Fortnightly Review

Diabetic retinopathy

Eva M Kohner

Of all the long term complications of diabetes, retinopathy raises the most interest—and the most arguments. This is not only because it is a common cause of visual loss in patients of working age. It is also because, although the clinical course is well understood, the pathogenic mechanisms responsible for the lesions and the visual loss are not clearly defined. Nor do we really understand why in some patients retinopathy advances very rapidly and even careful follow up and early treatment cannot prevent visual loss, while in others retinopathy advances slowly and remains mild for many years.

Nevertheless in the past decade many advances have been made. Although many pieces in the jigsaw of retinopathy are still missing, we start to have a view of what goes wrong, and we soon may even have ideas of how we can prevent the sight threatening forms of retinopathy.

Summary points

- Diabetic retinopathy is primarily a disease of retinal capillaries, which eventually become occluded
- Large areas of non-perfusion lead to new vessel formation while small areas in the perifoveal area lead to leakage and macular oedema
- Treatment by photocoagulation is effective in maintaining vision in most patients provided it is adequate and given early
- Strict control of diabetes seems to give the best chance for delaying the onset and reducing the severity of diabetic retinopathy
- Because early lesions are asymptomatic, screening for retinopathy is essential and cost effective

Clinical course of diabetic retinopathy

Diabetic retinopathy is primarily a lesion of the retinal capillaries. This later extends to the larger vessels: veins, arterioles, and arteries (fig 1).

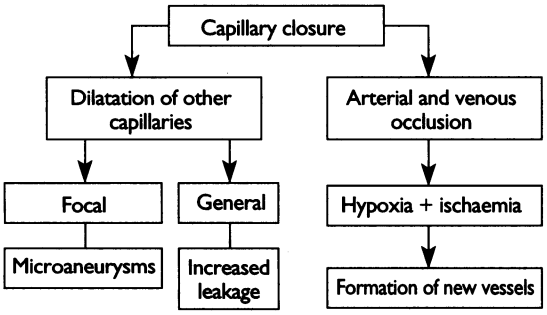

FIG 1—*Evolution of diabetic retinopathy*

Long before any clinically visible lesions develop there are histological changes, which include thickening of the basement membranes, loss of pericytes, and eventually the formation of microaneurysms, the earliest ophthalmoscopically visible lesions. In insulin dependent diabetes it is unusual to see such lesions before five years' duration of the disease; in non-insulin dependent diabetes up to 38% of patients may have microaneurysms at the time of diagnosis of diabetes, indicating that diagnosis in these patients may be long delayed.

The earliest lesions are seen only on fluorescein angiograms. They are small areas of non-perfusion. The response to non-perfusion of some capillaries is dilatation of others (fig 2). When this dilatation is localised, as seen most often, a microaneurysm forms, but dilatation can be generalised, and this is most commonly seen at the posterior pole in the macular region. Dilated capillaries are usually incompetent and leaky. It is this leakage from a reduced number of dilated capillaries that leads to the exudative and oedematous forms of the sight threatening diabetic macular oedema, diabetic maculopathy.

As more and more capillaries become occluded the larger vessels are affected. When arteries become involved there is always a large area of capillary nonperfusion (fig 2). When this occurs suddenly cotton wool spots are formed; when it occurs gradually only a featureless atrophic retina is visible. Large blot haemorrhages tend to form at the interface of the perfused and ischaemic areas of the retina. Dilated capillaries are seen in this largely avascular area and are known as intraretinal microvascular abnormalities. They may also form around cotton wool spots. Whether these abnormal vessels are new intraretinal vessels or just remaining dilated capillaries is largely immaterial; when present together with other lesions, especially abnormal dilatation and beading of the veins, they indicate that new preretinal vessels are likely to form in the next 6-18 months. Venous dilatation occurs relatively early in diabetic retinopathy and is of no specific importance. However, loop formation, beading, and reduplication, which probably indicate increased flow or occlusion, or both, are suggestive of imminent formation of new vessels. These lesions are therefore considered to represent preproliferative retinopathy (box 1; fig 3).

