CHAPTER 6

STRESS, VASOSPASM AND GENERAL DISEASE

“For this is the great error of our day . . . that physicians separate the soul from the body”.¹

Disease is dis-ease, lack of ease.

GWB.

INTRODUCTION

That psychological stress may cause organic disease is a common concept, but not one which is widely embraced in medicine, for no matter how many patients complain of it, and there are many, stress has been difficult to define precisely, and therefore not a very favored avenue of study among what one might call the more mechanistic medical sciences. Psycho-physiologists have certainly provided important insights into normal learning behaviour,² but their contribution to the understanding of abnormal states such as mental disease has been much less, and more in the realm of description and classification of the changes than any synthetic construction of their cause. Physiologists, for their part, have helped in the understanding of stress-related diseases by showing, for example, that the sympathetic nervous system,³ ⁴ adrenal medulla,³ and the adrenal cortex⁵ may all be activated during stress, but unfortunately no-one has provided an explanation of the way in which organ-specific disease may come about through disturbances of the mind or the emotions. Yet this is an area of such importance that it is essential to somehow delineate ways of proceeding to unravel the complex relationship between bodily disease and the mind.

As I see the problem, it is first necessary to discern some final common mechanism through which the mind might act to alter the function of specific organs before we can proceed much further. This strategy would also have the advantage of allowing the continuation of an essentially physiological approach to future research, whilst at the same time avoiding the difficulty of defining stress in psychological terms, at least in the first instance, because in this respect stress could now be regarded as that process which, working through the brain or mind, activates the common physiological stress mechanism in unusual degree. The most evident link between the emotions and various bodily functions is the autonomic nervous system, in particular its sympathetic component, which may be markedly activated during stress.³ ⁴ If the sympathetic nervous system is indeed involved in this relationship, then the simplest way it could affect any one of the many different bodily organs is not by an alteration of their specific functions such as secretion, absorption etc., but by a change in some function which is common to them all, and on this basis a change in local blood flow strikes me as by far the most likely. This could be brought about either through constriction of the small arteries or arterioles or, in the case where whole organs or
macroscopic regions of them are involved, constriction of their major arteries of supply. Believing nature to be fundamentally simple, and bearing in mind the increasing evidence that arterial constriction does occur at all of these levels,6-9 I have examined a number of acutely-reversible stress-related conditions in this light, and reached the conclusion that many can indeed be explained on such a basis. At the risk of seeming to put the cart before the horse, I should like now to state the general conclusion, and then go on to examine the evidence in the various organ-specific diseases that has led me to it, again confining attention to those clinical entities of acute onset in relation to stress.

I want to suggest here, as outlined elsewhere,6-9 that spasm of arteries of various sizes, most often precipitated by physiological or psychological stress, is an important initiating event in a number of diseases. And this includes more than transient or reversible ones, because although usually reversible, this mechanism could still cause irreversible ischaemic damage in the organ supplied if the reduction in blood flow were severe and prolonged, particularly where secondary local occlusive thrombosis supervened in consequence. Such a mechanism might explain a wide range of pathological conditions occurring in different organs or different regions of particular organs in relation to stress, the area involved being determined not only by the type of stress and the response of the patient’s psyche and his sympathetic nervous system to it, but also on that particular individual’s constitutional make-up as it concerned such aspects as his vascular anatomy (including the richness collateral circulation), his arterial reactivity, and variations in his vascular sympathetic nervous supply. Through these factors, a critical reduction in blood flow following stress could be localised to almost any region of the body, depending among other things on the severity of the sympathetic discharge, the degree of arterial constriction, the size and number of arteries involved, and the effects of all this on local tissue blood flow.

The case for an important role of arterial vasospasm in myocardial ischaemia/infarction (Ch. 3) and other cardiovascular disease (chapter 5), is, I believe, founded on a strong even if somewhat circumstantial basis. In extending the argument from the particular to the more general, I recognise that the evidence may often be more tenuous, and that the range of disease in which this mechanism is suggested to play a part is broad. Nonetheless, I am persuaded to present the general hypothesis by its implications of reversibility, by the fundamental importance of beginning to analyse the link between organ-specific disease and stress, and by the necessity to my mind of taking an overall or co-ordinating view in order to explain the nature of such disease.

In essence, I view it as unlikely that arterial spasm will be confined to relatively few areas of the circulation such as the digital arteries in Raynaud’s phenomenon,10 the cerebral vessels in migraine,11 and the coronary arteries in Prinzmetal’s angina,12 and because there are so many acute-onset conditions occurring in relation to stress where aetiology is obscure, it strikes me as particularly important to examine any proposed new mechanism, especially one such as this which holds such prospects for disease prevention and reversibility. Of course, to many seeing is believing and, in this sense, if we were to accept only anatomical or histopathological evidence as the final arbiter of disease mechanism, the present theory could never be accepted. But in a point I shall take up in a later chapter, at a time of increasingly sophisticated investigational techniques during life the final verdict about disease mechanisms is shifting more away from the level of anatomical pathology to functional pathophysiology. This is already evidenced, for example, by Maseri’s studies with Prinzmetal’s angina,13 so that in this sense the current view is far from untestable. Also, as Popper has pointed out,14 any good theory should not only have an explanatory power within its original frame of reference, but be capable of extension to areas beyond. In some ways, all I am attempting to do here is illustrate that the concept of arterial vasospasm can indeed be taken beyond areas like myocardial ischaemia to provide at least as
good an explanation for many acute-onset stress-related disorders as present theories, perhaps better. Moreover, because knowledge tends to be collected within the framework of existing theories, any new postulate which provides an acceptable explanation for a condition whilst at the same time accounting for a broader range of data than the previous, must be worth considering as an alternative.

Arterial spasm in man has become increasingly recognised in recent years, but in general has not been regarded as important in the pathogenesis of any but the more unusual forms of disease. This, I suspect, is largely because of the firm tradition in clinical physiology that it is only the small arterioles which constrict to provide resistance to blood flow within different regions of the circulation, with the larger arteries acting merely as passive conduits of blood. Indeed, so strongly has this belief been held at the clinical level in the past that arterial spasm has not been seriously looked for in most conditions until recently, even though in some, such as Raynaud’s disease, the evidence in its favour is almost inescapable. The late Sir George Pickering argued particularly strongly against what he considered to be a too-ready acceptance of arterial spasm as a pathogenetic mechanism in vascular disease. Having been impressed by what he saw before his eyes in the form of arterial thrombosis, and believing that vascular events could be accounted for in known pathological terms without the necessity for assuming that arteries ‘behave like whimsical children’ by going into ‘unprovoked spasms’, he went on to assert that vascular spasm was an ‘extravagant and improbable hypothesis.’

