Laboratory studies in drug-induced pancytopenia

Pancytopenia sometimes—and quite unexpectedly—results from treatment with a commonly used drug thought to be "safe." When a single drug has been used and the blood picture returns to normal on its withdrawal there can be little doubt about the association. Identifying the causative agent is much more difficult when several drugs have been given, even when a complete drug history is available.

The ideal solution would be some means of determining increased susceptibility to a drug in individual patients or of predicting acquired sensitivity to a particular agent. Studies of the response to drugs of colonies of haemopoietic precursor cells in vitro provide, at first sight, such a system. Each colony is the result of proliferation by a single precursor cell, and dose-response curves for one or more drugs can be produced by adding different concentrations of drug to replicate culture dishes. The number of colonies surviving each treatment gives an estimate of drug toxicity.

The possibility of making such studies depends on several factors. Among these are the mechanism by which the drug produces pancytopenia and the biological basis for the unexpected response. Benestad has recently distinguished between conditional (or idiosyncratic) responses and immunological effects. Conditional effects are probably due to abnormal target cells or drug metabolism and are present before, during, and after administration of the drug. Immunological "sensitisation" to a particular drug is seen only after more than one dose has been given; though the predisposition may be present before treatment it cannot be detected experimentally. Unfortunately, patients with pancytopenia rarely have sufficient colony-forming cells in their bone marrow to provide material for drug dose-response curves to be studied in the laboratory. Any measurement of the sensitivity of the patient's own bone marrow cells must therefore await recovery and regeneration of the colony-forming cells.

A circulating factor has recently been detected in sensitised patients which, in the presence of the causative agent, inhibits the growth of bone marrow colonies. This factor can be collected in serum and stored until colony-forming cells have recovered enough to provide the target cells for the experiment—or alternatively normal marrow can be used. The underlying mechanism is the development of a drug-dependent antibody that acts against haemopoietic precursor cells. This phenomenon has now been described in association with several drugs. Drug-dependent inhibition of granulocytic and erythroid colony-forming cells has been found in a patient with pancytopenia associated with quinidine. The inhibitory effect was seen only when the target cells were exposed to the patient's serum and quinidine together. A similar suppression of normal growth of bone marrow colonies has been seen in a patient with agranulocytosis induced by amidopyrine, and drug-dependent depression of granulopoiesis in culture has been induced by a serum factor from patients treated with diphenylhydantoin.

Attempts have also been made to detect genetically determined hypersensitivity to the action of certain drugs. Where possible the patient's own marrow is used to provide the target cells; but, again, the colony-forming ability of the marrow will be low during the pancytopenia. Marrow from relatives, however, may provide a valid alternative source of target cells. Some such studies have shown positive results. Bone marrow cells from a patient who had recovered from agranulocytosis induced by quinidine showed a greater-than-normal sensitivity to the drug in vitro. Other studies, however, showed no change in sensitivity to drugs in pancytopenic patients. Patients who had recovered from gold-induced neutropenia have been found not to differ from the normal population in their sensitivities to sodium aurothiomalate.

Aplastic anaemia is a rare and devastating form of pancytopenia that may be due to a drug or toxin, but it differs from other drug-induced pancytopenias in several respects. The patient has often had the drug weeks or months before the onset of clinical symptoms, and does not recover when the drug is withdrawn. Laboratory studies of drug-induced aplastic anaemias have, in general, been disappointing. These patients have very few colony-forming cells in their bone marrow and even after recovery the number of such cells remains low. Nevertheless, Ratzen et al were able to study the effects of chloramphenicol on colony formation in a random selection of patients and found a 60-90% inhibition of growth at therapeutic doses; but these were probably the dose-dependent, reversible effects on the marrow known to occur with chloramphenicol rather than the irreversible lesion that leads to aplastic anaemia.

Howell et al tested the sensitivities of colony-forming cells from two patients who had recovered from aplasia induced by chloramphenicol. They found that as the marrows recovered the cells were less sensitive than normal, suggesting that a resistant population had survived exposure to the drug. These data conflict with results obtained with other experimental systems; for example, Yunis showed that marrow from patients who had recovered from aplastic anaemia was more sensitive than control marrow. Evidence for a genetic susceptibility to aplastic anaemia has been provided from other sources, such as reports of aplastic anaemia induced by chloramphenicol in identical twins and among members of a family and of the same biochemical defect in two patients with aplastic anaemia and in their fathers.

