INFUSION IN INFARCTION

ormance in the presence of anciosa and others (March roblem in relation to the nacological antagonists—a n encountered in another that general vasodilatation beneficial effects of nitro- showed that adenylic acid ic heart, and we showed [3] pounds in heart and liver aminating enzymes at the se has subsequently been in,[4,5] and many active en- Among 9 patients with whom adenyl inactivating l, and the 7 with enzyme ed. Nitroprusside, as we ts these enzymes; but the rmance outlined by Dr. ot easy to explain. Libera- sthesia [6] and pneumonia [7] or symptoms. Adenosine itroprusside; and if nitro- as adenosine bradycardia hough in Dr. Franciosa's ificantly lowered. Maybe hetic stimulation following rt cannot increase its rate hocked state. The sympa- rs in failure) is associated with a more powerful systole from the concomitant coronary dilatation of the nitroprusside.

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CLINICS FOR THE TREATMENT OF EPILEPSY AND CONVULSIONS

SIR,—I read Dr. Jeavon's letter (April 22, p. 904) with some amazement. The need for special epilepsy clinics was discussed [8] at the 4th European Symposium on Epilepsy, held in Amsterdam in September, 1971. Among the participants there was a consensus that each country should endeavour to establish special centres for diagnosis, treatment, and rehabilitation of problem cases of epilepsy.

In the Netherlands, rapid evolution in the type of care offered at the special centres is reflected in the composition of the staff, which no longer consists solely of neurologists. At our Institute there are neurologists, psychiatrists, doctors of public health, education specialists both for children and adults, psychologists, and social workers, offering a multidisciplinary approach. This development is based partly on the findings of Smits,[9] who undertook a follow-up study of patients discharged from our Institute in the years 1961 and 1962.

Dr. Smits noticed that admission to this special centre led to definite improvement as far as freedom of seizures was concerned. Improvement in social flexibility and occupational progress, however, were much less evident. Our programme of treatment is now directed also at these aspects. I am convinced that such an approach can only be implemented successfully in a special clinic for the treatment of epilepsy and convulsions.

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ANTIBODIES AND INTRAVASCULAR CLOTTING IN LIVER CIRRHOSIS

SIR,—The markedly increased antibody titres for *Escherichia coli* observed by Professor Bjørneboe and his associates (Jan. 8, p. 58) and by Dr. Triger and his colleagues (Jan. 8, p. 60) in patients with liver cirrhosis suggests a relationship to other abnormalities. Fibrinogen-turnover rates, for instance, are significantly increased in these patients.[1-3] Tytgat [4] showed that the degree of abnormality in the fibrinogen survival relates roughly to the extent of liver involvement. The enhanced fibrinogen catabolism observed in these patients becomes normal or near-normal during treatment with heparin, suggesting that it results from a chronic disseminated intravascular coagulation.[3] In addition, patients with liver cirrhosis have increased fibrinolytic activity.[5,6] This is presumably due to decreased clearance of plasminogen activator by the diseased liver.[7]

Since there is at present no evidence that continuous intravascular coagulation constitutes a normal physiological event, or that fibrinogen consumption in a process of in-vivo coagulation is an essential pathway in fibrinogen catabolism, the source of the coagulant and plasminogen-activator activity remains to be determined. It may derive from the diseased liver, as suggested by Tytgat.[4] However, it may also originate in the intestine and escape clearance by a diseased liver as we previously proposed.[8] Animal studies provide evidence for its intestinal and microbial origin.

Rapid defibrination of blood and enhanced fibrinolytic activity are noted in the dog and rhesus monkey during the acute hepatic failure that follows total, one-stage hepatectomy.[8,9] Inhibition of fibrinolysis with E.A.C.A. fails to affect the defibrination.[8] Heparin, however, prevents it.[10,11]

In the absence of the liver the material responsible for the observed changes can hardly originate in the liver. Rutherford and Hardaway [11] noted that the defibrination observed during acute hepatic failure in the dog is absent in hepatectomised, enterectomised animals. We found that a limited enterectomy (leaving pancreas, duodenum, and stomach intact) preceding the hepatectomy also prevents the development of fibrinolysis.[12] These findings strongly suggest that an intestinal agent, rather than a pancreatic protease, is responsible for the observed changes. Presumably this agent is normally cleared by the liver but escapes unaltered in its absence. It is conceivable that also in chronic hepatic failure in man this same material is able

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to slip through the hepatic filter or bypass it altogether via portal-systemic shunts.