New vessels usually form from veins in the retinal periphery or on the optic disc. They arise only when there are large areas of avascular retina. They grow uncontrolled and develop a fibrous tissue covering. As the new vessels break through the internal limiting

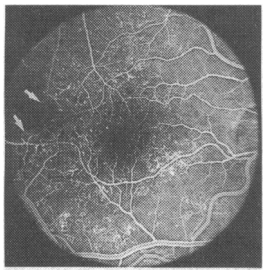

FIG 2—*Fluorescein angiogram of right macular area of patients with multiple capillary abnormalities, showing small areas of capillary closure. Large area of non-perfusion is associated with abnormalities of arterioles and venuoles (arrows)*

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Box 1—Preproliferative lesions

- Intraretinal microvascular abnormalities (IRMA)
- Venous changes (beading, loops, reduplication)
- Multiple cotton wool spots
- Clusters and large blot haemorrhages
- White lines replacing arteries

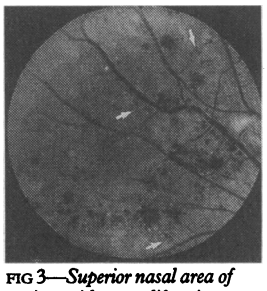

FIG 3—*Superior nasal area of patient with preproliferative retinopathy, showing venous beading, cotton wool spots, cluster haemorrhages, and intraretinal microvascular abnormalities (arrows)*

membrane they become attached to the posterior surface of the vitreous, which they use as a scaffold on which they grow. The retracting vitreous pulls on the vessels, causing haemorrhage; the expanding fibrous tissue tends to contract, causing retinal traction and detachment. The visual loss related to these abnormalities is sudden and unexpected. The new vessels themselves do not cause any visual symptoms; it is the complications of new vessels that are responsible for visual loss in most patients with insulin dependent diabetes. The sudden visual loss is in contrast to the visual loss seen in diabetic macular oedema, where vision fails gradually as the fluid accumulates at the fovea. Patients with insulin dependent diabetes may lose vision from macular oedema, but this is only occasionally profound or (especially when associated with renal failure) blinding. In older patients, usually those with non-insulin dependent diabetes, macular oedema is associated with ischaemia or extensive formation of hard exudate and is the main cause of visual loss due to diabetic retinopathy.

Pathogenic mechanisms

Several factors are important in the evolution of diabetic retinopathy. These are metabolic, endocrine, and haemodynamic. The factors are not independent but tend to interact. The key factor is a high glucose concentration, which triggers and maintains all the other abnormalities.

GLUCOSE TOXICITY

As diabetes is characterised by high blood glucose concentrations, this characteristic is blamed for many of the ills of diabetic retinopathy. On the clinical level it is well established that diabetic retinopathy, especially its proliferative manifestations, is more common and more severe in patients with poor control of diabetes.[1] Engerman showed that not only glucose but other hexose sugars can in dogs induce diabetic or diabetes-like retinopathy.[2] The mechanism of glucose toxicity in vascular cells has been reviewed by Lorenzi.[3]

Effect on pericytes

The earliest visible lesions, microaneurysms, occur only in areas where pericytes, an important constituent of the wall of the retinal microvessels, are lost. Cell culture has shown that normal proliferation of pericytes is inhibited by high glucose concentrations in the incubating medium. This inhibition is dose related and is observed from 15-20 mmol/l glucose. Glucose toxicity was thought to be related to activation of the polyol pathway, and early work suggested that it could be prevented or at least delayed by aldose reductase inhibitors.[4] More recent work suggests that this is not so; tolrestat, an effective inhibitor of aldose reductase, was able to reduce sorbitol levels in the pericytes by 98% but this did not stop the reduced proliferation. In contrast, aminoguanidine had a beneficial effect (unpublished data). This could mean that glycation is more important than sorbitol accumulation, or that other factors, such as nitric oxide synthetase activity, are key factors in pericyte loss. It is argued that pericytes do not proliferate in vivo, but it must be understood that in cell culture work pericytes are cultured by themselves, while in life endothelial cells and pericytes interact and endothelial cells have a controlling influence on pericytes.