Pickering’s views had a powerful influence in changing the climate of opinion away from arterial spasm, but I believe the time is now ripe for a re-opening of the case on the basis of more recent evidence. Firstly, a mechanism to produce arterial vasospasm undoubtedly exists. The arterial system is now known to be well-supplied with sympathetic nerves, many of which are coupled to a wide area of arterial smooth muscle by either direct or indirect means. In addition, vascular smooth muscle is quite capable of contracting in response to sympathetic alpha-adrenergic agonists. Under basal conditions, it is probably true that the diameters of the large and medium-sized arteries do not vary a great deal, but with sympathetic and particularly hypothalamic stimulation, quite marked constriction has been found experimentally. In man, too, arterial spasm has been demonstrated in a variety of conditions, including Raynaud’s phenomenon, migraine, subarachnoid haemorrhage, in the uterine arteries during menstruation, the umbilical artery and the ductus arteriosus at birth, during surgical manipulation of arteries, and in the coronary arteries during angiography, variant angina, and even in at least some angina of effort. However, because little attention has been given to the possibility, the evidence bearing on the role of vascular spasm in most organ-related disease is extremely limited. Finally, it is becomingly increasingly evident that under conditions of stress the sympathetic nervous system is indeed activated across a whole range of conditions.

DISEASES OF ESTABLISHED VASOSPASTIC NATURE

Raynaud’s Disease

This condition, characterised by a paroxysmal discolouration of the fingers, and often precipitated by cold or emotional stress, is almost certainly due to digital artery spasm.
Pathological changes are not usually seen in milder cases, but when severe and prolonged, evidence for thrombosis is frequently found. The present hypothesis would see the latter as secondary to intimal damage from an increased blood flow velocity at points of arterial constriction (see Ch. 4. The frequently-observed digital artery intimal hyperplasia in chronic cases, is also seen as being secondary to chronic repetitive intimal damage (see also Ch. 5).

**Migraine**

In classical migraine, Wolff’s concept that the aura and subsequent hemi-cranial headache are due to a decrease and increase in local cerebral blood flow respectively, has been confirmed — even if not in all patients — both directly at angiography, and indirectly from isotope blood flow studies. Despite some controversy, migraine is still considered by most to be a stress-related disorder occurring more in certain personality types. In particularly severe cases, cerebral atrophy and even cerebral thrombosis/infarction may eventually occur, and this is again consistent with the present view.

Let us now turn to other conditions that may come on acutely and run a remitting and relapsing course in relation to stress, to see how well they may be explained by traditional theories, and, if those explanations are inadequate, whether arterial vasospasm evoked by stress might provide an better interpretation of the evidence. You may think that to do so is to risk iteration to the point of tedium, but in many of the conditions we shall discuss there are very few insights into real basic underlying mechanisms of pathophysiology - as opposed to molecular biological insights - so I suggest that such exploration is well worthwhile. To paraphrase Langton: “A living organism is more than a simple, complicated biochemical machine.”

**ANALYSIS OF CENTRAL NERVOUS CONDITIONS**

**Epilepsy**

The complexity of disease description often seems to vary in inverse proportion to the extent of our knowledge about its cause. Certainly, this is true of epilepsy, because despite its impressive label as an “acute spontaneous cortical neuronal discharge”, we know really very little about pathogenesis. To understand its nature, it seems reasonable to first look among the known mechanisms of disease before postulating new ones. In this respect, our general considerations of chapter 2 would suggest that such a sudden-onset yet brief event should be due to an acute reversible obstruction of some hollow tube somewhere in the brain. Now, the only hollow tube structures in the brain are vascular ones. Also, neurologists since the time of and Gowers and Hughlings Jackson have recognised the close similarity between epilepsy and a condition we know much more positively to be of vasospastic origin, namely migraine. Because of this, I can think of no better way of viewing, say, grand mal epilepsy, than as severe ‘migraine’ of the motor cortex, but this time with emphasis being on the intra-cranial cerebral arteries, and the severity of their initial vasospastic phase. There is often very little to differentiate sensory epilepsy from
migraine, except for the rather more rapid progression and profound clinical course of the former, and even this might be due merely to a more transient and severe vasospastic episode in the artery or arteries concerned.

This vasospastic view of epilepsy would also fit with the pathological data obtained from patients dying with chronic epilepsy, status epilepticus, or after febrile convulsions, where there is often clear evidence of local cerebral atrophy. In point of fact, a vasospastic origin for epilepsy was originally proposed in the 19th century by Nothnagel, and subsequently supported by the studies of. Although most present-day investigators favour the view that any ischaemia is a secondary consequence of the epileptic fit rather than its cause, this interpretation is highly questionable, and might well represent more a shift in fashion than substance. Of course, few patients die of epilepsy, so that pathological material is not commonly available, but even in surviving patients, the occasional complication of local paralysis after epileptic fitting (Todd’s paralysis) would also be consistent with a focal ischaemic basis for the condition.

It is hard to find evidence bearing directly on causation either way, but there are at least some hints consistent with the present view. First, the vasospastic condition of migraine is more commonly associated with epilepsy than would be expected by chance alone. In addition, many of the anti-epileptic drugs have ‘dizziness’ as a side-effect. Some, such as phenytoin, are capable of causing a profound drop in blood pressure, even vascular collapse, when given intravenously at high dosage, consistent with a vasodilatory action of the drug. In this respect it is also interesting that phenytoin causes gum hypertrophy in some patients, because this could well reflect an increase in blood flow through the (external) carotid arterial territory. This would also be in keeping with the other occasional effect of this drug to produce facial hirsutism, a well-recognised side-effect of drugs with more generally acknowledged vasodilatory properties such as minoxidil.

