlier decades of this century these matters remained obscure, and the important practical issue was whether the then-known alkaloids were effective in the human subject, and, if so, whether they differed one from the other in the nature of their action.

Early Trials

These questions were considered by the Therapeutic Trials Committee of the Medical Research Council under the leadership of Sir Henry Dale. My then chief, the late F. J. Browne, of University College Hospital, was asked to consider a clinical trial. How this should be conducted was left an open question, but in a discussion which later took place I suggested the

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possibility of using the uterus at the sixth or seventh day of the puerperium as a test object. The risk of uterine rupture which might occur were the drugs given during labour would thus be overcome ; and, because a protective barrier of leucocytes quickly forms in the puerperal uterus, the introduction of a small balloon with careful antiseptic technique should not present danger or difficulty. Moreover, as a pelvic examination was routinely made at about this stage of the puerperium the patient would be subjected to little or no extra discomfort.

Encouraged by my chief, and with the co-operation of the patients, the trial was made. The results were successful beyond expectations. It was early found, for example, that the stimulating effect on the uterine muscle brought about by the child sucking at the breast could be graphically recorded (Fig. 1), and a still more spectacular effect on the uterus could be produced when a small dose of pituitary extract was administered by intramuscular injection.

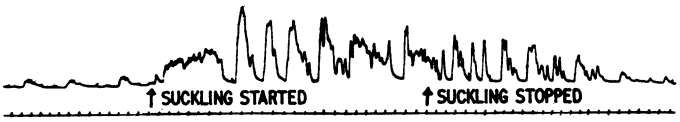

FIG. 1.—Tracing made with a small intrauterine bag introduced on the seventh day of the puerperium showing the stimulating effect of suckling.

Perhaps I may be allowed a little licence at this point in order to indulge in one or two personal reminiscences. As a recent-comer to the hospital I had sensed the need for caution in conducting clinical research. I knew that I had the support of my chief and of other senior members of the staff, but in some other quarters there was undoubtedly an atmosphere of suspicion which sometimes even approached hostility. This opposition I largely overcame by placing my recording gear out of sight in a small room adjacent to the ward. From this room a permanent communication had been established with the ward by means of a length of thin gas-piping which I had quietly placed between two convenient windows. I pray that the hospital authorities have now forgiven this secret injury to their fitments.

Financial resources at that time were also slim ; and it is perhaps my Scottish inheritance which makes me fill with pleasure when I recall that the cost of the enterprise was negligible. One shilling was used for the lead piping and five shillings for the purchase of an alarm clock which, fitted with electrical contacts and used in conjunction with the mechanism of a worn-out electric bell, enabled me to add minute-markings to the kymograph charts. These and other contrivances were all improvised from discarded hospital material. Only the clockwork-moving drum was specially requisitioned, and it was already part of the departmental equipment. The claim can thus be made that the discovery of the presence of the new ergot principle, later to be called ergometrine—which I shall presently describe—was accomplished at a total cost of six shillings.

Further Experiments

To return to the main story, the path was now clear for the investigation of the effect of the then-known alkaloids, ergotoxine and ergotamine. Experiment soon showed that both were reliable uterine stimulants, although slow to take effect, with a 20-minute delay after intramuscular injection. By mouth administration the effect was even slower and very long delayed.

Here, then, was the immediate answer needed. Both the alkaloids in question were active, and their effects on the puerperal uterus were indistinguishable one from the other.

Very naturally, and urged on with the support of Sir Henry Dale and of F. J. Browne, the field of the investigation was now extended. At that time the liquid extract of ergot —an old and well-established pharmacopoeial preparation—had been condemned by most pharmacologists because, being a watery extract, it could contain none of the then-known alkaloids. This opinion had, however, not gone unchallenged, and many clinicians still believed in its worth. Here, then, was the obvious first choice for further experimentation.

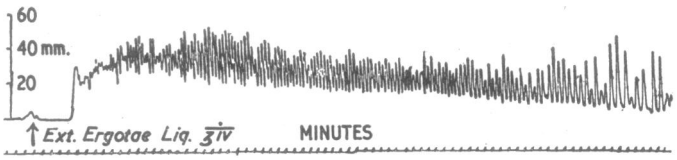

FIG. 2.—Tracing made on 11 March 1932 which showed the presence of a hitherto unidentified active principle in an aqueous extract of ergot—the "Dr. John Stearns's Effect."

