has been scientifically assessed,[2] when a controlled trial showed that 11-cis vitamin A produced no benefit in patients, reversing the clinical impression previously reported by the same authors.[3] The Russian remedy consists of courses of injections of yeast RNA and nucleotide preparations, each course lasting about one month, and two courses a year being recommended. This form of treatment has been given not only for the various types of retinitis pigmentosa, but also for hereditary retinal disorders such as Stargardt's macular dystrophy and for other inherited degenerations.[4]

Research is now being undertaken into the basic metabolism of the retina and a search is being made for the metabolic defects which may give rise to these genetically determined diseases. Some progress, albeit slow, has at last been achieved. But it would be naive to believe that a single therapeutic approach aimed at several genetically distinct disorders is likely to achieve meaningful results.

In otherwise untreatable blinding disorders there is considerable pressure on doctors, both from patients and from other well-meaning individuals and organisations, to produce some form of treatment. There is a temptation to publicise experimental therapeutic regimens before evidence is available about their theoretical basis for success or their clinical efficacy as assessed by scientifically designed trials. In slowly progressive disorders the design of such trials may be difficult, and results may take years to evaluate. Meanwhile, however, we must remember that apparent temporary improvement after treatment in such conditions may result from natural fluctuations in the course of the disease as well as from the placebo effect.

As yet there has been no scientifically acceptable evidence for the efficacy of the treatment of retinitis pigmentosa, which is now being assessed by Trutneva and her colleagues.[4] The paucity of information on the scientific basis for this treatment and its clinical effects, and the economic loss and psychological trauma suffered by patients seeking it, should both be deplored. Equally, the publicity that the treatment has engendered should be condemned. False hopes are cruel deceptions.

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[3] Chatzinoff, A, *et al*, *American Journal of Ophthalmology*, 1958, **46**, no 1, pt 2, 205.
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Sickle cell trait

The heterozygous state for the sickle cell gene, the sickle cell trait, is characterised by the presence of between 20% and 50% sickle haemoglobin. Undoubtedly in conditions of extreme anoxia these levels of Hb S may give rise to vascular occlusive episodes similar to those occurring in sickle cell disease. But in normal conditions do these amounts of abnormal haemoglobin have any pathogenic role?

The pathogenicity of sickle haemoglobin depends on the degree of anoxia in a particular capillary bed, which in turn is determined by environmental oxygen tensions, gas transfer in the lungs, and local circulatory conditions. For example, the sluggish, apparently poorly organised perfusion of the spleen makes it susceptible to vascular occlusive episodes in conditions of environmental hypoxia—such as in high-flying unpressurised aircraft, when 11 patients out of 16 with splenic infarction were found to have the sickle cell trait.[1] Similar episodes have occurred in climbers at high altitude.[2 3] The renal medulla is another capillary bed where conditions of oxygen tension, pH, and tonicity are all conducive to sickling, and renal disorders including pyelonephritis, asymptomatic bacteriuria, haematuria, and renal papillary necrosis are all more common in individuals with sickle cell trait than in the general population.[4–6] Nevertheless, while in these two examples there is both a logical mechanism and reasonable statistical evidence, any other possible pathogenicity of the sickle cell trait remains highly controversial.

Many case reports exist in which lesions compatible with a vascular occlusive origin have been described in patients with the sickle cell trait. The coincidence alone may have prompted the writing and publication of the report; but, while stimulating interest, such accounts have often lacked adequate diagnostic and statistical evidence for incrimination of the trait. Whereas most haematologists can diagnose the sickle cell trait with little difficulty, clinicians do not always appreciate that a positive sickle cell preparation and a normal haemoglobin level are also compatible with sickle cell-haemoglobin C disease and sickle cell-β^+ thalassaemia. Confirmation of the trait requires detection of Hb S by sickling or solubility tests and the electrophoretic demonstration of two major haemoglobin bands in the positions of Hb A and Hb S. Furthermore, the relative quantities of these haemoglobins may be important, since this electrophoretic pattern bears a superficial resemblance to that in the type of sickle cell-β thalassaemia containing HbA ($S\beta^+$ thalassaemia). In the latter condition the level of Hb A rarely exceeds 30%, whereas in the sickle cell trait levels below 60% are unusual. Hb A therefore predominates over Hb S in the sickle cell trait and the opposite occurs in $S\beta^+$ thalassaemia. Measurement of the amount of Hb S in the trait may be useful for other reasons, since logically any pathological consequences should be more frequent in cases with high levels of Hb S.

With the correct haematological diagnosis confirmed, proof of an association with the trait requires one of two conditions to be fulfilled. Either the characteristics associated with the sickle cell trait differ significantly from those associated with normal haemoglobin in a given population, or a significantly increased prevalence of the trait occurs in a defined pathological condition. In an example of the former type of study the height, weight, blood pressure, electrocardiographic patterns, and haemoglobin values were compared in people with AA and AS in a geographically confined Jamaican community. No significant differences were found,[5] but asymptomatic bacteriuria was significantly more common among women with the AS than with the AA genotype. Examples of the latter type of investigation include the finding of the sickle cell trait in 29% of cases of haematuria[7] or in 19% of cases of leg ulceration,[8] compared with a trait rate of 10·5% in the general population. Even such apparently valid statistical associations cannot, however, be interpreted as substantiating the causal role of Hb S: it is still possible that associated or even linked genetic factors may be important.

