Hypothesis into theory – the development of aetiological concepts of ischaemic heart disease: a review

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Good hypotheses die young. Most often they are rejected; sometimes, like the lipid hypothesis, they evolve into a well-supported theory with clinical and public health implications (Stamler *et al.* 1972). In my view this theory is now as tenable as many of the conceptual bases of current medical practice. Our understanding of the pathogenesis of atheroma is far from complete; but our knowledge of environmental and genetic factors which influence the natural history and severity of coronary atherosclerosis is very substantial.

New insights have been obtained into the development of atheromatous plaques (Ross & Glomset 1976, Ross *et al.* 1977). Possible mechanisms for the characteristic smooth muscle hyperplasia have emerged. In tissue culture, proliferation of arterial smooth muscle is stimulated by a factor released by aggregating platelets (Rutherford & Ross 1976); certain lipoproteins share this growth-promoting property (Chen *et al.* 1977, Bierman & Albers 1975). Evidence has been presented that each plaque contains a single clone of smooth muscle cells (Benditt & Benditt 1973, Benditt 1977); this concept could explain the patchy distribution of atheroma, and is quite compatible with our knowledge of the role of environmentally-determined risk factors (*Lancet* 1977). The rate at which the cholesterol-rich low-density lipoprotein enters arterial intima has been measured *in vivo* (Niehaus *et al.* 1977); it is directly proportional to the concentration of this lipoprotein in plasma.

Association and cause: epidemiology and experimental data

The epidemiology of ischaemic heart disease (IHD) has been extensively reviewed (Stamler *et al.* 1972, Inter-Society Commission for Heart Disease Resources 1970); it includes data from case-control studies (Lewis, Chait, Oakley *et al.* 1974; Carlson & Ericsson 1975), comparisons of populations with differing IHD mortality rates (Keys 1970, McGill 1968, Lewis *et al.* 1978, Oliver *et al.* 1975) and prospective within-population surveys (Stamler *et al.* 1972, Inter-Society Commission for Heart Disease Resources 1970, Carlson & Böttiger 1972, Miller *et al.* 1977, Carlson *et al.* 1975). Several variables have been found to be associated with IHD, including predictive associations, i.e. risk factors. The parsimonious interpretation is that these associations are causal.

Experimental data (including trials of preventive measures) favour this interpretation and suggest that hypercholesterolaemia, high saturated fatty acid consumption, cigarette smoking and hypertension are amongst the major causes of IHD. A current list of risk factors appears in Table 1. In several animal species, hyperlipidaemia followed by lesions resembling human atherosclerosis are induced by high saturated fat and/or high cholesterol diets (Rowsell *et al.* 1958, Kritchevsky 1969, Wissler 1968); such differences as may exist can reasonably be attributed to compression of the long natural history of human atheroma into brief experiments. This relationship is highly consistent and has been abundantly confirmed over the

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Table 1. Risk factors

Metabolic	Hypercholesterolaemia
	Hypertriglyceridaemia
	Low HDL levels
	Diabetes
Non-metabolic	Cigarette smoking
	Hypertension
	Personality type
Other risk-related factors	Familial aggregation
	Water softness
	Sedentary behaviour
	Obesity
	Stress
	High ESR
	Coffee
	Resting tachycardia
	Short stature
	Minor ECG abnormalities

past 70 years. In primates, gross diet-induced atheroma shows considerable regression when plasma cholesterol levels are reduced (Armstrong & Megan 1972, Wissler *et al.* 1975, Armstrong 1976). There is limited evidence for regression of human atheroma (Armstrong 1976, Barndt *et al.* 1977). These findings strongly suggest that hypercholesterolaemia is a cause of atheroma.

The 'natural experiment' of familial hypercholesterolaemia exemplifies the role of high cholesterol concentrations in atherogenesis. Fifty percent of affected men develop IHD by age 50, far in excess of the frequency in those unaffected (Slack 1969, Stone *et al.* 1974). In males IHD can be regarded as part of the natural history of this disease. In heterozygotes (but perhaps not in homozygotes) the arterial disease is typical atherosclerosis (Roberts *et al.* 1973).

