Post-ischaemic paraesthesiae in diabetes mellitus

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SUMMARY A quantitative assessment of post-ischaemic paraesthesiae has been made in 50 diabetic subjects and in a group of healthy age-matched controls. The results show a highly significant diminution of the paraesthetic response in the diabetic subjects. The degree of depression of the paraesthetic response was associated with the duration of the disease and the severity of the metabolic abnormality as determined by the degree of insulin dependence. Diabetics with the juvenile-onset type of the disease were more adversely affected than those with the maturity onset type. There was no consistent relationship between the degree of depression of the paraesthesiae and the presence of peripheral neuropathy. The significance of these results is discussed in relation to the factors which determine the composition of the ionic micro-environment of myelinated nerve and the level of electrical excitability of the nerve fibre.

Although paraesthesiae consequent on ischaemia of a limb have long attracted interest and many features have suggested their possible value in the study of peripheral nerve disease, the observations of Poole (1956a, b) have received less attention than they merit. Occlusion of the circulation with a sphygmanometer cuff applied above the elbow elicits ischaemic paraesthesiae within a few minutes, being perceived as a faint tingling, buzzing, or vibrating sensation in the hand before dying away some minutes later (Weddell and Sinclair, 1947). Release of the cuff and restoration of the circulation gives rise to the more distinct post-ischaemic paraesthesiae in which Merrington and Nathan (1949) recognize four elements—thermal, cramp, tingling, and a pricking ‘pins and needles’ sensation. Poole (1956a) determined the features suitable as criteria of normality in the clinical application of paraesthesiae tests, and showed that post-ischaemic paraesthesiae of the pricking ‘pins and needles’ type occurred with such great constancy in the upper limbs of healthy subjects between the ages of 12 and 60 years that their diminution or absence might readily attract attention as evidence of abnormality of peripheral nerve function. He studied three groups of subjects comprising those with acute infective polyneuritis, chronic and recurrent neuro-pathies, and those with megaloblastic anaemia and confirmed the view that paraesthetic responses were disturbed in these conditions, and that the extent of the depression provided a sensitive index which defined the presence and progress of neuropathies in such conditions as intoxications, vitamin deficiencies, alcoholism, malignant disease, and diabetes (Poole 1956b). In an attempt to obtain objective evidence of Poole’s observation, Seneviratne and Peiris (1968a) measured excitability changes in the sensory fibres of the median nerve during and after 30 minute periods of vascular occlusion of the upper limbs of healthy subjects. They observed that the low threshold fibres of the nerve went through a transient phase of hyperexcitability before being inactivated by the ischaemic process, while release of the cuff and restoration of the circulation were followed by a rapid increase in the excitability of the fibres which lasted for several minutes before the nerve regained its resting level of excitability. All control subjects experienced paraesthesiae during the ischaemic and post-ischaemic phases of nerve hyperexcitability. Measuring excitability changes in the nerves of 12 diabetic subjects, Seneviratne and Peiris (1968b) observed that the most characteristic difference between normal and diabetic nerves was the very limited extent...
to which the diabetic nerve was inactivated by a 30 minute period of complete vascular occlusion. The nerves of the diabetic subjects did not exhibit the phases of ischaemic and post-ischaemic hyperexcitability that are characteristic of the normal subject, nor did any of these diabetic subjects experience ischaemic or post-ischaemic paraesthesiae. Comparing the responses obtained from six diabetic subjects who had clinical and electrophysiological evidence of peripheral neuropathy with those of six age-matched diabetic subjects who had no evidence of neuropathy as judged by clinical testing and by conventional electrophysiological techniques, they found that both groups behaved in an identical manner. None of these diabetic subjects experienced paraesthesiae nor did any of them show the transient phases of nerve hyperexcitability during the ischaemic or post-ischaemic periods. The results obtained from this limited sample led Seneviratne and Peiris (1968b) to suggest that the absence of paraesthesiae evoked by vascular occlusion in the diabetic subject indicated the existence of some abnormality of peripheral nerve function which preceded the development of the signs, symptoms, and electrical criteria characteristic of a peripheral neuropathy.