The studies that should bear most directly on the present analysis are those on regional cerebral blood flow changes in patients with focal or partial epilepsy. However, findings here have been conflicting, with some studies showing a decreased regional cerebral blood flow at the epileptic focus in between attacks, and others reporting an increase. Even during the stimulated or epileptic phase, there are no uniform findings, for though most patients appear to show a high local regional blood flow at the site of the epileptic focus, this can represent either an increase or decrease over the baseline value. Moreover, it is not uncommon to find evidence of a reduced blood flow in the border-zone surrounding the epileptic focus, so that neither the anatomical nor the temporal relationships of focal epilepsy to changes in local blood flow are clear cut. These variable findings have been taken by most to indicate a fluctuating function and metabolism of the epileptogenic focus, but on the basis of the analogy drawn here with migraine where there is evidence of early vasoconstriction and subsequent vasodilatation, it might well be that the result observed depends on the stage at which blood-flow measurements are made. To analyse this point adequately would require sequential studies in the aura as well as the ictic phase of epilepsy, but such studies are not available. But because brain tissue is so easily damaged by ischaemic anoxia, it is not difficult to see how a quite profound ‘reactive’ hyperaemia might follow an episode of focal cerebral vasospasm perhaps too brief to be detected by routine nonsequential scanning studies. There is an old observation that facial pallor is an early sign heralding epileptic fitting, and this might be an indication of ischaemia in the carotid arterial territory early in the march of epileptic events.

It is no easier to establish a firm link between stress and epilepsy than in other condition, but there are certainly strong suggestions to that effect. First, there is evidence that epilepsy is more common in certain personality types. Perhaps even more important than personality per se is the
patient’s ability to cope with various life stresses.\textsuperscript{51} Following this line, it is thought by some that epileptic fits are more common after periods where emotional conflict has engendered suppressed rage.\textsuperscript{52} Wolf and colleagues have also induced epilepsy during barbiturate ab-reaction by stressful interview.\textsuperscript{53} Other evidence comes from the studies showing a beneficial effect of behavioural modification in the rehabilitation of children with epilepsy.\textsuperscript{54} Of course, none of this can be taken as more than suggestive, but in the absence of a clear understanding of aetiology on any other basis, the view here that may be precipitated by stress-induced vasospasm is at least worthy of further study.

Implicit in what has been said so far on vasospasm as a mechanism in general disease is that most irreversible damage from it is due to secondary thrombosis at or beyond the vasospastic site. But whilst this may be true in many organs, it need not always be so, particularly in organs like the brain where susceptibility to damage from even brief deprivation of blood supply is high. In those areas the strong possibility exists that irreversible damage may occur from reversible ischaemic episodes alone (i.e. vasospasm without thrombosis). Such considerations give rise to a special problem in analysing the role of ischaemia in cerebral disease, not only epilepsy but in other atrophic conditions such as senile dementia as well. Some of these aspects will be discussed in more detail later.

Let us now look at other acute-onset reversible stress-related conditions in organs elsewhere, first in the gastrointestinal tract.

GASTRO-INTESTINAL CONDITIONS

Duodenal Ulcer

In these days of biochemical reductionism as an approach to understanding disease, what was once thought to be a clear-cut psychosomatic basis for this and many other diseases\textsuperscript{51,55} now seems to have faded somewhat into the background. Nonetheless, duodenal ulcer is still acknowledged by many as a fairly classical psychosomatic condition, and there is evidence to support this.\textsuperscript{56} Psychosocial situations which lead to the general feeling of being deprived of one’s just due appear to be particularly important in precipitating ulcer pain and discomfort in many patients,\textsuperscript{51,56} and it is of interest that the similar moods of dejection, despair etc. have been noted by Wolff to cause pallor and ischaemia of the gastrointestinal mucosa.\textsuperscript{11} Clinically, so-called ‘chronic’ duodenal ulcer characteristically runs a periodic course with relapses and remissions presumably corresponding to recurrent episodes of breakdown and healing of the mucosa in the proximal duodenum, so that it certainly qualifies as an acute reversible stress-related condition for consideration under the present theory.

Until relatively recent times, the most widely-held view of ulcer pathogenesis was that there is some sort of ‘imbalance’ between mucosal resistance/blood flow from such factors as prostaglandins on the one hand and the degree of gastric acidity tending to cause mucosal breakdown on the other.\textsuperscript{57} Of course, the discovery of the centrality of helicobacter\textsuperscript{58,59} in duodenal ulcer, both in pathogenesis and prevention,\textsuperscript{60} has entirely shifted thinking on the subject. Nonetheless, important though this discovery has undoubtedly been, it seems unlikely to have given us the whole picture. For one, it does not explain at all the sharp focalisation of this disease anatomically to the duodenal cap. Morson and Dawson,\textsuperscript{61} among others, have recognised this,
and believe that the localising factor could well be ischaemia. In this respect, it is significant that there is a relative paucity of the arterial sub-mucous plexus circulation in the first part of the duodenum and adjacent lesser curvature of the stomach, because this could mean that the mucosa there might be particularly vulnerable to any local reduction of blood supply to the region, brought about for example by vasospasm of the gastro-duodenal artery. The stage would therefore seem set for a possible role of local ischaemia, and I would suggest that a likely factor precipitating episodic mucosal breakdown is sympathetically mediated vasospasm in relation to psychological stress.

Support for a vascular contribution comes from the observation that the prostaglandin synthetase inhibitors, such as aspirin, predispose to peptic ulceration. The prostaglandins, including PGE2 and PG12, are produced locally in the gut mucosa, and seem to act there, as elsewhere, to maintain local tissue blood flow. Further, prostaglandin synthetase inhibitors probably do exert their ulcerogenic effect by inhibiting this vascular protective function. To the same general point, Wolff and Wolff’s experiments with Tom and his gastric fistula clearly indicate the enormous potential for variation in the gastro-intestinal mucosal blood flow in response to psychological stress. It is also worth recalling that the ‘placebo’ cure rate in peptic ulceration is as high as 60% in some series, and this serves to emphasise the potential importance of the mind in this condition. I expect no more than the Scottish verdict of “not proven” in relation to my view that duodenal ulceration is at least in part precipitated by stress-induced vasospasm in the arterial supply to the first part of the duodenum, but I hope to have established that there is at least a case to pursue rethinking and further investigation along these lines. It certainly seems clear that duodenal ulcerative disease pathogenesis is much more complex than the helicobacter story alone.