Controlled trials of lipid-lowering regimes were reviewed by Shaper in 1975. Though none was impeccably designed, all three major dietary trials showed a lower IHD incidence in previously-healthy men, despite widely-differing experimental designs (Rinzler 1968, Dayton *et al.* 1969, Miettinen *et al.* 1972). This was so although the fall in cholesterol levels was fairly small, and although in one study the average age of the subjects was 65 years (Dayton *et al.* 1969). Earlier trials of secondary prevention of IHD were less consistent (Medical Research Council Research Committee 1968, Leren 1966), but recent studies with potent lipid-lowering drugs are encouraging. In the study by Carlson *et al.* (1977) the combination of clofibrate with nicotinic acid halved the incidence of non-fatal reinfarction, with a non-significant decrease in fatal events. The trial by Dorr *et al.* (1978) involved 2278 hypercholesterolaemic men, a more informative design than that of other studies which included subjects with 'normal' lipid levels and those with various types of hyperlipidaemia. A sustained reduction of serum cholesterol by about 1 mmol/l was produced by the drug colestipol. Coronary disease mortality was reduced in men with preexisting IHD (9 deaths cf 22 in the placebo group); there were 3 deaths from acute myocardial infarction (15 among controls). Men over 60 years of age and women did not show significant benefit.

The well-documented fall in IHD mortality in Western European countries during World War II does not implicate any individual environmental change: reduced saturated fat intake, decreased smoking and increased exercise may all have contributed. Of great interest is the 20% fall in IHD mortality in the USA between 1963 and 1975 (Walker 1977). A similar trend is discernible in the age group 35–54 in Australia (Working Group on Diet and Coronary Heart Disease of the Australian Academy of Science 1975). Again, responsible environmental factors have not been identified; mean serum cholesterol levels have decreased slightly and the ratio of polyunsaturated fat to saturated fat in the American diet has increased from 0.2–0.3 (as it is at present in the UK) to 0.5–0.6. Smoking habits are less likely to be implicated (Gordon & Thom 1975). Improved detection and treatment of hypertension may have contributed.

IHD mortality in ex-smokers is considerably less than in smokers (Hammond & Garfinkel 1969, Doll & Peto 1976). The incidence of fatal plus non-fatal cardiac infarction in hypertensives is now known to be decreased by treatment (Veterans Administration Cooperative Study Group 1972, Berglund *et al.* 1978), significantly so in the latter study.

There is, then, growing evidence to show that reduction in cholesterol levels, blood pressure and cigarette use all, independently, decrease IHD risk. As these risk factors are more synergistic than additive (Stamler *et al.* 1972) there are grounds for anticipating that intervention against all three factors may substantially reduce heart disease risk in men. There is as yet no evidence that cholesterol reduction is of value in women, nor in men aged over 60 years.

Assessment of abnormal lipid transport (Lewis 1976)

The ultimate decisions in this assessment are whether an abnormality of lipoprotein metabolism requires treatment, and the nature of such therapy. The clinician must analyse the risk of cardiovascular disease, and of other complications of hyperlipidaemia including pancreatitis and polyarthritis. His data base extends beyond measurements of cholesterol and triglyceride levels. The family history may reveal an aggregation of early-onset IHD, stroke or peripheral vascular disease (as a rough guide, prior to age 60). Such an aggregation is largely (Rissanen & Nikkilä 1977) but not entirely (Epstein 1976) due to familial hyperlipidaemias or hypertension. Family screening may be required to define the type and genetic basis of a hyperlipidaemia. Physical signs (xanthomas, arterial bruits) aid precise diagnosis. The younger the patient the greater the bias towards intervention, for the impact of risk factors must depend upon their duration. The significance of age may however be exaggerated: though it is true that hypercholesterolaemia ceases to be predictive of IHD risk beyond age 60, we know now that increased levels of low density lipoprotein, and low levels of HDL remain predictive in the elderly (Gordon *et al.* 1977*a*).

As a minimum, qualitative lipoprotein analysis is needed. Inspection of stored serum (Lewis 1976) distinguishes endogenous and dietary hypertriglyceridaemias, and helps identify non-fasting sera. Electrophoresis is not routinely required (Fredrickson 1975, Lewis 1976, Hazzard *et al.* 1973). But in moderate hypercholesterolaemia without xanthomas it may help recognize the uncommon patient in whom high density lipoprotein (HDL) levels are elevated, a seemingly-benign, sometimes familial disorder (Avogaro & Cazzolato 1975) for which no treatment is indicated.