Since the advantages of such a simple bedside diagnostic procedure are obvious, the experiments described in this paper were designed to assess the validity of the test. A larger group of control and diabetic subjects has been studied with a view to correlating the response with the severity of the diabetic state, the type of diabetes, the presence of peripheral neuropathy, and the duration of the diabetic state. These experiments were also designed to elicit information which would help to elucidate the basic problems relating to the normal production of ischaemic and post-ischaemic paraesthesiae and to the pathophysiology of the processes that lead to the absence of such paraesthesiae.

**METHODS**

Fifty diabetic patients whose ages ranged from 15 to 60 years were studied in this series, while 50 healthy subjects of a comparable age group served as controls. A diagnosis of diabetes mellitus was established using the criteria recommended by WHO (1965). All the diabetic subjects were in an adequate state of metabolic control for at least two weeks before their inclusion in this group. The severity of the diabetic state was assessed in terms of the quantity of a standard preparation of insulin which was required to maintain each patient in a state of metabolic control. Three grades of severity were recognized. Those who required no insulin and could be maintained in a state of control by dietary adjustment alone were considered as having 'mild' diabetes, those who required up to 40 units of insulin per day were in the 'moderately severe' group, while those who required over 40 units of insulin daily for adequate control were considered as having 'severe' diabetes.

The duration of the diabetic state was used to classify the subjects into three groups. The first group included those subjects who were known to be diabetic for less than five years, a second group those with diabetes for five to 10 years, and a third group included subjects whose history of diabetes extended for more than 10 years. These patients were also classified on the basis of the type of diabetes, the criteria recommended by Fajans and Conn (1965) being used to differentiate the juvenile type from the maturity onset type of diabetes.

A careful clinical examination was carried out on all diabetic subjects in order to assess peripheral nerve function, and all such tests were done by one of us. A system of scoring was designed so that each positive symptom or sign from a list was allotted one point, the maximum possible score being 15 points. The following symptoms and signs were contained in the list: pain in the legs, spontaneous paraesthesiae in arms or legs, loss of sensation in arms or legs, muscular weakness, sensory loss to pin prick in the legs only, sensory loss to pin prick in both arms and legs, loss of light touch sensation, loss of vibration sense at the ankle, at the iliac crest or at the wrist, calf tenderness, loss of deep reflexes, and muscular wasting. This system of scoring was used to differentiate the diabetic subjects into four groups. Subjects with a score 0 had no clinical evidence of peripheral neuropathy, those with scores of 1–5 had mild neuropathy, scores of 6–10 a moderate neuropathy, while those with scores of 11–15 had evidence of severe peripheral neuropathy.

In the control and diabetic subjects vascular occlusion was obtained by using an ordinary sphygmomanometer cuff placed on the upper arm with the lower border of the cuff 2 cm above the medial epicondyle of the elbow. In all cases the resting systolic blood pressure was measured, and vascular occlusion applied by rapid inflation of the cuff pressure to 60 mmHg above the resting systolic pressure. Ischaemia of the limb was maintained for 20 minutes, after which the cuff pressure was
released. All subjects were instructed at the beginning of the vascular occlusion to report the time of onset, site, nature, and time of cessation of any subjective sensations they experienced during the ischaemic and post-ischaemic periods. During the post-ischaemic period itself they were reminded at regular intervals of the need to report the details of any paraesthesiae they experienced, special attention being paid to the ‘pins and needles type’ of post-ischaemic paraesthesiae.

