in the stomach cause the final failure in the secretion of intrinsic factor.[7] The gastric atrophy is probably the result of excessive exfoliation[8] and is reversible, since treatment with corticosteroids can induce regeneration of mucosal cells with a return of secretory function.[9 10] The situation is perhaps analogous to that in autoimmune haemolytic anaemia.

Why does the absorption of vitamin B_{12} require the mediation of intrinsic factor? And how is vitamin B_{12} transported from the lumen of the gut into the cells of the terminal ileum and thence into the blood stream for distribution to the tissues? This apparently complex mechanism remains one of Nature's mysteries. The vitamin B_{12} released from food during digestion becomes bound to intrinsic factor (a glycoprotein secreted by the parietal cells of the stomach), and the intrinsic-factor-B_{12} complex is carried to the ileum by peristalsis. There it attaches to specific receptors on the brush border of the lining epithelial cells.[11] The complex is thought to fit into the ileal cell receptors by molecular complementarity as a key fits into a lock, but the exact nature of the receptor is unknown. The present evidence[11] suggests that vitamin B_{12} becomes detached from intrinsic factor when it passes into the ileal cell, but little is known about its pathway through the ileal cell and into the subepithelial capillaries of the portal system. In the blood vitamin B_{12} becomes bound to a specific carrier protein, transcobalamin II, an α-1 globulin.

How does vitamin B_{12} function in the body? Though cyanocobalamin and hydroxocobalamin are therapeutically effective forms of vitamin B_{12}, they do not function as such in the body. Like the vitamin B_{12} derived from food, they must be converted intracellularly into metabolically active forms that function as co-enzymes. Two co-enzyme forms are recognized—namely, methyl-B_{12} and 5′-adenosyl-B_{12}. And through its co-enzyme forms vitamin B_{12} has widespread biochemical ramifications.[12-15] In vitamin B_{12} deficiency methyl-malonic acid accumulates and is excreted in increased amounts. The measurement of urinary methyl-malonic acid after a valine load appears to be a good test for deficiency of this vitamin.[16]

The molecular biology of vitamin B_{12} is gradually revealing itself, though for man much is still unknown.[12] We are particularly ignorant about the way in which deficiency of vitamin B_{12} produces neurological lesions and how it affects the metabolism of nerve and brain tissue. Its role in haemopoietic cells, as well as in other proliferating cell systems, such as epithelium, is only beginning to be understood. We need to define more precisely the biochemical basis underlying megaloblastic haemopoiesis.

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Restless Legs

Patients who suffer from "restless legs" have been known to physicians for centuries, but the clinical syndrome was most clearly defined by K. A. Ekbom in 1944[1] and reviewed in greater detail in 1960.[2] Recognition is easy if the physician knows of its existence. Though it is not uncommon, its causation remains obscure. Ekbom[2] found that 5% of normal people suffered the symptoms to some degree. Though often stated to be commoner in women than men and in older than younger people, they are familiar to schoolboys and students and may affect both sexes and all age groups.

The essential feature of the condition is an intolerable creeping, internal itching, sensation, often defying description, occurring in the calves and lower legs, sometimes in the thighs, usually bilaterally, and developing towards the end of the day when the patient is either seated or—and particularly—in bed. So unpleasant is this sensation that the patient is compelled to keep moving his limbs, and this movement will bring relief. But many have to get out of bed and walk round or wave their legs on the edge of the bed, perhaps several times during the night, so that loss of sleep is a serious consequence to both the patient and his spouse. This disorder must not be confused with nocturnal myoclonus, when without previous discomfort a patient's limbs jerk violently just as he is dropping off to sleep.

Some patients cannot remain seated for any length of time. Others find that the symptoms are made particularly severe by long car, sea, or plane journeys, especially if motion sickness remedies such as the cyclazine group have been taken. It is the extreme unpleasantness of the symptoms, coupled with immobility and relief by movement, that characterizes the condition.

Theories of aetiology have been many and varied, ranging from disorders of the peripheral nerves, through vascular causes, to hysteria.[2] These patients are neurologically and electromyographically normal, and D. G. F. Harriman, D. Taverner, and A. L. Woolf found no abnormality after in-vivo staining of the intramuscular terminal nerve endings.[3] The association of symptoms with warmth, rest after exercise, or vibration and their relief by muscular movement suggest some vasomotor factor, and indeed some patients say they get relief from vasodilators, hot baths, or (paradoxically) cold sponging. Ekbom[2] recorded a greater than normal incidence after gastrectomy, and it is reported again at page 774 of the *B.M.J.* this week by Drs. N. K. Banerji and L. J. Hurwitz, who draw attention as well to an association with diabetes and uraemia. Also in this issue (page 796) Dr. J. D. Spillane records eight consecutive cases of patients who all suffered

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chronic pulmonary disease, but then gives reasons for preferring to consider this a "nervous manifestation of their invalidism" rather than a metabolic consequence of respiratory failure. Yet most patients with this disorder show no signs either of systemic disease or of psychoneurosis, though they soon become obsessed with the severity of their symptoms.