Quantitative lipoprotein studies have, until recently, been confined to research-oriented laboratories owing to the high cost of ultracentrifugation. Now simple precipitation methods (Ononugbu & Lewis 1977) and a micro-ultracentrifuge (Wieland & Seidel 1977) permit wider availability of lipoprotein measurements. The diagnosis of remnant hyperlipoproteinaemia (Type III, broad-β disease) requires lipoprotein analysis, though assay of apolipoprotein E may become a reliable alternative (Kushwaha *et al.* 1977). HDL quantitation greatly sharpens prediction of cardiovascular risk as well as detecting high HDL levels. It is not clear that demonstration of low HDL levels would enhance the effectiveness of preventive measures against IHD; HDL may be increased by correction of obesity or prescription of regular exercise but such advice is usually given, with or without knowledge of HDL concentration.

Selective screening for IHD risk factors

I believe that screening (case ascertainment) is indicated in the first-degree relatives of patients with substantial hyperlipidaemia, and in patients with diabetes, gout or chronic renal failure, amongst whom high lipid levels are common (Lewis 1976). The relatives of patients with early-onset IHD, stroke or peripheral atherosclerosis (i.e. before 60 years of age) should be screened for hyperlipidaemia and hypertension. Hyperlipidaemia should be sought in patients with otherwise-unexplained abdominal pain or polyarthritis. Possibly all hypertensives should have lipid studies in view of the major hazard conferred by multiple risk factors, and because of the lipid-elevating effect of some diuretics (Johnson *et al.* 1974).

In assessing patients with lipid transport disorders it is convenient to distinguish three groups:

Uncommon inborn errors

Three strongly-inherited disorders of lipid transport are over-represented amongst patients with IHD (Nikkilä & Aro 1973, Goldstein *et al.* 1973). One is familial hypercholesterolaemia (FH) affecting 2–3 persons per thousand (Carter *et al.* 1971, Goldstein *et al.* 1973). Another, familial combined hyperlipidaemia (FCH) has been estimated to occur in 4–30 persons per thousand in the USA. FH (Schrott *et al.* 1972) and probably FCH (Goldstein *et al.* 1973, Janus 1977) are autosomal dominant disorders. In one study (Nikkilä & Aro 1973) of myocardial infarction survivors aged less than 50 years, 6% belonged to families with FH and 24% to families with FCH. In another series (Goldstein *et al.* 1973) the frequencies in those aged less than 60 years were 4.1% and 11.3% respectively. Remnant hyperlipoproteinaemia, a rarer disorder, is likely to carry an enhanced risk of IHD, lower-limb atherosclerosis and stroke (Lewis 1976). Cutaneous xanthomas often lead to a presumptive diagnosis (Fredrickson *et al.* 1967). These disorders may be suspected from the family history. Tendon xanthomas are present in roughly 50% of adults with FH, and affected children sometimes have corneal arcus. Hypercholesterolaemia is the laboratory feature of FH; in FCH the levels of cholesterol and triglyceride, or of either lipid alone, are increased (Goldstein *et al.* 1973).

On the other hand, IHD risk seemingly is not increased in familial hypertriglyceridaemia (Brunzell *et al.* 1976, Janus 1977) and in hypertriglyceridaemia due to lipoprotein lipase deficiency (Fredrickson & Levy 1972, Zilversmit 1973). Abdominal pain, pancreatitis and eruptive xanthomas are the main manifestations. It is possible that hypertriglyceridaemia is associated with cardiovascular disease when inherited on the basis of FCH and remnant hyperlipoproteinaemia, but not when due to other mutant genes.

Some inborn errors, e.g. FCH, are ameliorated by simple dietary treatment (personal observation); but individualized therapy is necessary and many patients in this group require drug treatment.

'Common' hyperlipidaemias

IHD risk increases with plasma cholesterol level over a wide range of concentration (Stamler *et al.* 1972). This remains true of levels which are statistically normal (<95th percentile) in Westernized countries. If one regards as normal the range of cholesterol concentration seen in countries where IHD is rare, the majority of adults in the USA and Northern Europe have high levels (Blackburn 1976).