Even when pericytes survive, their function may be impaired by high glucose. Pericytes have contractile properties and are responsible for controlling the capillary diameter. For contraction to occur, diacylglycerol and protein kinase C have to be activated. Endothelin-1 is such an activator. High glucose concentrations reduce the effect of endothelin and the activity of diacylglycerol and protein kinase C.[5]

Effect on endothelial cells

In elegant experiments Cagliero *et al* showed that endothelial cells from the umbilical vein—in particular fibronectin, collagen IV, and laminin—incubated in high glucose medium secreted more basement membrane material than when incubated in normal levels of glucose.[6] The abnormal gene expression for these substances continues when endothelial cells are returned to normal glucose medium.[7] This finding is important because we know from the work of Oldridge and d'Amore that pericytes when in direct contact with endothelial cells control their proliferation.[8] Thickened basement membrane may prevent the contact between the two types of cells.

A further toxic effect of high glucose concentration is on the production and action of endothelin. Endothelin-1, a powerful vasoconstrictor, is produced in endothelial cells. In most tissues it is bound to smooth muscle cells. In the retina, receptors have been located on the pericytes, which act like smooth muscle. Endothelin-1 production in the endothelial cells is reduced in high glucose medium. The reduced endothelin concentration and the interference with activation of protein kinase C in pericytes could be a direct cause for dilatation of the capillaries. This dilatation is often noted in diabetic retinopathy and confirmed in histological studies.

High glucose and blood flow

In experimental animals, high glucose concentration (whether induced by bolus injection or gradual rise in glucose by infusion) results in a considerable increase in blood flow.[9] This increase is related to the concentration of glucose. In humans with mild diabetic retinopathy, improved control of diabetes usually results in prompt reduction of blood flow.[10] Increased blood flow is associated with conditions that worsen retinopathy; these include, beside hyperglycaemia, high blood pressure, pregnancy, and autonomic neuropathy. In contrast, conditions that reduce retinal blood flow tend to protect from advancing retinopathy; these include moderate carotid stenosis and raised intraocular pressure. In a study of 100 diabetic patients Patel *et al* found that blood flow in patients without retinopathy was similar to that in normal subjects but increased progressively with increasing severity of retinopathy. After effective photocoagulation of new vessels, retinal blood flow was significantly reduced.[11]

By increasing blood flow, high glucose concentrations also interfere with normal autoregulation. In its strictest sense autoregulation is defined as the ability of the blood vessels to keep blood flow constant under varying perfusion pressure. In non-diabetic patients blood flow stays constant or increases only slightly until the rise in mean arterial pressure is about 40%. At that level autoregulation breaks down and flow increases. In diabetic patients with blood glucose concentrations in the normal range (<10 mmol/l) autoregulation breaks down at a rise in mean arterial pressure of only 30%; in diabetic patients with high glucose concentrations (>15 mmol/l) autoregulation is absent even when the rise in blood pressure is only 15%, the blood flow increasing by 25%. At 40% rise in blood pressure the flow is double that at baseline

(unpublished data). This increased flow will increase the shear stress, which is directly related to blood flow. Such an increase will undoubtedly damage the endothelial lining of the vessel. Thus the deleterious effect of hypertension in diabetes can be explained (fig 4).

Shear stress is also directly related to the viscosity of blood. In diabetic patients viscosity is usually increased; again this is worst in those with the highest concentrations of glucose.

