evidence of persistent airways obstruction,[8] should now be regarded as an essential part of the assessment of children with asthma by general practitioners.

An association between allergy and childhood asthma has long been recognized, but, as McNicol and Williams point out in the second of their papers,[9] many features of asthma cannot be explained on the basis of type I (immediate) hypersensitivity. Though they found a higher incidence of hay fever, eczema, and positive reactions to skin tests in the children with asthma, no one feature unequivocally distinguished them from control children. For instance, 15% of control children gave positive reactions to skin tests, and it is probable that a still higher percentage would have done so if McNicol and Williams had included an extract of house-dust mite in the range of skin tests which they performed.[6] Similarly, they found it impossible to define a discriminatory value of serum IgE which was present in most asthmatic children and only rarely present in the controls. While their findings have not thrown any new light on the part which allergy plays in the pathogenesis of asthma, they suggest that bronchial hyperreactivity and allergy are independent factors. This would explain their observation that in some children there was no relationship between the clinical course of asthma and either the first appearance of or subsequent variation in some of their allergic manifestations.

The role of psychological factors in asthma is another aspect of the disease which has caused controversy. Some workers believe that a child's personality and his reactions to emotional stress are primary aetiological factors. Others consider that asthmatic children have a higher incidence of neurotic traits than normal children but are undecided whether these are the consequence or cause of asthma. As the Melbourne workers emphasize in their third paper,[10] one reason for these varying opinions is that often they have been based on studies of highly selected groups of asthmatic children whose clinical and physiological status was not properly defined. In this context the importance of classifying asthmatic children according to the grade of severity is clear from the Melbourne study. Its most important finding was that behavioural disturbances were uncommon in asthmatic children, and only in the group of the most severely affected children was their incidence significantly higher than in the controls. While these findings do not exclude the possibility that severe asthma is especially likely to occur in children of a specific personality type, a more reasonable interpretation might be that severe asthma itself is a potent cause of emotional disturbance in the child and in his family.

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Clues to Multiple Sclerosis

The search for clues to the aetiology of multiple sclerosis has already inspired many hypotheses. Among them is the possibility that heredity may play a part. Recently J. H. McIntyre, of Christchurch, New Zealand, has considered this question in a brief report.[1]

In the space of one year he himself has encountered four cases of multiple sclerosis (he prefers the older word "disseminated") in each of which he noted a well-established familial history. He rightly says that this may be a coincidence but poses the question whether this finding is suggestive of a familial tendency of a "sensitivity to some virus, possibly measles." On this problem at present speculation outweighs fact, but what is worth noting is that the risk of having the disease for a first-degree relative of a patient with multiple sclerosis is at least 15 times that for a member of the general population.[2]

But this increased incidence is not necessarily due simply to an inborn familial tendency to the disease any more than it is, say, in the case of leprosy. Certain other observed facts are worth considering. Firstly, the prevalence of multiple sclerosis is clearly related to latitude, being virtually zero in tropical areas, though there are certainly anomalies in the Japanese distribution. Secondly, there appears to be an interval of perhaps 10 to 15 years between a supposed exposure to infection and the appearance of neurological symptoms. Thirdly, as M. Haire and colleagues[3] have now shown, there seems to be a significant increase in the immunoglobulin G specific for measles (and to a lesser degree herpes simplex) in the cerebrospinal fluid of patients with multiple sclerosis. It is therefore tempting to use this combination of familial frequency, latitudinal prevalence, latent period, and measles immunoglobulin studies to support the hypothesis that in early life close-knit groups are subjected to environmental factors (including exposure to measles), and that they are subsequently influenced by other, as yet unknown, factors to develop clinical multiple sclerosis, which most authorities, including C. E. Lumsden,[4] consider can best be explained in terms of an antigen-antibody reaction.

It is now worth considering some new work which has come from the Medical Research Council's demyelinating disease unit in Newcastle-upon-Tyne. The sequence of events in the evolution of this work is worth summarizing here. R. L. Swank[5 6] has long urged the view that multiple sclerosis is related to the consumption of fats deficient in the unsaturated fatty acids. R. W. R. Baker and colleagues[7] showed that lecithin from the cerebral white matter of patients with multiple sclerosis contained more saturated fatty acids than did the white matter of control patients, and R. H. S. Thompson[8] noted changes in the serum lipid content of patients with multiple sclerosis. Following up these observations, J. H. D. Millar and colleagues[9] in a double blind trial reported a slight advantage to patients treated with linoleic acid, and from this J. Mertin and colleagues[10] put forward the view that supplements of linoleic acid might have an immunosuppressive effect on the development of multiple sclerosis. They report that both linoleic and arachidonic acid inhibited the macrophage electrophoretic mobility and that this inhibition was much higher for patients with multiple sclerosis than for controls. Their initial intention was to try to find laboratory support for the clinical observations of Millar and colleagues, but they then realized that they might use this inhibitory effect as a diagnostic test for the disease.[11] Their next step was to investigate the sera of families of patients with multiple sclerosis,[12] and in so doing they found that 41% of the relatives had the same macrophage anomaly, "though to a lesser degree." Other interesting findings are that sisters of the propositus more frequently gave anomalous results to this test than brothers and that in the group of patients they studied no patient was

found whose mother did not have the anomaly. On these findings it would seem that some familial factor does contribute to the production of multiple sclerosis and that it operates more strongly through females than through males.