The increase in risk becomes steeper in men whose cholesterol concentrations exceed 6.5 mmol/l (Stamler *et al.* 1972). For the clinician it is necessary to take particular note of levels above this value. In a representative sample of Londoners 25% had cholesterol levels exceeding this value (Lewis, Chait, Wootton *et al.* 1974).

Amongst normal subjects cholesterol concentration is to some extent inherited: twin studies indicated that up to 40% of its variability is genetically determined (Pikkarainen *et al.* 1966). Probably many genes are involved, hence the usage 'polygenic hypercholesterolaemia' (Carter *et al.* 1971). Many dietary factors influence cholesterol level: the intake of saturated and of unsaturated fats (Lewis 1976), of cholesterol (Mistry *et al.* 1977) and some forms of fibre e.g. pectin (Jenkins *et al.* 1975); relative body weight correlates, weakly, with serum cholesterol (Lewis 1976). Comparisons between populations reveal an almost linear relationship between intake of saturated fat, mean serum cholesterol levels and IHD mortality (Keys 1970). 'Common' hypercholesterolaemia thus reflects the interaction between environmental factors and genotype.

Within populations, a correlation between serum cholesterol level and estimates of dietary fat intake has seldom been apparent (*British Medical Journal* 1977). Given the inaccuracy of dietary assessment (Balogh *et al.* 1971, Liu *et al.* 1977), and of estimates of the amount and type of fat in particular (Truswell 1977), it would be surprising if they did. Yet such expectations have been voiced (Mann 1977). Within-population variability in saturated fat intake is small

compared with between-population differences. Other dietary components as well as energy expenditure impinge on serum cholesterol levels. In one study of a closed population, nevertheless, a positive correlation was obtained between fat consumption and serum cholesterol (Easty 1970). Genetic differences appear to be important: this has been invoked by Mistry *et al.* (1977) to explain the wide inter-individual differences they observed in responsiveness to high-cholesterol diets.

Cardiovascular risk appears to be enhanced to a lesser extent by 'common' hypercholesterolaemia than by FH; in the latter hyperlipidaemia is often more pronounced and is present from infancy. Because of its vast prevalence, however, 'common' hypercholesterolaemia is by far the greater source of risk among the populations of Westernized countries. It usually responds to dietary control.

Hypertriglyceridaemia appears to increase IHD risk in initially-healthy men (Carlson & Böttiger 1972). But in some studies this effect is inapparent once multivariate analysis is employed to exclude the influence of cholesterol levels (Wilhelmsen *et al.* 1973). However, two recent reports have reaffirmed hypertriglyceridaemia as an independent risk factor (Pelkonen *et al.* 1977, Carlson 1978). Conceivably the relative power of risk factors shows geographical differences. In Nikkilä's study (Pelkonen *et al.* 1977) risk increased when triglyceride levels exceeded 1.7 mmol/l. Most hypertriglyceridaemias respond to correction of obesity (Olefsky *et al.* 1974, Lewis 1976) with further benefit from the fat-modified diet (Chait *et al.* 1974). It appears unnecessary to restrict dietary carbohydrate (Sommariva *et al.* 1978). Hypertriglyceridaemia is often aggravated by alcohol (Chait *et al.* 1972).

A study of four European populations (Lewis *et al.* 1978) suggests that cholesterol and triglyceride levels are influenced in the same direction by some environmental variables.

3. High density lipoprotein (HDL) deficiency

Low mean levels of HDL are one of the metabolic characteristics of patients with IHD. This was recognized over 20 years ago (Nikkilä 1953, Barr *et al.* 1951), confirmed more recently (Lewis, Chait, Oakley *et al.* 1974, Carlson & Ericsson 1975, Berg *et al.* 1976), and was incorporated into an aetiological hypothesis by Miller & Miller (1975). Two ongoing prospective studies have indicated that low HDL concentration is predictive of increased cardiovascular risk (Gordon *et al.* 1977*a,b*, Miller *et al.* 1977); this risk factor status appears independent of other risk-related variables. In the Framingham study quite small differences in HDL concentration predict major differences in risk: this is not easily related to present concepts of the possible mechanisms. In the latter survey there have so far been relatively few ischaemic events; perhaps because of this, hypertension has not emerged as a risk factor as it has in other studies.

HDL has two major subclasses, HDL_2 and HDL_3 (Lewis 1976); concentrations of HDL_2 are subnormal in IHD (Fredrickson *et al.* 1968).

