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Interferon options

The recent accident in which a research worker at Porton became infected with a strain of Marburg virus has focused attention upon the options available for emergency treatment in such cases. Laboratory investigators or hospital staff known or thought to have been in contact with an exotic virus, particularly a highly infectious one known to have a high mortality and no established means of prophylaxis, usually receive immediate treatment with homologous antiserum or separated immunoglobulin, if available. In addition human interferon may be given. In both cases intensive care is maintained under conditions of strict containment.[1]

The Porton worker received human interferon and later homologous immune serum within 48 hours of a rise in his temperature on the fifth day after infection.[2] The human interferon was given twice daily for 14 days in doses of 3 million units—a total dose of over 80 million units. There was a dramatic fall of viraemia from 10^4 infective units/ml to about 10 units/ml during the first 24 hours of treatment.[3] Thereafter the illness abated: nausea and vomiting declined on the 12th day and there was no bleeding from mucosal surfaces. Whether the interferon (supplied by Professor K Cantell[4] and produced in peripheral blood leucocytes stimulated in vitro with Sendai virus) contributed in any way to this favourable outcome is impossible to say.

Interferon was discovered by Isaacs and Lindenmann[5] in 1956 as a result of the treatment of fragments of chick chorioallantoic membranes with influenza virus inactivated at 56°C for 1 hour. After incubation for a day at 37°C the cell-free supernatant fluid contained a substance that inhibited the growth of influenza virus in fresh membrane fragments. The virus-interfering substance, in this case chick-interferon, is a complex of interferons that differ in charge and molecular weight. The heterogeneous interferons[6 7] induced by viruses in mouse, chick, or human cells have molecular weights of 18 000-25 000 in the monomeric form and up to 40 000 or more in dimeric or heavier forms. Generally the interferons are antigenic proteins with essential disulphide bonds, stable at 56°C for 1 hour and at pH 2 for 24 hours at 4°C, trypsin sensitive, and nuclease resistant. They are members of the larger group of effector molecules (lymphokines[8]) which are released from specialised cells after stimulation by foreign antigens. These effector molecules subsequently act in vivo in the regulation of cellular processes and as a component of host defence against foreign antigens. There is, then, an intimate (but at present obscure) relationship between the activities of interferon and the immune response, a factor that should not be overlooked in emergency treatments with massive doses.

Unlike neutralising antibody, which acts directly on virus in the absence of cells, interferon acts to block virus replication in the cell.[6] The action is specific to the host and not to the stimulating antigen: so that a particular interferon may be stimulated by and active against a wide range of viruses, rickettsiae, protozoa, and bacteria. This non-specific interference is the basis of its possible role as a therapeutic agent, and of the usual assay method, expressed in terms of the sample dilution that will inhibit by half the in vitro infectivity of a standardised test virus.

The stage in virus replication that determines the formation of interferon, at least for RNA viruses, appears to be the synthesis of a double-stranded replicative form of RNA. This then reacts with the host cell genome to derepress the gene that controls interferon synthesis. Double-stranded polynucleotides of fungal or synthetic origin[9 10] may be effective inducers of interferon, as also may be non-infective viruses if they initiate limited RNA synthesis through retained activity of their RNA-directed RNA-polymerases. The mechanism of induction of interferon by DNA viruses is less well understood.

The direct local application of a significant dose of interferon within a day of infection or first clinical signs may control conditions such as virus conjunctivitis, herpetic lesions of the lips, or rhinovirus infection[11] of the nasal epithelium. Human leucocyte interferon depresses the level of virus antigens in the serum of patients with chronic active hepatitis so long as the treatment is maintained.[12] Such observations in man and animals[13 14] suggest that interferon acts at accessible sites to block an initial infection or reduce the infecting dose but is much less effective in controlling the outcome of an infection once this is established or generalised.[15] In emergencies, therefore, interferon should be applied very early and, if possible, at the site of infection: if application is delayed then even massive doses may fail to control the proliferation of virus at inaccessible sites. Clearly a strategy[15] is needed for using the very limited and expensive supplies of purified human interferon, which can be given either as single massive early doses or as many delayed and smaller doses. For infections by immunomodifying viruses, an advantage of the earliest application of interferon may be that if virus replication can be blocked before immune stimulation occurs then the worst immunopathological consequences of long-term virus excretion and the failure to clear virus-antibody complexes may be avoided.

Interferon inducers[7 9] offer a possible future option to the use of interferon itself. These have been administered as an alternative to interferon in several virus-animal systems,[10 12] and the results have tended to confirm the limitations of time of treatment and inaccessibility of site. Unfortunately the toxicity of synthetic interferon inducers may be closely associated with their antivirus activity. A further future option may be the use of an established live-attenuated virus vaccine as an interferon inducer. Such active non-specific interference by a sufficiently rapidly replicating vaccine may provide high interferon activities at the right place and at the right time.