In view of the many different conditions with which Ekbom's syndrome has been associated,[2 4] and our ignorance of its cause or causes, it would be reasonable to classify it as a functional disorder of nervous or vascular supply to the lower limbs, provided the term is used in its true sense of a disturbance of function rather than of structure and not interpreted to mean a psychoneurosis. Certainly diazepam, which helps many patients with disorders of vasomotor and muscular behaviour such as tension headaches, often also provides relief in this distressing syndrome,[5] and perhaps those who favour a vascular cause should pay more attention to the venous than the arterial side. Its association with relaxation[6] and its common development during the latter stages of pregnancy[7] may in this respect be relevant.

M.R.C. and the squeeze

Publicly and privately supported medical research in Britain consumed about £60m. in the year 1968-9. The universities provided about a third of this and the Medical Research Council financed about a quarter.[1] The Chancellor of the Exchequer in his October mini-budget told Parliament that the grants to Government research councils were to be cut.[2] What effect, then, will this have on the Medical Research Council?

In the year ended March 1970 the Parliamentary grants-in-aid to the M.R.C. were around £17·5m. To this sum were added contributions from Government departments and other sources making an overall income for the M.R.C. of £19·1m.[3] Total direct expenditure on such things as administration, the National Institute for Medical Research, the Clinical Research Centre, and other research units was almost £14m. Indirect expenditure amounted to £5·2m., and it is this area which is probably the most vulnerable in time of squeeze. For much of the direct expenditure, committed as it is to current spending on staff salaries and building maintenance, cannot easily be cut, at least not in the short term. As most indirect expenditure goes to support individual doctors and scientists working in universities and hospitals, they may understandably be worried about the future of their research projects. Past periods of Government financial stringency appear to have been associated with a drop in the numbers of applicants for grants. If this expression of anxiety about future prospects is more than a chance coincidence it is not generally justified by events, because the publicity surrounding Government cuts usually exceeds the magnitude of any real cut in resources available for research. Certainly the M.R.C. welcomes applicants for grants despite financial stringency, for the strength of its programme for indirectly supported research depends on a good supply of applicants.

The research carried out at the M.R.C's own centres and units broadly covers the main lines of medical advance, and its overall control lies with the council.[3 4] A useful feature of its indirect grants, which are of limited duration, is that the M.R.C. can pick original or promising developments it considers justify support but which have not reached a stage of meriting long-term funds or a special unit. Cuts in these grants could have a serious effect on research.

Fortunately it seems that despite the Government's much-publicized economies the M.R.C. will have more money (expressed in 1970 prices) for the academic year which started on 1 October 1970 than in the previous year. The amount budgeted for 1970-1 is about £22·4m., and will allow awards on short-term projects (three-year grants) to rise to £3·3m. from £3·09m. in 1969-70. £1·7m. is to be devoted to longer-term projects (five years) as compared with £1·42m. previously. From 1965 to 1970 the amount of money devoted to short-term research grants has gone up by about a half, and money for training awards has been doubled, as has that for long-term grants. In the same period the Council's total expenditure rose from £11m. to about £19m.[3] This is a good growth rate, and at constant prices the grant-in-aid has increased by 49·5%, a higher rate of real growth than either the N.H.S. at about 20·5% or the national economy. Despite the cost of the recently opened Clinical Research Centre, some of which has been met from special funds, the proportions of income allocated to the council's various activities have changed little in the past five years.

Medical research is a specialized and in some respects a small world, where mutual confidence counts for much and rumours of economies can rapidly undermine it. Fortunately there now seems little likelihood of Mr. Barber's mini-budget having any damaging effect on Government-financed medical research. This news should relieve most of the anxieties felt by doctors whose research work is currently supported by the M.R.C., and doctors who were thinking of applying for assistance should not be deterred from doing so.

The Jet Set

The advent of the jet airliner has made it possible to leave Europe in the morning, fly for nine hours, and arrive in the heart of the U.S.A. on the afternoon of the same day, there to be welcomed and later taken out to dinner at a time when people at home are having the morning milk delivered. Eventually the traveller gets to bed, but by now it is his normal breakfast time so he sleeps only a few hours and then rises, perhaps working till the dawn. Feeling out of sorts, he may meet many new faces and be required to make important new decisions. Under these conditions the business man is more likely to make an unwise choice, a statesman a gaffe, and an airline pilot an error.

We have internal clocks that govern near-24-hour (or circadian) rhythms of a large number of bodily functions. Our body temperature, for example, falls in the hours before breakfast and rises sharply till 10.00 a.m., and then remains high till 10.00 p.m. before declining again.[1] Our efficiency on tasks requiring sustained attention, judgement, and intellectual effort follows a similar 24-hour curve. When suddenly we are transported to a different clock-time, or when starting on

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