The hypothesis has been put forward that HDL is the main vehicle by which cholesterol is removed from the tissues (Glomset 1968), and carried to the liver from which it is secreted in the bile and, ultimately lost via faecal excretion. If this view is true then HDL deficiency could well promote accumulation of cholesterol in tissues (including arterial intima). Miller *et al.* (1976) have reported a negative correlation between plasma HDL concentration and tissue cholesterol pool sizes, a finding in striking conformity with this hypothesis.

Cultured fibroblasts and arterial smooth muscle cells acquire cholesterol by uptake of low density lipoprotein (LDL) from the medium (Brown & Goldstein 1976). LDL uptake is inhibited by high concentrations of HDL (Carew *et al.* 1976). On the other hand, synthesis of cell-surface LDL receptors is enhanced by HDL (Miller 1978). Bersot *et al.* (1977) have identified a small subclass, HDL-I, in which the property of inhibiting LDL uptake is confined.

Measurements of HDL or its subclasses may come to play a major role in improving our ability to predict IHD. In my view a conservative attitude to manipulation of HDL levels is required pending fuller epidemiological data from purposely-designed prospective studies and stronger evidence as to mechanisms which could mediate a protective effect.

HDL_2 levels are higher in women (Barclay *et al.* 1963), and appear to be partly under genetic control (Feinleib 1976, Berg 1978). Neither fact offers scope for intervention. Low HDL concentration is often present in hypertriglyceridaemia and may improve when this is treated. In acute studies, correction of obesity increases HDL levels (Wilson & Lees 1972). Clofibrate has the same effect (Wilson & Lees 1972). Regular physical exercise increases HDL concentration substantially (Lopez-S *et al.* 1974, Wood *et al.* 1976) as does the moderate use of alcohol (Castelli *et al.* 1977, Belfrage *et al.* 1977); while the former is more physiological the latter may offer better patient compliance.

Individual management

Few advances have been made since the subject was reviewed two years ago (Lewis 1976). Reduction of obesity remains a most rewarding measure, leading to persisting decrease in triglyceride and cholesterol levels (Olefsky *et al.* 1974) and in some short-term studies to increased HDL concentration (Wilson & Lees 1972). Except in lipoprotein lipase deficiency, long-term management involves restriction of fat intake to one-third of dietary energy, with a low proportion (8–10% of energy) of saturated fatty acids and partial substitution by polyunsaturated fatty acids.

Of the lipid-lowering drugs cholestyramine, clofibrate and nicotinic acid are currently the most valuable. In hypercholesterolaemic children cholestyramine obtains better compliance than diet (West *et al.* 1975). It produces substantial depletion of body cholesterol by increasing faecal bile acid excretion (Moutafis & Myant 1969). Recently Miettinen & Lempinen (1977) have observed that greater bile acid loss can be produced by ileal bypass than by cholestyramine, and this operation is probably under-used at the present time.

Implications for preventive medicine

Extension of these principles from individual patients to the population involves changes in life style to reduce all mutable risk factors, especially changes in diet, smoking habits and exercise. The scientific and ethical issues have been debated exhaustively (Blackburn 1976, Mann 1977, Stamler *et al.* 1972, Blackburn 1974, Rose 1976, McMichael 1977, Walker 1978, Stone 1978). The proposed changes are modest in degree (Joint Working Party of the Royal College of Physicians of London and the British Cardiac Society 1976) e.g. average fat consumption should be reduced by one-quarter, and an hour or two a week should be spent in exercise. It is clear that purely therapeutic approaches, necessary though they are, are inadequate to abate the IHD problem (Stamler *et al.* 1972, Tunstall-Pedoe 1977, Joint Working Party of the Royal College of Physicians of London and the British Cardiac Society 1976); and it is commonplace that much everyday medicine and dentistry is preventive: control of asymptomatic hypertension and diabetes, immunizations, antenatal care and cervical cytology.

If risk factor reduction is to be widely advocated its safety must be assured. This has not been an issue as regards anti-smoking advice or weight reduction by nutritionally-sound diets. Physical training in the previously unfit can prove hazardous unless carefully-graded programmes are followed and prior medical advice is sought by those at special risk.