In assessing the success or failure of laboratory studies in characterising agents responsible for aplastic anaemia we must take into account the many factors that may play a part in its development. Some of these are unlikely to be detected by tests designed to investigate cell sensitivity: one such example is the impairment of drug metabolism or excretion found in patients who had recovered from hypoplasia induced by phenylbutazone. As yet, laboratory studies on hypocellular marrows have yielded only limited data on the sensitivities of colony-forming cells in drug-induced pancytopenias and least of all in aplastic anaemia. We may, however, be able to extrapolate from the results of studies in the less severe pancytopenias to the mechanisms responsible for certain cases of aplastic anaemia.

Volkmann's ischaemic contracture

Paralysis and contracture of muscles of an injured limb were first described in 1881 by Volkmann, who blamed interruption of the blood supply by tight bandages. Though studies by Littlewood and Murphy suggested that a rise in pressure in the tissues beneath the fascia was responsible for the vascular embarrassment—Murphy even suggested fasciectomy for its treatment—surgeons were distracted by their experience of arterial spasm in vascular injuries in the first world war. The spasm was thought to be due to a nervous reflex conducted by the sympathetic system. In 1940 Lloyd Griffiths said that Volkmann's ischaemic contracture was due solely to arterial injury with reflex spasm of the collateral vessels. This is still taught to medical students, even though arterial spasm cannot be produced by sympathetic stimulation, directly or reflexly, or relieved by interrupting the sympathetic action.

Volkmann's contracture is simply a consequence of the swelling of soft tissues in an unyielding osteofascial compartment. It may result from injury to the artery proximal to the compartment or from direct insult to the compartment itself. The condition is seen most often as a complication of supracondylar fractures, but it may occur in many other fractures in the arm or leg. Volkmann's contracture represents a middle course in the response to trauma—the mildest course resulting in complete recovery, the most severe giving gangrene and possibly the full-blown features of the crush syndrome.

The artery may be damaged either at the moment of injury or in the subsequent manipulations of the fracture. A minute intimal tear is enough for clotting to occur in the main vessel and also in the collateral vessels near by. In such cases the treatment is to remove the clot, excise the damaged segment, and restore the continuity of the artery. Holden believes that simply stretching the vessel without an intimal tear can also induce ischaemia. Apparently if the intra-arterial pressure is reduced the vessel may collapse because of the unopposed tension in the vessel wall. This critical closure may be diagnosed by exploring the vessel and overcome by injecting a bolus of fluid through the narrow segment. Whatever the mechanism, however, successful treatment will clearly depend on recognising the syndrome quickly and referring the patient promptly to a vascular surgeon.

Volkmann's contracture affects muscles that lie within confined osteofascial compartments: the anterior tibial, the peroneal, and the deep posterior compartments of the leg and the flexor and extensor compartments of the forearm. The capillary walls are damaged by ischaemia and by allowing fluids and coloids to escape into the tissues, with subsequent increase in their volume. The greater the damage the more the tissues swell, in turn causing more ischaemic damage. The treatment is generous fasciectomy to allow the tissues to swell without the dangerous rise of pressure.

Mubarak and Carroll recently reported no decline in 21 years in the frequency of Volkmann's ischaemic contracture in the Hospital for Sick Children, Toronto, despite the attention given to the problem. The condition is relatively uncommon, but it should always be kept in mind in any patient with an injured limb. The signs and symptoms are variable and unreliable. Pain is the most common feature; not relieved by rest, it becomes progressively more severe and is made worse by passive stretching of the ischaemic muscles. Unfortunately, however, pain is sometimes absent altogether. Once the diagnosis is suspected the doctor should look for abnormal physical signs. Nerve tissue is the most sensitive to ischaemia, and a careful examination of those nerves passing through the area under suspicion may give an early diagnostic indication. Abnormalities of the peripheral pulses and skin colour are less reliable signs, but both should be examined. The intracompartmental pressures can be measured by the wick catheter technique, but these are not usually available to surgeons; thus clinical judgment remains the most important factor in assessing and preventing the disorder.

Young doctors working in accident and emergency departments are the most likely to see patients with this condition, and they need to be reminded of the possibility of complications. They should seek help at once if they are suspicious, for any reduction in the numbers of patients suffering from Volkmann's ischaemic contracture must come from the vigilance and training of these doctors. No patient should have pain from a limb in plaster. If he has, he must be seen quickly and his limb carefully examined, if necessary with the plaster removed. The price of failure is high: a ruined limb for which surgery can offer only limited improvement.

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2 Murphy JB. Myositis. JAMA 1914;63:1249-55.