At that time the liquid extract was still freely employed in the hospital and, accordingly, the full dose was administered to a patient on the seventh day of the puerperium. The subsequent hour was memorable. In the adjacent side-room I watched, rather sceptically, the movement of the recording needle. First a few meaningless excursions ; then with startling suddenness the needle rose (Fig. 2). Up and up it went until the movement resolved itself into vigorous and sustained oscillations. This was activity of a different order and different quality from any I had previously witnessed. My first impression was that something had gone wrong with the recording system, but a quick check showed that this was not so. Next I supposed that the patient must be behaving in some unprecedented manner ; but no, in the adjacent ward I could see her sitting in bed unconcernedly eating her lunch. My third and lasting impression was one of sheer astonishment.

> "Then felt I like some watcher of the skies
> When a new planet swims into his ken."

Leaving my work, and with a mind still full of wonder, I made my way home. I had seen the uterus behave in an unprecedented fashion. I had seen it contract with startling suddenness, and I had seen it contract, not after parenteral injection, but after the administration of a crude ergot extract by mouth. While thus lost in thought there flashed on me the true meaning of Dr. John Stearns's words. The events of the day were now crystal-clear. I had stumbled on the long-forgotten "Dr. John Stearns's effect."

In retrospect, it is indeed strange that the quick action of the aqueous extract had not already been established ; by placing his hand over the puerperal uterus any careful observer can detect the change caused by the drug. But interest in research and patience for clinical observation are possessed by few, and such observations as had previously been recorded had been vague, unconvincing, or soon forgotten.

New Chemical Fractionation

Then started a period of great activity. Sir Henry Dale was informed. He had long suspected that ergot held further secrets, and now he reacted with characteristic enthusiasm. The findings must be confirmed. A new chemical fractionation of ergot must be instantly started. His chief research chemist must be brought into service. Dr. H. W. Dudley was the man named, and with him I was soon to work in close and happy association. Sad it is to record that less than four years later —and, strangely, on the very day when his full report on the chemistry of the newly discovered principle was first published —Dudley, then aged 49 and at the height of his abilities, succumbed to a fatal illness.

The task of isolating the new oxytocic substance was more difficult than had been foreseen. There was neither chemical nor animal test by which its presence could be detected. Each successive fraction—and there were many scores of them—had to be examined by the only method available, the administration to a puerperal woman and the subsequent

graphic recording of the behaviour of her uterus. Each new batch of raw ergot had to be tested for potency before being subjected to fractionation. More than once supplies ran out and we had to nurse our patience till a new harvest arrived from Spain. True it is that Dudley had almost at once achieved a remarkably high degree of purification, but not till nearly three years had elapsed did final success seem to be at hand.

Shortly before Christmas Eve, 1934, I heard Dudley's voice over the telephone; he seemed strangely excited. Deep red crystals, beautifully shaped, had made their appearance in his latest fraction. Surely it must be the sought-for principle. It was tested. It was quite inert. It was a poor Christmas Eve for both of us. But a few days more, and another pure crystalline substance was forthcoming; and from the various chemical reactions that had now been evolved it promised to be of more than ordinary interest. A quick method of external recording was employed. The preparation was undoubtedly active. Another few days and on 9 February 1935 a beautiful tracing by the internal method was obtained. The crystals reproduced to perfection the Dr. John Stearns's effect (Fig. 3).

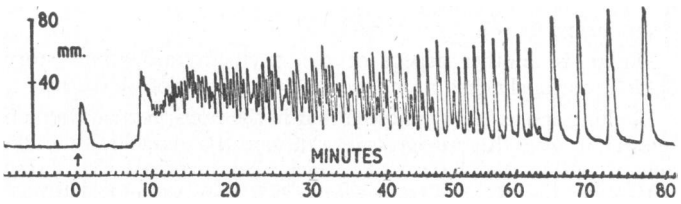

FIG. 3.—The first intrauterine tracing made with the newly isolated alkaloid—later to be called ergometrine—showing a perfect "Dr. John Stearns's Effect."

A council was held with Sir Henry Dale. Publication of the results would be delayed a few weeks to ensure that the chemical features could first be worked out with full accuracy. The method of preparation would be published in full, no patent rights or proprietary interests would encumber the new drug; it would be free for any manufacturing firm to produce. The name would be ergometrine. All this came about and the first announcement of the new alkaloid appeared in the *British Medical Journal* of 16 March 1935.

Meanwhile, in other centres similar work had been in progess. And from three of them—from Baltimore, from Chicago, and from the Sandoz firm in Basle—the nearly simultaneous announcement was made of the isolation of a new water-soluble ergot principle. The relationship of these various substances was fully discussed in the *British Medical Journal* of 7 December 1935 (p. 1114). As might be supposed, all of them were found to be identical.