**Ulcerative Colitis**

This is another gastro-intestinal condition which sometimes comes on acutely in relation to stress, so it, too, seems reasonable to examine in the light of the current vasospastic view of such disease. The clinical picture would certainly fit the general criteria, not only its association with a background of stress, but its acute onset in relation to it in many patients, and its frequent episodic nature. Of course, the pathological picture is not simply one of ischaemic colitis, either in its distribution or its microscopic appearances, because there, ischaemic atrophy and necrosis of the superficial mucosa tend to dominate the picture, whereas in ulcerative colitis, the mucosa is often the site of hyperaemia, oedema, superficial inflammation, ulceration, crypt abscess formation, and eventually fibrous scarring with hyperplasia of the surviving bridges of intervening mucosa. This superficial hyperaemia seems unlikely to be due merely to a congestion from stasis, as might occur in ischaemic colitis, because such measurements of colonic blood flow as have been made suggest that it may be increased, even if in somewhat labile fashion.

Despite all this, the pathogenetic differences from ischaemic colitis may not be nearly as great as we think. Thus, in an organ of such bacterial colonisation as the large bowel, evidence of superficial inflammation after mucosal ulceration from any cause would not be too surprising. And if we take a more dynamic view of ulcerative colitis, and allow that the lability of colonic blood flow may reflect alternating periods of ischaemia and subsequent reactive hyperaemia, it could well be that many of the histological features are caused by initial ischaemic mucosal damage and...
ulceration followed by post-ischaemic hyperaemia, oedema, inflammation, mucosal hyperplasia and attempts at tissue repair. On this basis, one could understand how ischaemic damage might arise in acute episodes from local vasospasm involving the inferior mesenteric arterial system, and how attempts at healing in between such episodes could result in regeneration and hyperplasia of the surviving mucosa, each time with an inflammatory reaction being mounted against the damaged tissue and the bowel organisms invading it to aggravate the situation. And being often interrupted by the next episode of ischaemia before resolution were complete, healing might never be totally effective, so that a picture of chronic inflammation could gradually emerge. Hastening this would be the tendency for prolonged bouts of ischaemia to cause secondary thrombosis in the small arteries to the intestinal mucosa. Such thrombosis has not only been described, but also assigned an important contributory role in the pathogenesis of chronic ulcerative colitis by some investigators.\textsuperscript{70}

There is no direct evidence favouring this process of alternating vasospastic ischaemia and subsequent reactive hyperaemia as the basis for human ulcerative colitis, but there are certainly experimental studies consistent with it,\textsuperscript{71} and to me, episodic spasm of this type does provide a better explanation for the clinical time-intensity relationships of this disease than present theories, and one which gives a much more satisfactory account of the broad range of its pathological changes. What is more, it offers one of the few rational ways of understanding how ulceration could occur in response to stress. Previous explanations based on the proposition that increased parasympathetic drive causes hyper-function of the colon, increased gut motility and hyperaemia\textsuperscript{68} do not at all explain why actual ulceration should occur. The often-noticed patchy anatomic distribution of the ulcerative process over the colonic mucosa might also be accounted for by a variable degree of vasospasm in different branches of the inferior mesenteric arterial tree and/or variation in collateral anastomotic blood supply from adjacent areas of relatively normal blood flow.

This mechanism does not, of course, exclude the possibility that other factors may contribute importantly to the pathogenesis of inflammatory bowel disease. For example, unusual (i.e. damaging) antibodies and other immunological reactions\textsuperscript{72,73} mounted in response to local tissue injury and bacterial invasion on the one hand, and primary involvement of some infective agent\textsuperscript{74} on the other, could all be important. But the point I wish to make is that none of these provides an adequate explanation for the whole picture, and certainly none for the acute onset, relapsing nature, and patchy anatomical distribution of ulceration within the colonic mucosa. No primary antibody should behave like this, and no primary infection should recur in such manner.

Pseudo-membranous Colitis

Having raised the view that there are parallels with ischaemic colitis, one condition which appears histologically very similar to that is so-called pseudo-membranous ulcerative colitis, which sometimes occurs as an idiosyncratic reaction to oral antibiotic therapy. This is now thought to be caused by super-infection with the organism Clostridium difficile following antibiotic sterilisation of the gut,\textsuperscript{75} but in the context of a histological appearance so like ischaemic colitis it is worth asking whether the bacterial toxin mediating this might be acting via the production of mucosal ischaemia.

Appendicitis
Vasospasm in acute abdominal disorders may not be confined to medical conditions, and might be well worth considering in various acute-onset surgical conditions where there is no satisfactory explanation of cause. Acute appendicitis could be an example, because it is by no means always explained by local obstruction to the appendical lumen. Pathologically there is often ulceration of the appendical mucosa with accompanying evidence of inflammation and, as in ulcerative colitis, this might be accounted for by mucosal damage during an episode of ischaemia with subsequent inflammation in response to that damage once blood flow had been restored. The appendical artery is a relative end-artery, and vasospasm in it would therefore be particularly liable to cause ischaemic damage. In severe cases, gangrene of the appendix sometimes occurs and then pathological examination may show thrombotic occlusion of the appendical artery, again consistent with the present general view that severe prolonged episodes of vasospasm may lead to secondary vascular thrombosis.

**RESPIRATORY DISORDERS**

**Bronchial Asthma**

One well-recognised acute-onset reversible condition that occurs in relation to stress is bronchial asthma. Here, of course, the hollow tubes which become acutely obstructed during attacks are the bronchioles rather than the vascular passages. Indeed, there would be no reason to doubt that this was the primary event in all types of asthma if it were not one peculiar aspect difficult to account for on this basis alone, namely post-exercise asthma. Most theories of asthma hold that the vagus nerve is of central importance in the mediation of bronchospasm, whether it be activated reflexly when allergens absorbed from the bronchial mucosa react with the mast cell in the presence of reagin antibody, or from more direct vagal stimulation under conditions of psychological stress.