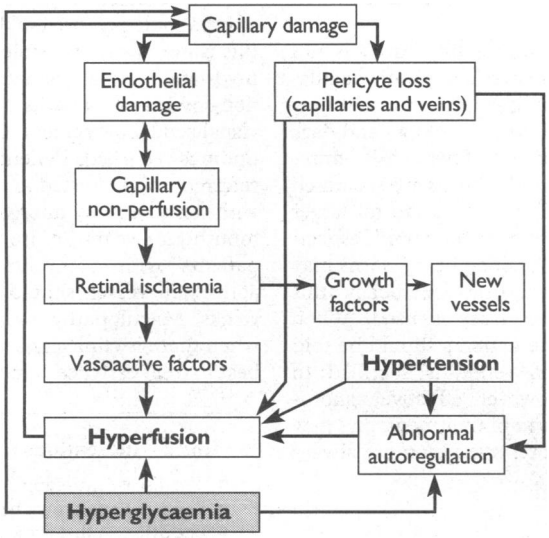

FIG 4—*Role of hyperglycaemia in evolution of diabetic retinopathy*

FACTORS IMPORTANT IN CAPILLARY CLOSURE

Probably the most important factor in capillary wall damage is the high glucose concentration damaging endothelial cells and leading to increased shear stress and increased viscosity. Other features are also related to endothelial cell damage. Increased platelet aggregation, probably secondary to the vessel wall damage, may hasten occlusion of capillaries. Aspirin, a powerful antiaggregating agent, has been shown to slow progression of early diabetic retinopathy.[12] Decreased red cell deformability associated with reduced insulin concentrations will increase viscosity. White cells may add to vessel wall damage by liberating toxic substances, thereby increasing oxidative stress.

Basement membrane thickening is caused not only by increased formation of basement membranes but also by glycation of the proteins, which leads to reduced breakdown and also stiffening of the vessel wall. In Took's theory this stiffening leads to locking of the vessel wall: it loses its ability to change diameter to conform to metabolic needs.[13]

CONSEQUENCES OF CAPILLARY CLOSURE

Small areas of capillary closure result in dilated capillaries and increased intracapillary pressure. This will lead to leakage through the vessel wall. Normally, fluid leaking out of the vessels is absorbed and returned to the circulation by a sodium pump. If this is impaired—for example, by administration of probenecid—fluid will accumulate. In diabetes there is evidence that this outward pumping action, located in the pigment epithelium, is impaired.[14] Thus increased leakage and reduced removal of fluid results in fluid accumulation, which is greatest in the macular region, giving rise to macular oedema and visual loss.

Large areas of capillary occlusion, with involvement of arterioles and venules, lead to formation of new vessels. We do not know exactly what the steps and factors involved in this process are, but ischaemia and hypoxia both seem to be important. A hypoxic retina seems to liberate factors that stimulate the growth of new vessels. Endothelial cell cultures in hypoxic medium seem to express more messenger RNA for insulin-like growth factor (IGF-1) and basic fibroblast growth factor than is usual. The receptors are also more sensitive to the fibroblast growth factor liberated from extracellular matrix and dying endothelial cells.[15] Furthermore, basic fibroblast growth factor can transform endothelial cells from the stationary to a motile spindle form.[16] This is important because the first step in new vessel formation is dissolution of extracellular matrix. This is brought about by secretion of proteoglycans by the endothelial cells (the stimulus for this is not clear) and is followed by cellular migration and proliferation.

High concentrations of IGF-1 have been found in the blood of patients with active proliferating new vessels; these concentrations were reduced after effective photocoagulation. High concentrations of IGF-1 were also found in the vitreous of diabetic patients. High concentrations of IGF-1 may be secreted by the liver; an increase in growth hormone and abnormal control of growth hormone secretion is well documented in diabetic retinopathy.[17,18] However, as IGF-1 concentrations are reduced after effective photocoagulation and no other change in treatment, the retina may play an important part in regulating IGF-1 secretion.[19] The role of growth hormone is even less clear. Ablation of the pituitary was a most successful treatment of proliferative diabetic retinopathy,[20] and the effectiveness was related to the degree of growth hormone deficiency.