Clearly further work is required in the development of this particular thesis, and it may be that these initial findings will prove to be less solid than they seem. Yet this demonstration of the possible familial and environmental implications is impressive.

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Control of Spasticity

To Mason Good (1764-1827) spasticity meant "want of pliancy of the muscle fibres."[1] Hughes Bennett (1848-1901) used the term "muscular hypertonicity" and was among the first to put forward the concept that "muscular hypertonicity is abolished when there is interruption of any portion of the reflex arc of which the muscle is the terminus."[2]

During the following years the terms muscle "tonus" and "hypertonicity" were used widely but so inconsistently that it was suggested that adjectives such as slack and taut were to be preferred for the description of the state of muscles as judged by passive movements of the limbs.[3] Accurate quantification of muscle tension under varying conditions requires far more sophisticated techniques.[4 5] Spasticity occurs, as Hughlings Jackson said, when having been "cut off from the higher centres the anterior horns in question are let go and gain autonomy."[6] Some ten years later Sherrington confirmed this concept experimentally, since he found that, by disconnecting the spinal cord from the cerebral hemispheres and basal ganglia, the tone of the extensor muscles of the animal becomes greatly increased.[7] Using such decerebrate preparations, Sherrington made observations of unrivalled importance on the control of muscle tone. They led him to conclude that muscle contains receptors which can reflexly excite muscular contraction.[8]

As cumbersome recording systems became more refined, it became possible to stimulate a single motor nerve fibre supplying the striate muscle fibres, which are the constituent elements of the muscle spindle. Study was also made of the resulting excitation in a single afferent nerve fibre from the self-same spindle.[9] This work helped to establish that there are specific motor nerve fibres to the muscle spindles, and that they are separate from the motor fibres to the ordinary muscle. Thus it can be said that motor neurones of two types are situated in the anterior horns of the spinal cord—namely, large nerve cells supplying the muscle, and small cells supplying the muscle fibres within the spindles. Since the fibres of these two types of motor neurones also differ correspondingly in size, the two motor neurone systems are distinguished by prefixes "alpha" and "gamma" in accordance with the classification of nerve fibres based on their diameters.[10]

One of the cardinal phenomena in the regulation of muscle tone is that firing of the gamma motor neurones sets up afferent impulses which impinge on and activate monosynaptically the alpha motor neurones serving the related musculature. Both types of motor neurones are excited and inhibited by various elements within the spinal cord as well as by projections from higher parts of the central nervous system. It must be recalled that a single alpha motor neurone may have as many as tens of thousands of synaptic knobs on its surface.[11] At any given moment it is therefore exposed to a vast number of converging impulses. Thus the development of spasticity depends partly on an excess of excitatory factors and partly on the deficit of inhibitory factors.

Broadly, two types of spasticity can be recognized under experimental conditions, due to the hyperactivity of either the alpha or gamma motor neurones. Spasticity due to the latter cause can be temporarily abolished by the injection of dilute procaine near a motor nerve, since the gamma motor fibres by virtue of their small size are particularly susceptible to the action of local anaesthetics.[12] Spasticity can be altered by various other manoeuvres. Spindle activity can be depressed by local cooling of the muscle or enhanced by vibration of the muscle.[13 14]

Alcohol has been found to depress motor neurones of the spinal cord. It does so by enhancing the activity of the Renshaw cells, which silence the alpha cells.[15] The first attempt to control spasticity was by surgical means and consisted in section of the posterior spinal nerve roots.[16 17] This treatment was revived recently in modified forms.[18 19] With the isolation in 1935 of the principal active constituent of curare, this and various other neuromuscular blocking agents were tried for the relief of spasticity, but as they also impair voluntary movements they were found to be unsuitable. Mephenesin, an interneuronal blocking agent, was found to relieve spasticity without causing paralysis. But its therapeutic application is limited by the large doses required when it is taken by mouth.[20] Later, chlordiazepoxide and diazepam, also suppressors of polysynaptic reflexes, were found to have some favourable effect on spasticity.

The origin of baclofen, the latest drug introduced for the control of spasticity, can be traced to serendipity. Much of our present knowledge of stretch reflexes has been gained from the study of stretch receptors found in crustacean abdominal segments. As long as a constant stretch is maintained, the single sensory neurone from the crustacean receptor discharges with remarkable regularity. Ernest Florey found that the generation of these impulses could be inhibited by extracts of mammalian brain.[21] With his team he later identified the relevant active principle of the brain extracts as gamma aminobutyric acid (GABA).[22] By means of microelectrode technique it was later shown that GABA also has an inhibiting action on mammalian cortical and cerebellar neurones.[23] GABA may indeed be an inhibitory synaptic transmitter, and Florey's prediction that GABA may prove "to play an important part in the control of neurophysiological activity" has in many ways been confirmed.[22 24] Attempts to increase the inhibitory functions of the central nervous system by the administration of GABA, either parenterally or orally, have proved unsuccessful. J. W. Faigle and H. Keberle[25] attributed this lack of response to the fact that GABA is a strongly hydrophilic substance, which therefore cannot penetrate the lipophilic