Post-exercise asthma, though, is very difficult to account for by this means alone. For one thing, it is reportedly not prevented by the administration of atropine, and in any case it would be hard to understand why an increased vagal drive should occur immediately following exercise. In looking for mechanisms which might explain the condition, it seemed to me reasonable to first examine it in the light of the known physiology of exercise, and here it seems possible that the bronchial circulation, in keeping with that in many other internal organs, might undergo a reflex sympathetic vasoconstriction during exercise, so as to bring about a degree of bronchiolar ischaemia even in normal subjects, and perhaps even more in patients susceptible to this form of asthma. If this did occur, we would expect a corresponding exaggeration of reactive hyperaemia to the bronchiolar mucosa following exercise in asthmatics, and this could give rise to abnormal capillary fluid exudation into the submucosa, so reducing the diameter of a perhaps-already-narrowed bronchiolar lumen. Any water loss from hyperventilation during exercise could also lead to a local increase in tissue osmolality, and this could further add to the degree of post-exercise bronchiolar wall oedema and lumen narrowing. Mucosal hyperaemia would also tend to increase the rate of transport of any allergen residing on the bronchial mucosa towards the underlying mast cell, perhaps involving an allergic component to post-exercise asthma as well. Allergen transport of this nature is certainly regarded by some as important in the more usual forms of asthma.
Unfortunately there is again very little direct evidence bearing on the mechanism proposed. The bronchial arterial system does seem to be supplied with sympathetic nerves, and alpha-adrenergic agonists are known to be capable of inducing asthma under some circumstances, so that the stage certainly seem set for a sympathetic involvement in post exercise asthma along the lines suggested. One test of the proposition would be the effect of prior alpha-adrenergic blockade on the occurrence and severity of post-exercise asthma. Sly and colleagues attempted to analyse this by giving the alpha-blocking drug phentolamine to susceptible subjects before exercise, and measuring peak expiratory flow velocity 10 minutes afterwards. This had no effect, but the half-life of this drug is very brief, and more recent studies with the longer-acting alpha-receptor blocking drug indoramin do indeed suggest that alpha-blockade may be useful in preventing post-exercise asthma. This finding has been amply confirmed. Of course, because the bronchioles and arterioles contain smooth muscle lying side by side, it is difficult to unravel the precise mechanism mediating the action of this or other vasoactive/broncho-active substance, including the prostaglandins, in this condition.

Recently, it has been shown that post-exercise asthma may be largely prevented by breathing cold dry air during the post-exercise period, leading to the view that the condition may indeed be due to a reactive hyperaemia of the bronchiolar circulation, with the increased rebound oedema after exercise narrowing the bronchiolar lumen. Actually, as things have turned out, a direct effect of cold air as the sole cause of bronchiolar vasoconstriction is unlikely. But on the basis of the present theory, cold air during exercise might well act on the bronchiolar arterioles to aggravate the degree of vasoconstriction already achieved there from reflex sympathetic mechanisms, with consequent greater rebound hyperaemia, oedema and bronchial swelling once the exercise period had passed. This view of post-exercise asthma remains, of course, hypothetical because of the lack of hard direct evidence, but it does offer a rational explanation of an aspect of asthma very difficult to understand on any presently held basis.

**ACUTE RENAL FAILURE**

In the context of the present examination of disease, acute-onset conditions of the nephron are of interest from several points of view. Firstly, one often sees evidence of impairment of renal function out of all proportion to any observable histological change, and as we shall discuss in more detail in a later chapter, when this occurs we must be alert to possible functional mechanisms contributing towards the disease - of which ischaemia is one.

**Acute Blood Loss**

A condition relevant to the present investigation is acute renal failure secondary to acute blood loss. This provides yet another example of acute-onset conditions occurring in response to stress — but this time with the stress being of a physiological rather than psychological nature, — viz. a vascular shut-down or ischaemia secondary to an increased sympathetic nerve outflow to several organs, including the kidney, as part of the body's attempts to maintain arterial pressure and cerebral blood flow in these circumstances. Renal blood flow may fall sharply as part of this adjustment, and with it glomerular filtration and urine formation fall as well. The early phase of this 'pre-renai' impairment of kidney function is due entirely to renal ischaemia, potentially reversible
when the circulation is restored. But when the ischaemia is more prolonged, reversion to normality after apparent blood volume replacement does not always occur, and then a good deal of controversy surrounds the explanation of why. In this context, one or two comments may be appropriate.

First, where blood has been lost from the circulation, it is not always easy to judge accurately the extent of its replacement from the standard clinical parameters of blood pressure, pulse and central venous pressure. The first two tend to be controlled at the level of the large arteries via the baroreceptors in the aortic arch and carotid sinus, and a return of blood pressure to normal at this level might give no indication whatsoever about the pressure prevailing in the smaller arteries and arterioles more distally in the various organ beds, including the kidney — which is what matters in the present context. It might be thought that a low central venous pressure should still give the indication of any under-transfusion in this situation, but severe sympathetic discharge may cause not only arterial constriction but veno-constriction, so reducing venous capacitance in the small veins, and shifting blood volume from the peripheral to the central venous compartments. This in turn tends to maintain central venous pressure in spite of a low circulating blood volume and underperfusion peripheral organs, so giving a false sense of circulatory normality. Of course, intensive care physicians responsible for the management of patients with acute renal failure have long known the importance of assessing the peripheral circulation (say in the toes), as well as measurements of central venous and arterial pressure, in judging the adequacy or otherwise of circulatory fluid replacement, but just why these central parameters should be such poor guidelines in this situation has never, to my knowledge, previously been explored. And even subtle changes can be very important. For example, without changing systemic arterial pressure at all, an experimental reduction of circulating blood volume can cause an almost complete shut-down of renal blood flow, glomerular filtration and urinary output.

If both the overt and the more subtle signs of circulatory insufficiency are recognised and rapidly corrected, the acute ischaemic impairment in renal function following blood loss is quite reversible. However, where ischaemia has become prolonged, the renal dysfunction enters a less-reversible stage, related basically to ischaemic damage within the kidney. This much is unquestioned, but there is a great deal of controversy on how the renal failure is then mediated, and I should like to pause to look at this.