Although several factors in new vessel formation are known, the precise steps are still awaiting elucidation. The imbalance between growth stimulatory and inhibitory factors may be crucial, but at present we do not know the individual function and interaction of these factors.

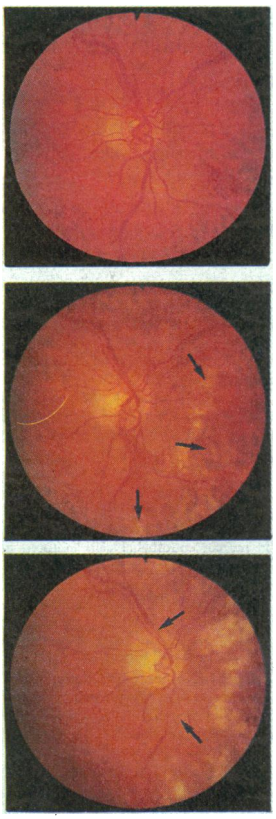

FIG 5—*(top) Disc new vessels before photocoagulation. (middle) Photocoagulation scars (arrows) on nasal side, above and below disc. Very light photocoagulation; new vessels have not regressed. (bottom) With heavier photocoagulation the new vessels have completely disappeared; light fibrous tissue remaining harmless*

Treatment of diabetic retinopathy

The only effective treatment of diabetic retinopathy is photocoagulation. This treatment is effective for the sight threatening lesions of macular oedema and proliferative retinopathy. For complications of new vessels (haemorrhage, detachment, and membrane formation) vitrectomy offers sight restoring possibilities, but in most instances adequate photocoagulation given in good time will prevent the complications of the new vessels.

PHOTOCOAGULATION

Photocoagulation for new vessels was shown to be effective as long ago as 1977.[21] It is particularly effective in preventing visual loss due to new vessels on the optic disc and in eyes with high risk characteristics. For the treatment to be effective it has to be early—that is, before a clinically important amount of fibrous tissue has formed, before the new vessels are firmly established, and before they bleed. The treatment also has to be adequate: it is important to treat all areas of avascular retina. The type of laser used is immaterial; most of those used for retinal work will have a beneficial effect. Regression of new vessels is usually seen within 3-4 weeks; if it is incomplete further treatment has to be given (fig 5). In nine out of 10 patients given early treatment, either the new vessels disappear or only inactive vestiges remain. In some patients over 7000 argon laser burns are necessary to get rid of the new vessels. Once treatment is effective, results are long lasting—in the Hammersmith series, two thirds of patients with initially good vision maintained this over 10 years.[22]

In maculopathy, treatment has less of an effect. Only six out of 10 patients benefit, and the long term effect is less striking.[23] However, here too early treatment seems to be most effective, as shown in the British multicentre study[26] and, more convincingly because of

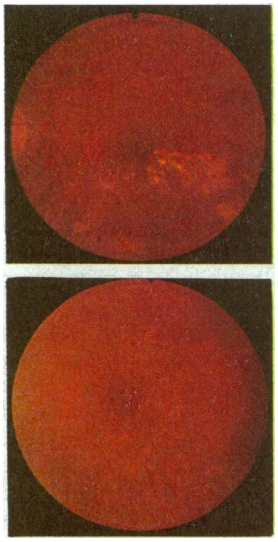

FIG 6—*(top) Left macular area showing large hard exudate ring with microvascular abnormalities and haemorrhages within the ring. Visual acuity 6/18. (bottom) Same area, six months after photocoagulation completed. Hard exudate completely gone, but other new lesions lateral to macula. Visual acuity 6/9*

the larger numbers, the early treatment of diabetic retinopathy study.[25,26] Photocoagulation is most effective in patients with exudative maculopathy—treatment of the microvascular lesions in the centre of hard exudate rings is almost always successful (fig 6). This type of maculopathy is the most common. Cystoid oedema, for which grid treatment is used, responds less well, and ischaemic maculopathy, in which a large area of perifoveal non-perfusion is associated with intracellular oedema, almost never responds to treatment.