A quantitative assessment of the ‘pins and needles’ paraesthesiae was made by determining a post-ischaemic paraesthesia index (PIP) index. The index was numerically equal to the product of the duration of the ‘pins and needles’ paraesthesiae in minutes and the PIP score, which was determined by the severity of the paraesthesiae as experienced by the subject. This scoring was done on a 3 point scale. Score 0—no post-ischaemic ‘pins and needles’ paraesthesiae; score 1—mild pins and needles paraesthesiae confined to the fingers; score 2—severe paraesthesiae felt in the fingers and palm usually accompanied by other reactions of discomfort or distress—for example, grimaces or whistling.

**RESULTS**

Of the sensations that healthy subjects experience during the post-ischaemic period, the ‘pins and needles’ sensation is the component which is most easily recognized by the subject. Preliminary observations provided evidence that the times of onset and cessation of this variety of paraesthesia could be easily recognized by all subjects and that the results obtained on one occasion could be reproduced some days later when the other arm was tested. All healthy controls reported that thermal paraesthesiae occurred with great constancy, but though its time of onset was easily perceived, its duration could not be determined as the time of cessation of the thermal sensation could not be determined with any certainty. All healthy subjects also experienced some tingling, vibration, or ‘buzzing’ sensation immediately after the thermal paraesthesiae but neither the times of onset nor times of cessation of these sensations could be determined reliably. The sensation of post-ischaemic muscle cramp was experienced by only some of the healthy controls. The PIP index was therefore determined with respect to the duration and severity of the pricking, ‘pins and needles’ sensation alone.

The results expressed in Table I and Fig. 1 show that all healthy controls had uniformly high PIP indices and that there was no significant difference in the indices between the separate age groups. Comparison of the results obtained from the healthy controls with that of the diabetics shows a very highly significant difference of the PIP indices between the two groups.

**TABLE 1**

<table>
<thead>
<tr>
<th>POST ISCHAEMIC PARAESTHESIAE INDEX (PIP INDEX) IN CONTROL AND DIABETIC SUBJECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Healthy controls</td>
</tr>
<tr>
<td>Mean PIP index</td>
</tr>
<tr>
<td>Range of index</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Diabetic subjects</td>
</tr>
<tr>
<td>Mean PIP index</td>
</tr>
<tr>
<td>Range of index</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Significance of difference of PIP index between control and diabetic group</td>
</tr>
</tbody>
</table>

**FIG. 1.** Age distribution of PIP indices in control (blank bar) and diabetic (solid bar) subjects.
Post-ischaemic paraesthesiae in diabetes mellitus

In the diabetic patients the mean index was uniformly low in all age groups, there being no significant difference in the distribution of the index between the different age groups. Only one of the 50 diabetic subjects had a PIP index which was of normal magnitude. This was a 45 year old man who had a very mild diabetes of two years’ duration, and was being maintained in an adequate state of metabolic control by dietary restrictions alone.

When the severity of the metabolic state of the diabetics is determined in terms of the degree of dependence on insulin, the frequency histogram of Fig. 2 shows that the severity of the diabetic state seems to be a factor relating to the degree of diminution of the PIP index. Thus 65% of those with severe diabetes had an index of 0,

![FIG. 2. Effects of severity of the diabetic state on the percentage distribution of PIP indices in subjects with mild diabetes (blank bar), moderate (stippled bar), and severe diabetes (solid bar).](image)

while all the rest had indices of less than 10. In contrast, only 33·3% of the mild diabetics had indices of 0, 33% had indices of 1–5, 26·7% had indices of 6–10, while 6·7% of this group had indices over 10. These results indicate that even subjects with the mildest grade of diabetes had a mean PIP index which was significantly smaller than that of the healthy control group, while within the diabetic group itself, increasing severity of the diabetic state was associated with diminution of the PIP index.