**Acute Tubular Necrosis/Vasomotor Nephropathy**

The less reversible phase of renal failure which follows acute blood loss, has, until recently, been termed “acute tubular necrosis”, but is now more usually referred to as “acute vasomotor nephropathy”, and this dual terminology highlights the continuing controversy about its cause. Briefly, as discussed by Levinsky, the two differing views on the origin of the reduced urine flow place emphasis on two quite different aspects of this condition. Those who favour an importance of tubular damage believe that ischaemic tubular necrosis allows tubular debris and other proteinaceous material to block the onward tubular flow of urine, and that a secondary back-leak of glomerular filtrate then occurs through the damaged tubular basement membrane. Others hold that the evidence from both experimental models and man points to a persistent reduction in renal blood flow as the most likely cause of oliguria. The following way of seeing the condition may help to resolve this controversy, for it suggests that both views may be correct, and that the dominance of any particular one will depend on the time at which the renal failure is observed. Early on, the evidence for acute and quite severe
vasoconstriction (probably through sympathetic nervous activation\(^{98}\)) is strong. This constriction probably involves not only the arterioles, but the small arteries such as the arcuate renal arteries as well.\(^ {97}\) Early in the course of this condition, therefore, it may be that oliguria is indeed caused by a primary reduction in renal blood flow. But later, if the ischaemia is maintained, ischaemic necrosis of the tubules seems bound to occur eventually. Then, osmotic swelling of the renal tubules will tend to obstruct the onward passage of any glomerular filtrate, and with time this could become the major factor causing the oliguria. At this relatively late stage, even if the ischaemia were reversed, any returning blood flow would often merely allow fluid to exude through the damaged and leaky renal tubular capillaries, so as to increase interstitial fluid pressure as well. Now, in an organ as confined from expansion (by the renal capsule) as the kidney, this could add an important force tending to collapse the renal tubules even further at any points of osmotic swelling from previous ischaemic damage.

In sum, the present view of vasomotor nephropathy suggests that while the kidney remains ischaemic, a reduction in renal blood flow is indeed the primary cause of impaired renal function. But with prolonged ischaemia, secondary damage to the renal tubules could cause their osmotic swelling. And even if blood flow were then restored, the renal tubular damage might not be reversible, particularly given that the associated capillary damage might have allowed leakage of excessive fluid into the extravascular renal compartment, thereby raising interstitial pressure and tending to collapse the tubules still further. This synthesised view seems to me to provide a good explanation of the many different aspects of acute renal failure, and one not considered previously.

Even the process of tubular necrosis is usually reversible given time. Occasionally however, it is not, and then it is worth considering whether prolonged ischaemia from vasospasm in the small arteries might have given way to a less reversible form of arterial obstruction, namely secondary thrombosis. There is very little evidence on this point, but it seems to me a possibility worth bearing in mind.

**Acute Glomerulonephritis**

Another aspect of acute renal failure of pathophysiological interest is acute glomerulonephritis. Here, we have come to recognise that many of the so-called "glomerulo-nephritides" are due to a glomerular injury mediated in part by immunological mechanisms, and this raises the question that in some patients the body's immunological defences (e.g. formation of immune-complexes) against antigenic stimuli may, on balance, do more harm than good. Some immunological reactions in the kidney certainly invoke an inflammatory response,\(^ {99}\) and whilst we normally think of inflammation as being of benefit, it is clear that on occasions it may not be, at least as far as the kidney is concerned. This idea that immunological mechanisms, albeit perhaps unusual or aberrant ones, may sometimes cause tissue damage, is not new, but until recently we have tended to see it as restricted to such areas as asthma, anaphylactic shock, etc., and the studies on glomerulonephritis have shown that it may be of much more widespread importance. However, rather than try to dissect these renal immunological mechanisms in detail, I should like to move on to consider the more general immunological disorders, namely auto-immune disease.
AUTO-IMMUNE DISEASE

In this chapter we have so far confined attention to diseases where both the clinical and pathological features are consistent with a vasospastic mechanism. This has particularly emphasised reversible conditions of sudden clinical onset in relation to stress, where the pathological features are consistent with ischaemia, atrophy and/or necrosis, even if perhaps sometimes masked by the relative transience of each episode. But as one who approaches disease pathogenesis essentially from a clinical viewpoint, I cannot help but wonder whether there may be similar mechanisms in other patients who present with acute-onset disorders of remitting and relapsing nature in relation to stress, even where there are none of the more obvious hallmarks of ischaemia pathologically. We have already discussed the case of ulcerative colitis where these constraints apply and have concluded, albeit tentatively, that it might nonetheless have an ischaemic basis. I now want to focus attention on the auto-immune disorders from a similar standpoint, and to look first at rheumatoid arthritis.

Rheumatoid Arthritis

This is classically a disease which runs an acutely relapsing and remitting course, where recurrences over the years tend to be brought on by periods of acute stress. Now, if we were to view this condition only from the pathological standpoint, there would not be the slightest reason for thinking that ischaemia might be involved at all in pathogenesis. Rather, the evidence would seem very much to the contrary, with all the hallmarks being of inflammation and hyperaemia. Indeed, it is generally believed that this is a chronic inflammatory process, perhaps initiated by some persistent virus or other, and mediated in part by the unusual immunological reactions that these patients tend to show. I do not deny the importance of this inflammation, be it mediated through immunological mechanisms or otherwise, but I do question whether the episodic nature of the inflammatory process can be explained entirely by a primary abnormality of the immune system, or by some persistent or repetitive viral infection. The clinical picture of rheumatoid arthritis is just not what we would predict from such mechanisms, and although I can accept that they may contribute to pathogenesis, they seem insufficient alone to account for the usual clinical course of this disease.

In attempting to analyse this situation, it first seems probable that in these circumstances each bout of inflammation is initiated by some form of local tissue damage. The difficulty is to incriminate any of the known exogenous agents as the factor causing this damage. The strongest contender would be an infectious particle of some type, for example a virus, but such infection would not be expected to recur in any episodic way - except perhaps under two very special circumstances. The first would be where there were some generalised immunological defect that allowed repeated infections by common viruses. However, it must be said that this is unlikely in rheumatoid arthritis, not only because no such generalised defect has been found, but even with therapeutic immunosuppression, rheumatoid arthritis is not one of the consequences. This leaves the possibility of persistent or repeated infections with unusual viruses, but again one can only say
that despite all efforts, there is not the slightest evidence that this is the case. We certainly
cannot account for the episodic clinical course of classical rheumatoid arthritis on any viral basis
alone, and the same holds true for other postulated infective agents such as mycoplasma. In the
absence of evidence supporting a role for exogenous agents in rheumatoid arthritis, we
should examine the possibility that there may be endogenous origins to the joint damage and
inflammation. In this context, one of the very few ways in which inflammation can be invoked by
endogenous means is through damage from ischaemia. The point I therefore make, relevant to the
general theme of this book, is that episodic and transient bouts of ischaemia of the involved joints
from vasoconstriction could be the factor triggering each inflammatory flare-up in the clinical
course of rheumatoid arthritis, particularly in those episodes where there is a relationship to stress,
whether it be physiological (e.g. cold) or psychological in nature. I emphasise the importance of
seeing this mechanism as a trigger initiating local ischaemic damage, and in no way wish to
diminish the potential contribution of immunological or other mechanisms in mediating,
aggravating or even localising the clinical condition that follows. But several points need to be
made.