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Primary dysmenorrhoea

Between 5 and 10% of girls in their late teens or early twenties are severely incapacitated by dysmenorrhoea for several hours each month.[1] Time is lost from school and work, and the financial loss to employers must be substantial. For some of those afflicted reassurance and a mild analgesic may make life bearable, but many others demand more from their family doctors and gynaecologists. Powerful analgesics tend to be habit-forming and are best avoided. In true, primary dysmenorrhoea suppressing ovulation by one of the oestrogen-progestogen oral contraceptive pills is likely to give relief. Even so, not all women are happy to have this treatment, and some find the side effects too troublesome to continue. Cervical dilatation has long been accepted as a reasonable minor surgical procedure where there has been no relief from medical treatment. Slow dilatation of the fibromuscular tissue at the level of the internal os is said,[2] in properly selected cases, to cure 60% of cases and help another 20%. There is, however, always the risk of cervical damage and recurrent abortion in later life.[2] Presacral neurectomy did have a vogue at one time once all simpler procedures had failed, but it has now become unfashionable.

Åkerlund *et al*[3] have recently reported on myometrial activity and uterine blood flow in 11 women aged 19 to 33 who were so disabled by primary dysmenorrhoea that they were off work from one to three days each month. All had intrauterine pressures between 200 and 350 mm Hg during uterine contractions, and these high pressures were associated with a decrease in local uterine blood flow. Whatever the cause of this uterine hyperactivity (and the authors believe that excessive prostaglandin synthesis is a possibility), treatment with the selective β_2-receptor stimulator terbutaline gave considerable relief to all their patients. Within minutes of the injection or infusion of 100 μg of terbutaline uterine contractions were either totally inhibited or their frequency and amplitude notably reduced, with well-defined periods of relaxation between contractions. At the same time local uterine blood flow increased significantly. The effect of the terbutaline lasted between one and two hours; the pain then gradually returned. Five patients had continuous recordings made from this point onwards, and both the myometrial contractions and the associated variations in local uterine blood flow were found to revert to their original pattern. Unfortunately the treatment induced distressing side effects: an increase in the heart rate, palpitations, tremors, and flushes. In a pilot study of giving the drug by mouth several patients stopped treatment because of these side effects, especially tremors.

From their own studies and from a careful review of published work Halbert *et al*[4] concluded that prostaglandin concentrations were raised in some but not all patients with primary dysmenorrhoea. They believed that excess production of prostaglandin was likely to be only part of the problem; in some patients the myometrium might be unduly sensitive to certain prostaglandins. In the belief that primary dysmenorrhoea and associated gastrointestinal symptoms were caused by excessive amounts of prostaglandin arising from the breakdown of premenstrual endometrium Schwartz *et al*[5] treated patients with flufenamic acid, an inhibitor of prostaglandin synthesis. Sixteen women with typical, severe primary dysmenorrhoea (in whom treatment with other analgesic, spasmolytic, and tranquillising drugs and with placebos had been ineffective) were given 125 mg of the drug three times daily. The drug gave symptomatic relief in all 16 cases.

These results do suggest that excessive prostaglandin formation may play a key part in primary dysmenorrhoea. Nevertheless, the authors wisely advise that the wider use of flufenamic acid for dysmenorrhoea should await the results of more extensive laboratory tests for toxicity and teratogenicity.

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Inside the nucleus pulposus

When we stand upright over half our body weight lies above the lower lumbar and lumbo-sacral joints. The intervertebral discs may carry a load of perhaps 40 kg on an area of rather less than 20 cm^2. Muscle tone adds to the load—which, furthermore, is normally concentrated on the central nucleus pulposus. The pneumatic effect of the abdominal cavity (large but low pressure) may reduce the load on the disc,[1] particularly when lifting or straining, but even so direct measurements have shown pressures of 5 to 15 kg/cm^2 (70 to 217 lb/in^2) in normal disc nuclei of the lower lumbar spine.[2] The pressures are least when reclining, higher when standing, and higher still when sitting. The nucleus pulposus can withstand these high pressures and yet provide a flexible fulcrum for intervertebral motion because of its unique composition.

The nucleus is a three-dimensional lattice gel, a network of collagen fibrils in a matrix of mucopolysaccharide. There are a few scattered cells resembling chondrocytes. The very high pressures preclude any vascular supply—and perhaps also explain why the nucleus contains no nerves or nerve endings. In health its semifluid consistency confers an "isotropic incompressibility," a capacity to transmit compressive forces evenly in all directions, including peripherally to the elastic constraint of the annulus fibrosus. The nucleus pulposus is mostly water, and this water is retained not by osmosis or by a rigid casing (discs may be punctured with relative impunity) but by the physicochemical properties of the colloid gel—namely, the affinity of the protein-polysaccharide complexes for tissue fluid.[3] When less than fully hydrated the gel will absorb water even from hypertonic solutions or against strong mechanical pressure until it is fully saturated.[4]

Age brings chemical changes in the nucleus, and these affect its mechanical properties.[5] After childhood the nucleus is no longer sharply demarcated from the annulus fibrosus. The collagen fibres of the nucleus become macroscopically coarser and merge gradually with those of the annulus.[6] The proportion of collagen in the dry weight slowly increases, and the collagen fibrils themselves age and on *x*-ray crystallography show increased orientation and crystallisation.[7] The proportion of mucopolysaccharide decreases, and with age it changes its chemical nature,[8] the ratio of keratan sulphate to chondroitin sulphate becoming increased. The proteoglycans become of smaller molecular size and form fewer aggregates with

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