One result of this multiple work and multiple discovery—in many ways a most useful development—was the confusion of names which arose. Some of these have now passed from use, but in the U.S.A. the official name eventually adopted was ergonovine, while a well-known proprietary brand continues to be termed Ergotrate. In Switzerland the Sandoz firm retained Stoll's original name of ergobasine; but in most European countries and throughout the British Commonwealth the name of ergometrine is usually employed.

The newly discovered alkaloid—much simpler in chemical structure than the previously known alkaloids—has the merit of a powerful action on the uterus, of availability for use by mouth or by intramuscular or intravenous injection, and of comparative freedom from toxic side-effects. It is now used the world over, and probably provides the best single method of checking post-partum haemorrhage and of curtailing the third stage of labour and the trickle of blood which so often occurs while the placenta is still retained.

Rather surprisingly, recent years have brought occasional reports of unexpected hypertension after the administration of ergometrine. In the circumstances under which the drug is used in this country this effect is extremely rare, but the possibility must be kept in mind and reasonable dosage not exceeded. Pharmacological experiment to explain this rare effect is now under way.

Post-pituitary Gland Principles

Turning now to pituitary extract, here again there is a story—not so well known perhaps as that of ergot—but a story which shows once more how the unexpected finding or chance observation may alter medical progress.

In the year 1906 attention was directed to the newly found property displayed by extracts of the adrenal gland in causing an elevation of blood-pressure. In the laboratories of Burroughs Wellcome and Company a young research worker, Dr. Henry Dale, was testing extracts of this and of other so-called ductless glands, and had confirmed the fact that in pituitary extract there was also a substance that had a significant effect on the blood-pressure of the experimental animal—in this case the cat. Fortunately for medical science, this cat was a tabby and not a tom. The experiment finished, Dale was attracted by curious objects at the sides of the abdomen which, on inspection, he identified as the uterine horns. But they were cord-like and white. Was there some anomaly of development in this particular cat? Was there perhaps a menopausal change—if, indeed, such a phenomenon can be imagined in a cat? Or was there a possibility that the horns might be normal but in a state of intense spasm? With Dale the answer could not long remain in doubt. Further extracts were prepared and further experiments devised. And now the explanation was clear. Pituitary extract had the unsuspected property of causing an instant and intense contraction of the uterus.

Unfortunately, perhaps, this remarkable discovery was not at first adequately publicized but appeared as a note in a paper that dealt primarily with the properties of certain ergot extracts. Not until three years had elapsed did Blair-Bell, to whom Dale had furnished samples of his extract, publish the first account of its use in clinical obstetrics. But more extensive reports were soon to appear in German and Swiss journals; and before long the use of pituitary extract was the foremost topic of discussion in obstetrical circles the world over.

Then history repeated itself. One hundred years earlier ergot had been used and had been abused. It had hastened the progress of "lingering labour" but it had also caused the death of many a woman from uterine rupture, and many a foetus had perished because of intrauterine asphyxia. Now it was the turn of pituitary extract. There had been those who had declared that pituitary extract, being "physiological," must therefore be safe. Their glib pronouncements were soon shown to be gravely in error. Recklessly used, pituitary extract was at least as dangerous as the older drug. And this was not surprising, for the strength of the early commercial preparations was quite uncertain and varied as much as eightyfold.

Imagine, now, the effect of such uncertainty in dosage. Instead of an action on the uterus suppose it is an action on the gut. Let us take, for example, the case of castor-oil. If the maximum dosage is 1 ounce, how would an unfortunate child react to a dose of 80 ounces? But this outrageous uncertainty, or something very much like it, prevailed in the early days of pituitary extract, and it was not until the early 1930s, thanks to the efforts of Dr. J. H. Burn working under Dale—later Sir Henry Dale—in the National Institute for Medical Research at Hampstead, that the preparations were satisfactorily standardized.

But even with standardized preparations the response of individual women to pituitary extract is not entirely predictable, and it remained for Theobald to introduce, in 1948, the now well-known method of administering the drug in extreme dilution by slow intravenous infusion. The oxytocin "drip,"

as it is called, can be regulated to the needs of the individual patient, and, should overstrong action be produced, can be stopped with the certainty that the uterine effect will subside within one or two minutes. The oxytocin drip or, more recently, pituitary extract in tablet form suitable for mouth absorption ("buccal" Pitocin) is the method of administration generally employed in present-day work.

So far, I have pictured the use of pituitary extract during labour. But the nature of its action also makes it very suitable for hastening the third stage of labour and for combating post-partum haemorrhage. Opinions are divided whether for these specific purposes pituitary extract is as consistent and reliable as ergometrine, but this is not a question that need be discussed in detail now. It is enough to state that to Nixon and Smyth (1957), of University College Hospital, we are indebted for much careful work on uterine action and the evaluation of the many methods of employing oxytocic drugs.