Interestingly, the onset of the defibrination in the anhepatic animal coincides with the development of gram-negative sepsis. Preoperative pretreatment of animals with oral neomycin profoundly alters the results of the blood-culture and delays the onset of septicæmia and of the defibrination syndrome.[13] Hence the possibility that the coagulative and fibrinolytic agent is an endotoxin deriving from gram-negative organisms present in the gut, which is known to exert coagulative and plasminogen-activator activity in vivo,[11 16] presents itself. So far, we have been unable to demonstrate in the laboratory the escape of endotoxins from the gastrointestinal tract under a variety of experimental conditions,[17] despite a great deal of evidence in the past to the contrary. The results of Professor Bjørneboe's and Dr. Triger's studies would suggest, however, that in patients with hepatic cirrhosis *E. coli* or their antigens escape from the intestine. Whether the antigens are endotoxins, and if so whether they are responsible for the defibrination syndrome observed in these patients, remains to be established.

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PROGNOSIS OF ASTHMA

SIR,—As one of the few in this country who have found a major interest in asthma and allergic complaints, and whose practice includes many children, I was delighted to see Dr. Galant's letter (Feb. 19, p. 437). This is because I feel very strongly that in Britain asthma is usually misunderstood, often undiagnosed, and often mistreated or neglected by those who deal with the young asthmatic in the vital formative years.

It is most notable that his references to long-term results of specific therapy with allergens are from America or Scandinavia, quoting 72% recovery by the age of 16, in contrast with 22% without specific therapy, and that there are no comparable studies from this country. This is because children in Britain seldom have the opportunity to benefit from this type of therapy, so that it is probable that most children with asthma here enter adult life disabled to a greater or lesser extent by asthma.

There are good reasons for the belief that this surmise is correct. For example, relatively few physicians in Britain are interested in clinical allergy. Only three consultant appointments exist in which an interest in allergy is included in the contract. Following his untimely death, a consultant physician who was one of the leading allergists in the Sheffield region was not replaced by another with similar interests. With little or no career structure, it is not surprising that our future physicians have no encouragement to become allergists. It might be said that allergy is a neglected art in Britain, and not to be taken seriously. This assertion is supported by the recent decision that the British Allergy Society should now be known as the British Society for Allergy and Clinical Immunology.

It is worth examining the reasons for this situation. Firstly, the usual therapeutic approach is suppressive, with little or no consideration of causation. Secondly, the practice of allergy has been notable in the past for lack of objectivity in results. Meaningless terms such as "marked", "moderate", or "slight" improvement are still used without precise definition in assessing results, objective measurement being the exception. Thirdly, lip service is paid to history-taking, the correct questions to ask seldom being known, and undue credulity is given to skin tests, especially intradermal tests, without objective demonstration of their significance or otherwise. I found [1] how fallacious skin reactions can be: only grass pollen, house dust, and house-dust mite extracts gave good correlation with objective nasal provocation tests.

Furthermore, it is still possible for a general practitioner to send his patient privately to a commercial establishment for skin-testing and the recommendation of a vaccine based mainly on the results. Such vaccines often contain so many allergens as to be more accurately described as "foreign protein cocktails", which lead to disillusioned doctors and disappointed patients. Even in hospitals such polyvalent vaccines are sometimes recommended. Even if some relevant allergens are in the mixture, the proportion will be insufficient to produce more than a placebo effect. In any case, allergens cannot yet be standardised, and in some instances I have shown allergenic extracts of one make to be quite incapable of provoking a nasal provocation reaction, while another caused an alarming and diagnostic result.

It should, therefore, be no surprise that the allergist is regarded with suspicion, while immunology, dealing with sera or animals rather than patients, but producing objective results, acquires, and rightly, the status of a scientific discipline. The gradual unravelling of the fundamental mechanisms which cause the manifestations of allergic disease in our patients is a fascinating story. Unfortunately, not only do recent discoveries have limited application to clinical practice at present, but also, even worse, very little research effort or money is being devoted to the *clinical* study of allergic disease, and to the training of those who could apply the further results of immunological research to actually treating patients.

Surely it would be better health economics to try to ensure that most of our asthmatic children recover by the age of 16 and are no longer a charge on the Social Services and the Health Service, instead of entering adult life handicapped physically and educationally, often unable to live life to the full. A recent, but by no means isolated, experience is worthy of mention. A girl of 15, admitted to hospital twenty-two times with asthma in her short life, had just completed three years at a special school for asthmatic children, costing the local authority £1000 per year. Admitted to a general hospital for the first time, since she was now 15 years of age, she was referred for allergy studies, proved to be house-dust sensitive, desensitised until demonstrably negative to provocation test, and within a few months became completely free from asthma. Unfortunately, she is left with a distorted chest, but is now very happy in an office job and has not had a day off work in a year. She would never have "grown out of it" and would certainly have been a burden to herself and the community. What a waste of our resources!

In this country, with a total school population of 8,507,457 in 1970, Dawson et al.[2] found an incidence of asthma of 4·8% in Aberdeen, and Smith [3] an incidence of 4·2% in Birmingham. Taking the probable incidence as roughly 5%, and using total numbers to emphasise the size of the problem, no less than about 430,000 children under 16 in Britain may have asthma. Of these only 94,600 (22%) will get better anyway, leaving 336,000 (78%) as chronic problems to themselves and to the community.

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