Photocoagulation is often successful, but it is not without side effects. After panretinal photocoagulation, especially if this is heavy owing to resistant new vessels, there is almost always visual field loss and dark adaptation may become impaired. This can be minimised and in many cases avoided if burns are separated by areas of viable retina and the burns are no larger than 200 μm. Colour vision is often impaired, especially if the treatment is perifoveal. Too heavy burns may result in choroidal neovascularisation; luckily this is infrequent when the argon laser is used. When receiving photocoagulation the patients should be told that peripheral and diseased retina is sacrified to maintain central vision. However effective, photocoagulation is a destructive form of treatment, and new forms of treatment that will preserve vision are always being sought.

VITRECTOMY

Vitrectomy can restore vision in eyes that have lost vision from the complications of new vessels. It is always a time consuming and expensive operation and should be carried out only by vitreoretinal specialists experienced in the procedure. With increasing skills and operative techniques the results are often impressive, and some specialists advocate earlier vitrectomies at times when vision is still good but tractional complications are severe. It should be remembered that timely adequate photocoagulation will eliminate the need for most vitrectomies.

Prevention of sight threatening diabetic retinopathy

CONTROL OF DIABETES

Since high glucose is the hallmark of diabetes, control of this was thought to be of paramount importance in preventing diabetic retinopathy. Early work by Job *et al* suggested that more physiological insulin treatment could slow the advance of retinopathy,[27] but valid randomised controlled studies could not be performed until the 1980s when home monitoring and estimation of glycated haemoglobin became available. Technological improvements (pumps and pens) also allowed for more intensive treatment of diabetes. Short term studies did not show improvement of non-proliferative retinopathy,[28] but longer follow up showed that progression of retinopathy was reduced in those with better control.[29] The recent study from Stockholm,[30] and most importantly the diabetes control and complications study reported at the American Diabetes Association in 1993 show beyond any doubt that in patients with insulin dependent diabetes, intensified treatment with insulin reduces the incidence of diabetic retinopathy by 60% and also reduces the progression of retinopathy from background to the proliferative form by 60%. No such dramatic effect is seen in patients with non-insulin dependent diabetes; after 10 years the United Kingdom prospective diabetes study has found no striking differences between treatment groups.[31]

SCREENING

Once retinopathy is present, even if control is good retinopathy may advance. Photocoagulation is most effective when applied early, before there is any visual loss and before there are complications of new vessels. Since early retinopathy is symptomless, and since effective treatment is available for the prevention of visual loss, screening for retinopathy is a worthwhile procedure (box 2). The St Vincent declaration emphasises the aim of reducing diabetes related blindness by a third[32]; for this it is essential that we establish screening programmes. Ideally all diabetic people should be screened by a dedicated doctor trained in ophthalmology, preferably an ophthalmologist, but this is not always possible. Either optometrists or non-mydriatic retinal cameras can be used, but with non-mydriatic cameras the peripheral retina is never visualised. The screening should be regular and the findings recorded. Patients with retinopathy should be referred to interested ophthalmologists. While those with only a few microaneurysms can be seen six monthly or yearly, more urgent referral is needed for patients with preproliferative lesions. Those with active new vessels should be treated within two to four weeks. Maculopathy is thought to be less urgent, but when there is clinically important macular oedema it is best to treat early, certainly within six weeks.

Box 2—Indications for establishing screening

- The disease must appear in a defined population
- The population must be identifiable
- The disease must present a health problem
- There must be an effective treatment for the disease
- Screening must be cost effective in financial terms and concerning quality of life

Screening should be yearly[33] for patients with insulin dependent or non-insulin dependent diabetes. There is no evidence that less frequent screening will suffice or would be easier to carry out.

It is possible that good control of blood glucose, adequate screening, and early treatment will reduce blindness related to diabetes. It is hoped that further research will identify the pathogenic steps and that this will lead to more effective forms of treatment so that in future no one with diabetes will have to lose vision.