Pituitary Shock

Let us now consider a side-effect of pituitary extract which has figured largely—perhaps too largely—in obstetrical literature. This is the sudden pallor and collapse—even death—that may follow the administration of an over-large dose, especially if it is given by the intravenous route. In the early days pituitary shock was a grave menace which prejudiced many against the use of the extract in any and all circumstances. I myself have witnessed the death of a woman who had been given an intramuscular injection and the injection repeated within 10 minutes. And here is the clue to the danger. The ampoules in use at that time contained as much as 10 international units of pituitary extract. It follows, therefore, that this unfortunate woman received, within a few minutes, at least four times the dose that would nowadays be regarded as maximum. The danger of large doses, and specially of repeated doses, is now generally recognized, although the administration of 5 units by intravenous injection was, to my knowledge, a common practice until very recent times in some South American countries.

The cause of pituitary shock is probably complex, but there is reason to believe that an important element is the constriction of the coronary arteries of the heart. This brings me now to a fuller consideration of the pharmacological action of pituitary extract.

So long ago as 1928, Kamm, working in the Parke Davis Laboratories in America, showed that pituitary extract could be split into two fractions, one predominantly oxytocic and one predominantly vasopressor. These fractions were subsequently marketed under the names of Pitocin and Pitressin, respectively.

In Pitocin obstetricians had a preparation largely devoid of vasopressor action, and hence, presumably, largely devoid of the tendency to induce pituitary shock. This is the position to-day. In the strictly limited dose which is now employed, and in the use of a preparation from which the vasopressor fraction has been substantially eliminated, we have a relatively safe method of making the uterus contract.

But this is not all. One of the most remarkable achievements in the field of hormone research has yet to be mentioned.

Du Vigneaud, of Cornell University, after long years of biochemical study, identified the active principles of the posterior lobe of the pituitary gland. These were already known to be polypeptides. To identify the individual components in this group—highly complex and highly unstable—and to isolate those that possessed a pharmacological action, was indeed a remarkable accomplishment. Yet this was done; and even more astonishing was the successful synthesis of these active principles—an achievement beyond the comprehension of anyone belonging to the older school of chemistry.

By the work of Boissonnas in the Sandoz Research Laboratories these synthetic preparations were made available to clinicians, and the oxytocic product, Syntocinon by name, is now extensively used in obstetrics. Because it is entirely free from vasopressin it is regarded as even less likely to produce pituitary shock than is the oxytocin derived from natural sources, although I am of the opinion that under modern conditions of use the danger of pituitary shock is already quite remote.

Syntocinon can be conveniently combined with ergometrine. This preparation, marketed by the Sandoz firm under the name of Syntometrine, has the advantage of a rapid action when given by intramuscular injection; Embrey, working with me in Oxford, has shown that the average latent interval is two and a half minutes. It should be noted, however, that this is considerably longer than the latent interval after the *intravenous* injection of 0.25 mg. of ergometrine, which is rather less than one minute; and when one is faced with post-partum haemorrhage much blood may be lost in that short time. Nevertheless, Syntometrine is of great use to midwives, who are not always trained in the technique of intravenous injection and who, because of the bad name previously earned by the uncontrolled use of pituitary extract, are discouraged by their supervisors from using the older preparation.

There is another aspect of the oxytocin-vasopressin story which, curiously, has never received the attention it merits.

So long ago as 1934 I showed that in the non-pregnant human uterus it was the *vasopressor* and not the oxytocic fraction which caused the organ to contract. So surprised was I that I became convinced my test bottles had been wrongly labelled. Through the courtesy of Parke Davis's representative in London my fractions were returned to the parent laboratory in Detroit for reassay. In due course I received their report. In curt and barely polite words I was told that *no* mistake had been made.

My paradoxical observations had, however, not been so surprising as at first appeared, for Robson (1933) and others had already shown in animals that the precise action of the two pituitary fractions was variable and to some extent interchangeable.

Later I was able to follow up this work with a fuller report, published in 1941. Briefly it was as follows:

Summary of Action of Pitocin and Pitressin on the Intact Human Uterus

	Pitocin	Pitressin
Non-pregnant	0	+ +
Early pregnancy (after 8th week)	Very feeble	Feeble
" " uterus already active	+	+ +
Late pregnancy (after 36th week)	+ +	+
Parturient	+ + +	+
Early puerperium	+ + +	+
6th to 9th day of puerperium	+	+

More recently Embrey, working with me in Oxford, has shown that, with regard to the non-pregnant uterus and the uterus in early pregnancy, the observations made with the naturally occurring hormones are also true of the synthetic hormones. Any lingering doubt that the parodoxical actions of the early pituitary fractions were due to an incomplete separation of the naturally occurring principles could thus be set aside. We can therefore accept the fact that the uterine response to vasopressin and oxytocin is not constant but varies with the biological state of the uterus, and that the names given to the two undoubtedly separate principles are to some extent misleading.