The safety of 'prudent diet' recommendations is inferred from two sources. Experience with several dietary trials has been reassuring (Ederer *et al.* 1971, Heady 1974). An increased incidence of gallstones occurred in the Los Angeles trial involving a high polyunsaturated fatty acid intake (Sturdevant *et al.* 1973), but not in the Helsinki trial (O Turpeinen, 1974, personal communication); lithogenicity of bile increases in some subjects at the extremely high polyunsaturate/saturate ratio of 7:1 (Grundy 1975). By contrast the prudent diet has a P/S ratio of about 1:1; and as it is also designed to reduce obesity its net effect on gallstone frequency may well be favourable. The second source of reassurance is the vital statistics of Italy, Greece and Yugoslavia where habitual diets resemble the prudent diet with saturated fatty acids as 8–9% of food energy, polyunsaturated fatty acids up to 7%. Total mortality rate and cancer mortality rate in middle age are somewhat lower in such countries than in Scotland,

England–Wales and the USA; IHD mortality is of course considerably lower in these Mediterranean countries (World Health Organization 1977).

Implications for industry

The only vested interest admissible in medicine is that of the patient. This is no less true of preventive than of therapeutic medicine. Often the issues are clear cut, as with environmental pollution and the narcotic drug trade. Where the issues are more complex as with the roles of smoking and diet in ischaemic heart disease, doctors must be free to exercise their best scientific judgment uninfluenced by sectional interests.

It is unfortunate that a few elements within the UK food industry are currently adopting a defensive posture with regard to prudent diet recommendations. This is creating an entirely unnecessary polarization of interests. The wish of the food manufacturer to show a profit has not been shown to conflict with the wish of the individual to avert a heart attack.

It would be unreasonable to hope for effective re-education of the public in less than 10–20 years. The farming and food processing industries in the UK are highly efficient; given time they are well able to adapt to changing demands. If they promptly accept the need for moderate, not radical nutritional changes, there is abundant time to set about accommodating them. By undertaking this they will be seen to be acting responsibly in the interests of the nation's health. Milk, cheese, poultry and meat will of course remain highly desirable foods; but efforts are required to reduce the ratio of saturated fat to protein in these commodities, and in the diet. Changes in techniques of animal husbandry, food processing and in farming patterns may be necessary; revised food legislation is called for (Short 1977, Select Committee on Nutrition and Human Needs, United States Senate 1977). With some diversification and some reduction of imports of hard fats (benefiting British farming and the balance of payments) the profitability of our food industry need in no way be threatened.

Priorities in a community programme

Anti-smoking campaigns, promotion of physical fitness and counselling against obesity are non-controversial today, and rightly so. Yet dietary proposals still elicit critical comments (McMichael 1977, Mann 1977). It is instructive to consider the pattern of risk factors in Japan, where IHD is strikingly uncommon compared with other industrial societies (Keys 1970). Diabetics in Japan have one-eighth as much IHD as do American diabetics (Goto *et al.* 1974, Keen 1976). Hypertension and obesity are no less prevalent in Japan than in the West; cigarette consumption is similar. Alone amongst the risk factors serum cholesterol levels are far lower in the Japanese (Keys 1970) due largely, as far as is known, to their low intake of saturated fatty acids (Keys *et al.* 1965, Epstein 1967). Thus the risks of IHD conferred by diabetes, hypertension and smoking are small when saturated fat intake is low.

Rigorous proof is clearly lacking that IHD mortality will fall if the prudent diet is widely adopted. Yet the evidence, outlined above, is far more substantial than that pertaining to exercise, smoking and obesity; none of these has been subjected to controlled trial or linked with IHD by a convincing hypothesis as to mechanism. The reduction in IHD mortality amongst doctors who quit smoking (Doll & Peto 1976) is noteworthy, but the quitters and smokers are self-selected groups who may differ in respect of other known or unknown risk factors. Similarly, those who exercise assiduously also differ in other aspects of life style from the sedentary majority (Hickey *et al.* 1975). Hence the quality of evidence concerning serum cholesterol reduction is in no way weaker than that pertaining to other risk factors.

Conclusions

A preventive approach to IHD, directed against all modifiable risk factors, is supported by compelling evidence from many disciplines. The requirement for ongoing research is undoubted, but it would in my view be unethical to withhold from the public the benefits of current knowledge.

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