First, an inflammatory response to local damage may not always be purely reparative. As
mentioned above in our discussion of glomerulonephritis, immune complexes formed in response
to foreign antigens may on occasion be of a type and size liable to be precipitated in the kidney
rather than cleared, and in that position do more harm than good by evoking a local inflammatory
reaction within the glomerulus. We know that patients susceptible to rheumatoid arthritis also
have unusual antibodies, including rheumatoid factor, and these could have a similar effect to
 aggravate primary joint damage or produce secondary damage during the process of rheumatoid
inflammation. Just where the balance might lie in rheumatoid arthritis between the potentially good
and harmful effect of the immune response, and even of the inflammatory response itself, is not
clear. But we do know that such immunological mechanisms probably play a role in causing the
vasculitic lesions in rheumatoid arthritis and other ‘collagen’ diseases, so they certainly have to be
taken into account. Second, along with the possibility that vasospasm around joints may be an
important factor in disease localisation, unusual antibody responses could help localise the
condition as well. My brief is not to deny such mechanisms, but to highlight the importance of
finding the trigger that sets them in train.

A first sight, the observation that the prostaglandin inhibitors (non-steroidal anti-inflammatory
drugs or NSAIDs) may be useful in limiting rheumatoid symptoms might be taken not only as
evidence favouring a dominant role for inflammation, but more importantly as evidence against a
role of vasospasm, because these inhibitors tend if anything to restrict local blood flow, so it could
be argued that they would therefore aggravate rather than ameliorate any local vasospastic
damage. But if the inflammatory response to the ischaemic damage were itself damaging in the
way suggested above, it might become difficult to draw any conclusion simply from the effects of
these agents on blood flow alone. The benefit of reducing damage by inhibiting the inflammatory
response in those circumstances might well outweigh any detrimental effect from aggravation of
the original ischaemia. Moreover, limitation of inflammation does not discount the possibility of a
continuing underlying ischaemia. We should careful, in this respect, to distinguish between clinical
improvement of inflammatory symptoms and reversal or amelioration of the mechanisms
underlying them. The effects of steroids in suppressing joint inflammation may well be a good
example of this. Patients on steroids occasionally develop aseptic necrosis of the articular heads
of some joints, and NSAIDs may actually accelerate the progression of osteoarthritis. Such a
process would be quite compatible with an aggravation of ischaemia by these drugs. We do not
even know whether, on balance, the symptomatic treatment of patients with any of the anti-
inflammatory drugs, steroid or otherwise, favourably influences the pathological outcome of the disease or worsens it.\textsuperscript{103}

To emphasise the point that immunological mechanisms can be involved in both the manifestations and pathogenesis of some aspects of the autoimmune disorders, and to show how damage from ischaemia might trigger these, let us consider one or two other conditions where the immunological changes have been a little better worked out.

**Thyrotoxicosis**

Primary thyrotoxicosis or Graves’ disease is part of the spectrum of ‘autoimmune’ thyroid conditions subsumed under name ‘Hashimoto’s disease’, which ranges from thyroid underactivity to overactivity or thyrotoxicosis. It is now clear that this thyrotoxicosis is due to antibodies to the TSH (thyroid stimulating hormone) receptor.\textsuperscript{104,105} Such antibodies can be viewed, on receptor theory\textsuperscript{106}, as locking into the receptor in a manner favouring agonistic rather than an antagonistic orientation of the receptor-hormone complex, so driving the thyroid to overactivity. But fascinating as these ‘auto-antibodies’ may be, and important as they undoubtedly are in the functional manifestations of this disease, it is difficult to accept that they simply arise \textit{de novo}. Some see them as being evoked by exogenous viruses, perhaps in a ‘hit and run’ manner,\textsuperscript{107} or by the expression of cryptic antigens\textsuperscript{107} or endogenous retrovirus vestiges,\textsuperscript{108} but it is still hard to understand how such views could explain the fluctuating course which is so often the hallmark of thyrotoxicosis — unless the antibodies were due to different viruses on each episodic occasion, or to some other factor or factors stimulating antibody production with each bout. There is certainly an autoimmune aspect to pathogenesis, and I have suggested elsewhere that a lot of that depends on just how the highly variable major histocompatibility (MHC or HLA) loci involved in antigen recognition ‘see’ cryptic cellular antigens when they are, for whatever reason, expressed. Some people within any population seem to raise antibodies reacting ‘self’ antigens, whereas others do not. My view is that much of our genome is made up of viral elements from past evolutionary integration (see Ch. 9), and whether or not the immune system treats them as ‘foreign’ when they are re-expressed, depends on the genetic makeup of our MHC complex.\textsuperscript{109}

Having so said, the question remains of just what precipitates each recurrent episode. In this respect, stress is certainly a contender. Parry’s original description of thyrotoxicosis was of an acute onset following an episode of severe stress,\textsuperscript{110} and others since have highlighted the importance of emotional factors.\textsuperscript{111,112} One suggestion is that the stress relationship can be explained by an inhibition of mechanisms normally concerned with immunological surveillance and suppression of auto-antibody production, possibly through an effect of cortisol from the adrenal gland to inhibit normal T lymphocyte suppressor cell function.\textsuperscript{113} Perhaps so, but thyrotoxicosis is not one of the conditions observed when patients are deliberately immuno-suppressed in other contexts.