Use of Sparteine

The story of oxytocic drugs does not stop with ergot and oxytocin. Many other naturally occurring drugs or synthetic products have been employed, some because they are tradi-

tionally credited with a uterine action, some because of interest aroused by pharmacological research. It would be pointless at this time to attempt any complete list. One drug, however, is now arousing interest and deserves special mention. This is a purified lupanine base to which the name sparteine has been given.

Sparteine, a naturally occurring alkaloid, has been known to pharmacologists for many years. So long ago as 1873 it was employed as a corrective for certain cardiac irregularities. Because of a supposed analogy between the heart muscle and uterine muscle, and also because of certain pharmacological observations reported by Tamba in 1921, it was occasionally employed in the hope that it would induce the onset of labour or speed the progress of labour already started. With the introduction of standardized and of synthetic preparations a new interest has been stimulated, and there is now a considerable literature relating to this drug, more especially in the American journals.

In this country sparteine has been given a trial in several centres. Embrey and Yates (1964), in Oxford, have shown by tocograph tracings in the human subject that it has an undoubted oxytocic effect which in quality resembles that of oxytocin although with an action somewhat less consistent.

A Backward Look

The clinical trial of sparteine continues, but meantime it would be prudent to bear in mind the history of other uterine stimulants. First there was astonishment on discovering the effect. Next there was a cautious employment of the drug in labour. Then came the period of uncritical and reckless use. Lastly, there was the sober realization that a substance beneficial in reasonable dosage, or in the presence of weak uterine contractions, becomes a danger when administered in high dosage or when the uterus is already briskly active.

Here let me recall the words of the late Joseph B. DeLee, long the doyen of American obstetrics. He was referring to the misuse of pituitary extract, but equally well his warning might be applied to all oxytocic agents. "A streamlined labour," he said, "is as safe as a streamlined parachute."

And now to add a grim note. Already cases of uterine tetany and of uterine rupture are reported following the use of sparteine. The wheel completes its circle.

I started this lecture by referring to the mortality from post-partum haemorrhage. Many of our present-day students have never witnessed the sudden torrential bleeding so dreaded by our obstetric forebears; far less have they heard of any death from this cause. This, then, is the token of the debt we owe to the pharmacological laboratories of many countries where patient co-ordinated research—often wearisome, often unspectacular, often without hint of practical application—may in the end yield a reward which, reckoned in the saving of human life, places it among the enduring achievements of medical science.

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The Benign Form of Multiple Sclerosis: Results of a Long-term Study

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"... enfin il n'est pas rare de voir des intermissions complètes qui ont pu faire espérer une guérison définitive."
CHARCOT, 1872.

In a disease so variable in its course as multiple sclerosis, prognosis in an early case will remain beyond the grasp of the physician unless an effective form of treatment is forthcoming. In the meantime some light can be thrown on this problem by studies which, although not truly prospective, follow uniform methods of diagnosis and evaluation of disability over a span of years. One such study was completed in 1959 (McAlpine, 1961). It was confined to 241 patients in whom the disease had begun between January 1930 and December 1949 and who had been seen at the Middlesex Hospital within three years of onset. In all but one case the diagnosis had been "multiple (or disseminated) sclerosis," qualified sometimes by the adjective "probable," "possible," or "suspect."

Of these 241 patients, 83 (34%) had died, 80 (33%) were disabled in varying degree, and 78 (32%) were "unrestricted" —that is, "without restriction of activity for normal employment and domestic purposes but not necessarily symptom-free" (McAlpine and Compston, 1952). All the patients in this group were working either away from or at home and could walk at least half a mile (0.8 km.) without a rest or support from a stick.

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Present Study

A further five-year follow-up of these 78 patients has been completed. In the autumn of 1962 57 were examined and information about all but one of the remainder was obtained by letter. During March–May 1964 63 patients attended for examination, letters were received from general practitioners in nine instances, while five patients (one living in West Africa and another in U.S.A.) replied to questions regarding their health (Table I).

The three patients who died were in category "unrestricted." Two were classified as possible cases.

A single woman aged 28 noticed "pins and needles" and slight weakness of the right hand on 11 September 1937. About 15