The sickle cell trait reaches a high prevalence among Black populations (8% in North America, 11% in the Caribbean, and 20-30% in equatorial Africa), and evidently most carriers suffer little or no disability from it. Extreme caution is required, therefore, in interpreting reports attributing pathological consequences to the trait. A recent study in the USA appeared to indicate that aspects of physical and mental development were impaired in children with the AS compared

to those with the AA genotype.[9] The groups were not, however, matched by socioeconomic and other factors that might have contributed to the observed difference, and the selection of subjects from twin studies may have further complicated assessment. A study from Jamaica (p 1371) appears to reach different conclusions. Both investigations concerned small numbers of people, and clearly more extensive studies are required; but the prevalence of the trait and the far-reaching implications of any possible pathogenicity demand that these should be based on impeccable diagnostic and epidemiological criteria.

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Radiotherapy and the heart in Hodgkin's disease

Many treatments in medicine and surgery are not totally safe. To put a risk into perspective we need to study its incidence in various circumstances and, in the case of drugs or radiation, at various dosage levels. Every risk and every hope of benefit must be weighed against the hazards and benefits of alternative courses of action (or inaction). If we are too complacent, patients may be put at risk before the danger is fully appreciated. If we are too alarmist, those who would benefit from a treatment may be denied it because of exaggerated fears of its effects.

A recent report in the *American Journal of Medicine*[1] has described two fairly young men who had coronary attacks some years after successful treatment for Hodgkin's disease, and one of them died. Was mediastinal radiotherapy responsible? While agreeing that other factors may have played a part (one of them had smoked 40 cigarettes a day), the American authors argued that it probably was. They had found four other reports of young men who had died in similar circumstances, necropsy confirming that coronary disease, not recurrent Hodgkin's disease, had caused death.

Isolated reports of this kind serve a useful purpose but may easily give a false impression of the size of the problem. Reviews[2–4] of all the experimental and clinical evidence, undertaken over the last 50 years, have concluded that the heart stands up surprisingly well to radiation, often showing not the slightest electrocardiographic or histological abnormality even after absorbing large doses. When electrocardiographic changes have occurred they have been mostly trivial and transient and sometimes due to other causes.[3] Many thousands of patients with breast cancer have survived in good health for many years after quite intensive radiation to part of the heart in the course of radiotherapy to the parasternal lymph glands. No evidence has been found of any increased incidence of heart disease in these women.

When the mediastinal glands are irradiated in Hodgkin's disease the dose absorbed by the heart (or a portion of it) will vary considerably, not only with the dose chosen for the target lymph glands but also according to the technique. For this reason the incidence of cardiac effects reported from one centre (for example, 6% at Stanford University[4]) may not apply to another. Many centres seem to avoid these complications completely, perhaps partly by giving a dose which others might regard as less than optimal. At the other extreme, Byhardt *et al*[5] recently reported no fewer than 24 cases of pericardial effusion in 83 patients given mediastinal radiation. Nevertheless, 10 out of the 24 were symptomless; Hodgkin's disease itself occasionally affects the pericardium; and radiation was given mainly by a single anterior beam giving an average pericardial dose of 5325 rads. This was more than the mediastinal glands themselves received and is considerably above the dose received by the heart when treated by some of the techniques commonly used in other centres.

Patients with existing heart disease might be thought to be especially at risk, but there is no evidence that this is so. Indeed, controlled experiments in dogs have actually shown a beneficial effect, radiated animals showing a higher survival rate after coronary artery ligation.[6]

Hence probably there is no good evidence that heart muscle and its blood supply are any more susceptible to radiation than any other muscle. Most radiotherapy centres use a dose technique for mediastinal Hodgkin's disease which probably carries only a small risk of contributing to future heart disease. But vigilance and further study are required, preferably always with expert assessment of the dose received at different points in the heart and mediastinum.

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Boys who are too tall

Being too short or too tall may be a social or psychological disability—and sometimes both. Yet it is easier to find a consensus of opinion on a height that is too short for psychological comfort than to determine what would be considered excessive. Last year we reviewed[1] attempts to limit the height of healthy girls whose growth promised to make them excessively tall. More recently Zachmann *et al*[2] have attempted to limit the growth of boys whose predicted height was over 198 cm.

Clearly the success of attempts to limit children's growth must depend on the accuracy with which eventual height can be predicted. The work of Tanner and his associates[3] does allow a usefully accurate prediction for normal children. Pathological causes of excess height, such as an over-secretion of growth hormone or cerebral gigantism, have to be excluded. For boys from 4 to 12 years the prediction of eventual height is accurate within ± 7 cm. Using this method, Zachmann's group found that the best results from treatment with testosterone came in boys at the onset of puberty whose bone age was about 12 years; they calculated that eventual height was curtailed by 8 cm. As they point out, their treatment was completely