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Fully informed consent can be needlessly cruel

Jeffrey S Tobias, Robert L Souhami

The past 20 years have seen a welcome change from the traditional paternalist view of the patient as passive recipient of medical advice. This development results from the increasing range of treatment options now available, the wider discussion of these choices both within the profession and more publicly by the media. Patients now wish to participate in decisions about their clinical management to a far greater degree than formerly.

At the same time clinical choices have become increasingly underpinned by reliable outcome data, chiefly as a result of randomised clinical trials, which are now accepted as the best method of determining the relative benefits of competing treatments.[1] Such trials have been highly influential in changing the clinical management of common conditions both in the United Kingdom and elsewhere.[2,3] In our own specialty of cancer medicine, new approaches in chemoprophylaxis and in screening, novel chemotherapy techniques, unconventional radiotherapy fractionation, and so on can be rigorously evaluated only by randomised clinical trials. Though expensive, time consuming, and labour intensive, these trials are fully justified by the considerable human and financial implications of erroneously introducing a doubtfully effective remedy. They are also essential for providing quantitative evaluation of the degree of benefit obtained with a successful new treatment.

Many investigators have found that the practical and ethical problems of conducting randomised clinical trials greatly inhibit their incorporation into clinical practice. As an extreme position, some oncologists have even argued that such trials will have to be replaced by other methods of evaluation,[4] but no methods have yet been developed that would eliminate the possibility of moderate biases which might distort the results of a new treatment capable of producing a small but important survival difference. To undermine the use of randomised clinical trials when no alternative has been found is unhelpful. Good medical care for the individual patient should be entirely compatible with enthusiastic recruitment into randomised trials. We must not label randomised clinical trials as unethical just because they are difficult to perform.

Practical difficulty of informed consent

One of the most important ethical and practical difficulties in randomised clinical trials concerns the nature of informed consent. Every patient has the right to be treated in the best possible way for his or her condition and to be as well informed as he or she wishes about the possible approaches available. On the other hand there is the urgent need to validate new treatments. The conflict that may arise between these positions has resulted in many cancer physicians feeling (and expressing) considerable anxiety about the constraining effects of the informed consent procedure as an essential prelude to a patient's participation in clinical trials, particularly randomised clinical trials.[5]

The issue of informed consent has thus become a major barrier to the successful conduct of randomised clinical trials in cancer. The many practical difficulties have led to low levels of recruitment, especially where there is a substantial difference between the treatment policies being compared. In our judgment the medical profession has been unnecessarily defensive and, by and large, has failed to point out that the ethical positions which have been generally accepted are themselves contradictory and impractical. In our view, attempts to gain the "informed" participation of patients in randomised clinical trials are already doing harm in many individual cases.

Most clinicians recognise that the anxious patient sitting opposite them in the consulting room requires, above all, reassurance and a clear exposition of what needs to be done to provide a cure. An increasing degree of frankness on the part of the doctor, for the most part laudible and constructive, may cause considerable anxiety in those patients who would prefer to be directed rather than to participate as an equal partner. It might surprise many to know that this group of patients may include highly sophisticated professionals,[6] for instance the late Dr Franz Ingelfinger, for many years the editor of the *New England Journal of Medicine* until shortly before his death from cancer. Having been diagnosed as suffering from a potentially terminal illness, he wrote:

"I received from physician friends throughout the country a barrage of well-intentioned but contradictory advice ... as a result not only I but my wife, my son, and daughter in law (all doctors), and other family members became increasingly confused and emotionally distraught. Finally when the pangs of indecision had become nearly intolerable, one wise physician friend said "what you need is a doctor." He was telling me to forget the information I already had and the information I was receiving from many quarters, and to seek instead a person who would tell me what to do, who would in a paternalistic manner assume responsibility for my care. When this excellent advice was followed, my family and I sensed immediate and immense relief. The incapacity of enervating worry was dispelled, and I could return to my usual anxieties such as deciding on the fate of manuscripts."

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