Figure 3 shows that the duration of the diabetic state is another factor related to the diminution of the PIP index. Thus 80% of the

![FIG. 3. Effects of duration of diabetic state on percentage distribution of PIP indices in subjects with diabetes of less than five years duration (blank bar), 5 to 10 years (stippled bar), and over 10 years' duration (solid bar).](image)

![FIG. 4. Distribution of PIP indices in diabetic subjects with the juvenile onset type of disease (solid bar) and maturity onset type (blank bar).](image)
subjects who had been diabetic for over 10 years had no paraesthesiae, while the remaining 20% had indices of less than 10. In contrast, the subjects whose diabetes was of shorter duration had uniformly higher indices. Of those with diabetes of less than five years duration 45% had indices of 0, 47.5% had indices between 1–10, while 7.5% had indices over 10. Here, too, it is evident that even those with diabetes of very short duration had indices significantly smaller than those of the control group, while increasing duration of the diabetic state related to increasing diminution of the PIP index.

Figure 4 shows that the type of diabetic lesion, whether it was of the juvenile or maturity onset type, seemed to relate to the diminution of the PIP index: those with the juvenile type having significantly lower indices than the maturity onset types. A further comparison was therefore made between the subjects of these two groups, to determine whether this difference was in fact due to the nature of the diabetic lesion, since the earlier results have shown that the severity of the diabetic state and the duration of the disease are both factors which relate to the diminution of the PIP index.

The results expressed in Table 2 show that the diabetics of the juvenile onset type have consistently lower PIP indices than the maturity onset types when comparison is made between the two groups, whether in respect of the severity of the diabetes or the duration of the diabetic state.

The results of Table 3 show that there does not seem to be a consistent relationship between the severity of the peripheral neuropathy and the degree of diminution of the PIP index. Thus among the 25 subjects who had a complete absence of post-ischaemic paraesthesiae were five subjects who had no clinical evidence of neuropathy. Among the five diabetics who had the severest paraesthesiae and highest PIP indices were four who had evidence of mild to moderate degrees of peripheral neuropathy.

**DISCUSSION**

These results confirm the observations of Poole (1956a) that paraesthesiae can be elicited in healthy subjects with great constancy. In this study, an attempt has been made to obtain a quantitative assessment of the post-ischaemic paraesthesiae response by determining the duration and severity of the paraesthesiae. This post-ischaemic paraesthesiae index (PIP index) has been determined with reference to the ‘pins and needles’ component only, because this was the element which occurred with the greatest constancy in the healthy controls, and because it was the component whose duration could be assessed with some certainty. Even though this index is determined on the basis of a subjective assessment of the severity and duration of a sensory experience, it achieves a measure of reliability and validity in that the results obtained from an individual are reproducible, and because of the degree of uniformity which occurs within the control group. All control subjects had consistently high indices, while the duration of the paraesthesiae was in good agreement with the results obtained by Poole (1956a). The durations of the post-ischaemic paraesthesiae in the healthy subjects of this study were also in close accord.

**TABLE 2**

<table>
<thead>
<tr>
<th>Severity of diabetes</th>
<th>Juvenile onset type</th>
<th>Maturity onset type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects</td>
<td>Mean PIP index</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 5</td>
<td>14</td>
<td>1.0</td>
</tr>
<tr>
<td>5–10</td>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>Over 10</td>
<td>2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**TABLE 3**

<table>
<thead>
<tr>
<th>PIP index</th>
<th>Total no. of subjects</th>
<th>Percentage distribution of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No neuropathy</td>
<td>Mild neuropathy</td>
</tr>
<tr>
<td>0–5</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>1–5</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>6–10</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>Over 10</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>
with the duration of the phase of post-ischaemic hyperexcitability of the peripheral sensory fibres of the median nerve as determined by Seneviratne and Peiris (1968a).