My suggestion is that ischaemia from vasoconstriction following repetitive stress in these patients falls largely on the thyroid gland. When severe, and when arising in an (in)appropriate MHC context, this would lead to immunological damage of the thyroid follicular cells, as evidenced histologically in lymphocytic infiltration and follicular lymphocyte collections. And once damaged, normally cryptic thyroid cell antigens would be released to the general circulation, and now readily ‘seen’ by the immune system as unusual or ‘non-self’, often as vestiges of their past retroviral origins, with resultant antibody being mounted against them\textsuperscript{109} — in the case of thyrotoxicosis, against the TSH receptor. From a clinical standpoint, the common episodic course of this condition
and its relationship to stress could be accounted for by a new wave of antibody production with each bout of ischaemic thyroid cell damage. Pathologically, in the case where the thyroid damage merely caused exposure of hidden or ‘cryptic’ cell-surface antigens rather than their release, much of the immune reaction might occur locally, against the still-bound antigens, with the only result being a lymphocyte infiltration within the thyroid gland.\textsuperscript{113}

**Myasthenia Gravis**

Myasthenia gravis is another ‘autoimmune’ disease, but one where the important antibody from a functional standpoint is directed against the acetyl-choline receptor on the motor end-plate of striated muscle, this time locking it into an antagonistic rather than an agonistic configuration, so interfering with neuromuscular transmission to cause muscular weakness.\textsuperscript{114,115} This, too, is a disease that runs a fluctuating course \textsuperscript{116}, and one where relapses may be precipitated by acute psychological stress.\textsuperscript{117} So it also bears examination in the light of the current vasospastic theory of initiation of such disease.

The trouble is that even where a sympathetic discharge does occur following stress, it is unlikely to give rise to vasospasm in striated muscle, because at least in the so-called ‘defence’ reaction the muscle bed is the one site that does not undergo vasoconstriction at all, rather the reverse.\textsuperscript{118}

The thymus gland has been known for many years to be linked with myasthenia gravis in some way, and it has recently been shown that the epithelioid cells of the thymus also bear acetyl-choline receptors.\textsuperscript{119} These are now thought to be the source of the antigen stimulating the production of an antibodies that happen to cross-react with the acetyl-choline receptor in striated muscle. Because of this, I would suggest that relapses of weakness are precipitated by vasoconstrictor damage to the thymus gland that in turn triggers exposure of the thymic epithelioid cell acetyl-choline ‘receptor’ to the immune system. This seems to me a reasonable suggestion in the absence of any other clue of how such episodes of auto-immune antibody production might come about.

I am in no way suggesting here that aberrant autoimmune mechanisms in this group of diseases are unimportant. Indeed, quite the contrary, because as we have seen, these antibodies may contribute not only to the pathophysiology of some of the functional aspects of these disorders, but even to the evolution of the underlying disease process itself.\textsuperscript{109} The points I wish to emphasise are, first, that these antibodies may often stem from re-expression of antigens derived from genomic retroviral sequences signifying the manner our past evolutionary history.\textsuperscript{109} Second, it is improbable that these antibodies arise \textit{de novo}.

So when we recognise that exacerbations of many of these autoimmune diseases may be precipitated by acute stress and run a relapsing and remitting course in relation to it, it seems perfectly reasonable to draw the analogy with clinical situations of similar pattern, and to suggest that vasoconstriction may be the link between stress on the one hand, and the target organ damage giving rise to these antibodies on the other. In this regard, vasospasm which falls more on some arteries or arterioles of organ supply than others could account, at least in part, for the localisation of auto-immune disease states in relation to stress — for example vasoconstriction affecting the thyroid arteries or arterioles more than other vascular beds in patients with thyrotoxicosis.

In this way, the MHC phenotype, as well as organ-specific localisation of the sympathetic vasoconstrictor response to stress, are both seen as being involved in the pathogenesis of
autoimmune diseases, especially in relation to their frequent fluctuating clinical course.

We might note in passing that the sorts of antibodies produced under these various circumstances could also be giving us some indication of the level of cellular damage underlying them. Thus, with minor vasoconstrictor ischaemic damage, one might only expect alterations of the cell surface membrane, and therefore only antibodies arising against these. Where the damage were more severe, to involve say, the nucleus of the cell, various anti-nuclear antibodies might result. If ischaemic damage is indeed the trigger to auto-immune disease in the way suggested, then systemic lupus erythematosis and its associated DNA antibodies could be taken to reflect more extensive cell damage. Where such episodic damage were severe enough to actually kill cells in these circumstances, auto-immune phenomena as a reaction might be all one would find. But repetitive damage short of cell death might well cause profound disturbances of the cell genome, with consequent re-expression of evolutionarily-old genetic material, including retroviral elements, as the basis for antigenic stimulation of autoimmune conditions.

The present view of auto-immune disease, then, is that it may well be initiated by local vasoconstriction ischaemia of the organ or organs concerned, and that this subsequently triggers an inflammatory response, albeit of somewhat unusual nature because of the involvement of aberrant immunological mechanisms in its mediation.

CONCLUSION

In this chapter I have considered clinical conditions which run a relapsing and remitting course in relation to stress, in the light of the current vasoconstrictor theory. I cannot pretend that this has been an unbiased exercise. On the contrary, having developed the construct, in earlier chapters, that vasospasm may be important in specific vascular diseases, this section has deliberately set out to examine conditions of similar clinical pattern to see whether they, too, may be similarly explained. The stimulus for this approach was the view that it would be unlikely for sympathetically-induced vasoconstriction to be restricted to a special few areas of the circulation. Also, it seemed particularly important to examine any mechanism which had the potential for prevention and reversibility of disease.

At the very least it is clear that in attempting to understand these clinical patterns of disease, mere biochemistry and immunology cannot tell all. If we are to gain real insight into their nature we must provide working hypotheses which take account of the clinical as well as the more molecular aspects of the disease processes. Present day thinking tends to be far too much influenced by the reductionist molecular biology to the virtual neglect of pathophysiology and, as much as anything else, this chapter is an attempt to emphasise the importance of adopting a more balanced view.

Later in this book I intend to take up this general point on disease mechanisms further (Ch. 10), and discuss its possible relevance to other areas of conditions of obscure origin, but for the moment I want to pass on to a completely different area, namely the nature of cancer, and of the evolutionary process.

A final note before we leave what some will think is a rather iterative approach to understanding disease mechanisms. Even the uninitiated reader will have noticed that many of the references I quote are relatively old. True, though I have tried where important to update the
current text from the first edition of this book (1989). But, in a sense, the real test of such a theoretical text as this is whether it stands up to any criticism new data may have brought forth. I think it does, but you must be the judge.
References

22. Lewis T. Experiments relating to the peripheral mechanism involved in spasmodic arrest of the circulation in the fingers, a variety of raynaud's disease. Heart. 1929; 15:7-101.