The differences between the PIP indices of the control and diabetic group are very highly significant, only one of the 50 diabetic subjects having an index that lay within the range of normal values. The results also show that the degree of diminution of the PIP index seemed related to the duration of the diabetes and the severity of the metabolic state as determined by the degree of insulin dependence—increasing duration and severity of the disease being associated with greater lowering of the PIP index. The results also indicate that diabetics with the juvenile onset type of the disease are more adversely affected than those with the maturity onset type, this distinction persisting even when the two groups are made comparable with respect to the duration and severity of the disease. Increasing age is itself not a factor relating to the diminution of paraesthesiae in subjects who are between the ages of 15 and 60 years, nor is there any consistent relationship between the diminution of the PIP index and the presence of clinical evidence of peripheral neuropathy. The results show that diabetic subjects with neuropathy tend to have lower indices than those without it, but this is a relationship which could also be due to the association which is known to occur between the presence of neuropathy and the duration of the diabetic state.

This pattern of diminution of the paraesthetic response among diabetic subjects is of interest because it throws some light on the problems relating to the mechanisms which are responsible for the causation of post-ischaemic paraesthesiae in healthy subjects. Although there is, as yet, no consensus of opinion regarding these mechanisms, the available evidence (Merrington and Nathan, 1949; Nathan, 1958; Seneviratne and Peiris, 1968a) suggests that the ‘pins and needles’ sensation arises as a result of an increased excitability of low threshold sensory fibres of peripheral nerve which occurs during ischaemic and post-ischaemic periods. Seneviratne and Peiris (1969, 1970a,b) have suggested that nerve ischaemia leads to the efflux of K’ from the axon and that the accumulation of this K’ in a periaxonal space leads to the progressive depolarization of the axon which passes through a transient phase of ischaemic hyperexcitability before further depolarization results in conduction block. Restoration of the circulation leads to the rapid reabsorption of the K’ from the periaxonal space into the axon, and repolarization of the fibre which once again passes through a transient phase of post-ischaemic hyperexcitability before the repolarization is complete. This hypothesis postulates the existence of a periaxonal diffusion barrier which serves to hold the K’ efflux in close proximity to the axon membrane and to limit the rate at which it diffuses into the endoneurial spaces of the nerve trunk. Seneviratne and Peiris (1968b) have demonstrated that the absence of ischaemic and post-ischaemic paraesthesiae of diabetic subjects is due to the reduced rate of change of excitability of the peripheral nerve during the ischaemic and post-ischaemic periods, and suggest that this is the cause of its resistance to inactivation by ischaemia. Seneviratne and Peiris (1969, 1970a) attribute this abnormality of the diabetic nerve to an increase in the permeability of its periaxonal diffusion barrier to K’. In a recent paper, Seneviratne, Peiris, and Weerasuriya (1972) have cited evidence which suggests that the polyanionic mucopolysaccharide gap substance which surrounds the bare axon at the node of Ranvier serves as the periaxonal diffusion barrier. The increased permeability of the diffusion barrier may be due to a reduction in the quantity of this gap substance at the node, or to a qualitative change in the nature of the mucopolysaccharide matrix which results in a reduction in its capacity to bind K’ ions and hold them in close proximity to the axon at the node. Preliminary evidence (Seneviratne, 1972) indicates that such a reduction in the K’ binding property of the nodal gap substance can, in fact, be demonstrated in nerves of humans and alloxan diabetic rats. This suggests that the increased resistance of peripheral nerve to inactivation by ischaemia is due primarily to an alteration in the immediate ionic environment of the axon itself, rather than to an alteration in the energy metabolism of the axon which enables it to maintain its function under anaerobic conditions, and lends support to Simpson’s (1962) concept of an ionic micro-environment of the nerve fibre. Simpson drew attention to the fact...
that the micro-environment within the nerve sheath was an important factor in maintaining the normal function of nerve, that it was kept relatively constant in healthy nerves despite wide fluctuations in plasma constitution, and that changes in the ionic environment of the axon could be the ultimate cause of excitability changes.

The hypothesis that the resistance of nerve to ischaemic inactivation is determined by factors which alter the ionic environment of the nerve is supported by several lines of evidence. Absence of the paraesthetic response and resistance of the peripheral nerve to inactivation by ischaemia occurs not only in diabetes but in several other conditions which are not associated with a gross abnormality of carbohydrate metabolism. Poole (1956b) observed the absence or diminution of paraesthetic response in patients with megaloblastic anaemia, acute infective polyneuritis and bronchial carcinoma; Seneviratne and Peiris (1970b) demonstrated increased resistance of peripheral nerve to ischaemic inactivation in patients with chronic liver disease who had normal glucose tolerance curves; Christensen and Ørskov (1969) observed these features in patients with uraemia, while Shahni and Russell (1969) suggest that it occurs in patients with motor neurone disease. A second line of evidence derives from the fact that the degree of resistance can be changed by experimental alterations of the periaxonal K' ion concentration. Seneviratne, Peiris, and Weerasuriya (1972) have shown that an increase in the serum K' ion concentration produces a significant reduction of the ischaemic inactivation time of cat peripheral nerve. Insulin increases the resting intra-axonal K' ion concentration, and nerves from healthy animals pretreated with insulin show an increased rate of K' efflux when they are exposed to anoxic conditions, leading to a local increase of the periaxonal K' ion concentration. These nerves have inactivation times in anoxia which are considerably shorter than that of control nerves (Seneviratne and Peiris, 1970a). Steiness (1961) and Gregersen (1968) have demonstrated a normalization of the ischaemic vibration perception threshold in early diabetics during active insulin therapy, and the results of this study show that the degree of diminution of the paraesthetic response is related to the severity of the diabetic state as determined by the degree of insulin dependence. These relationships could be due to the role of insulin in determining the rate and amount of K' ion efflux from the axons during ischaemic conditions. The results of this study also indicate that diabetics with the juvenile onset type of the disease have consistently smaller paraesthesiae indices than diabetics with the maturity onset type of disease. This relationship, too, may be due to the greater sensitivity to insulin of the diabetic with the juvenile onset form of the disease.

Further evidence that the resistance of a nerve to ischaemia is determined by the ionic microenvironment of the axon is provided by the observations of Gregersen and Pilgaard (1971). They recognized that the serum calcium ion concentration was also a factor determining the resistance of nerve to ischaemia; hypercalcaemic states being associated with an increase in inactivation time. They noticed, however, that a six-hour calcium infusion into a normocalcaemic patient, raising the serum Ca" ion level from 9-6 to 13-8 mg/100 ml., was without effect in changing ischaemic vibration perception threshold in an old. Frankenhaeuser and Hodgkin (1957) have shown that the action of Ca" ions on the system controlling membrane Na-K permeability explains its effect on excitability; the nerve becoming more excitable in low Ca" ion concentrations because a smaller depolarization is now required to increase its Na' conductance to the critical level at which the inward Na' current exceeds the outward current carried by the K'. Using the isolated squid axon, Frankenhaeuser and Hodgkin (1957) showed that changing the external Ca" ion concentration produced immediate changes in the fibre threshold. The much longer time lag observed by Gregersen and Pilgaard (1971) may hence be a measure of the effectiveness of the buffer properties of the nodal gap substance of healthy myelinated nerve, which because of its polyanionic characteristics serves to maintain the constancy of an ionic microenvironment in the immediate vicinity of the node.

The evidence cited above suggests that the diminution of the paraesthetic response and the increased resistance of nerve to inactivation by ischaemia are due primarily to changes in the properties of the nodal gap substance which in
turn determines the changes in the ionic environment of the nerve. The pathogenesis and nature of this change are quite unknown. Although segmental demyelination of peripheral nerve is commonly associated with the increased resistance of nerve to ischaemia, the experimental observations of Seneviratne and Peiris (1968b) and Gregersen and Pilgaard (1971) show that increased resistance to ischaemia does not necessarily follow demyelination and, conversely, that nerves which exhibit no clinical or conventional electrophysiological evidence of dysfunction may exhibit increased resistance to inactivation by ischaemia. This view is supported by the results of this study which show no consistent relationship between the presence of neuropathy and diminution of the paraesthetic response.

REFERENCES


