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Van die Redaksie/Editorial

Hepatitis B-vaksien — wie behoort dit te kry?

'n Inaktiveerde hepatitis B-vaksien wat in die VSA as Heptavax-B (Merck Sharp & Dohme) bekend staan, is in November 1981 deur die Food and Drug Administration gelisensieer en verlede Junie wyd in die VSA beskikbaar gestel. Huidige inligting dui daarop dat hierdie vaksien binnekort ook in Suid-Afrika beskikbaar sal wees, alhoewel die vrystelling daarvan hier deur die geweldige aanvraag asook deur sekere beperkinge op die vervaardiging daarvan van die plasma van menslike hepatitis B-draers vertraag word. Die geskiedenis van die ontwikkeling van hierdie vaksien (wat unieke eienskappe het) word in detail in 'n redaksionele artikel deur Alter[1] in die *Journal of the American Medical Association* verstrek. Die kenmerke van die nuwe vaksien word ook deur Krugman[2] in dieselfde tydskrif beskryf. Aangesien daar waarskynlik 'n tekort aan voorraad van die vaksien sal wees en aangesien 'n kursus van drie inspuitinge iets soos $100 sal kos, moet die gebruik daarvan aanvanklik slegs tot die hoë risiko-groepe beperk word.

Hierdie groepe word in albei artikels aangehaal. Daarbenewens het Mulley *et al.*[3] onlangs van 'n beslissingsontleding gebruik gemaak om die moontlike koste en voordele van alternatiewe inentingstrategieë in verskillende hoë risiko-bevolkinge, te bepaal. Dit het hulle d.m.v. die beantwoording van die volgende drie vrae gedoen: Wie sal die meeste by inenting teen hepatitis B-virus baat? Onder diegene wat daarby sal baat, vir wie sal inenting 'n kostebesparing wees? Watter rol speel sifting vir voorafgaande infeksie en veronderstelde natuurlike immuniteit in die formulering van inentingsbeleide? Die vraag is belangriker as wat dit op die oog af mag lyk aangesien daar 'n definitiewe verband tussen hepatitis B-virus en die latere ontwikkeling van lewerkanker is.

Die vaksien kan dus heel moontlik die eerste antikankervaksien wees. Mulley *et al.*[3] het aanvalsyfers, voorkomssyfers van immuniteit, en die jaarlikse frekwensie van toevallige parenterale blootstelling in drie verteenwoordigende bevolkinge beraam: homoseksuele mans, interns en die algemene bevolking van die VSA. Hulle het beraam dat die inenting van vatbare persone die mediese koste vir bevolkinge met 'n jaarlikse aanvalsyfer bó 5% sal bespaar (dit sluit natuurlik die homoseksuele mans in).

Koste behoort egter nie die eerste oorweging te wees in die besluitneming oor die beoogde doelwitte van die nuwe vaksien nie. Alter[1] stel die volgende elf kategorieë voor: eerstens, alle gesondheidswerkers wat direkte kontak met die pasiënte het, veral dié wat aan die bloed of bloedprodukte van pasiënte blootgestel word. Tweedens, pasiënte op renale dialise wat 'n groot gevaar van blootstelling loop, alhoewel hierdie risiko grootliks gedurende die afgelope paar jaar verminder het. Derdens is dit bekend dat die pasiënte en die personeel van inrigtinge (veral in inrigtinge vir geestesiekes) 'n groot gevaar loop. Vierdens moet pasiënte met oorerflike of verworwe wantoestande wat gereelde oortappinge vereis, vir inenting oorweeg word. Eweneens moet pasiënte met leukemie of ander kwaadaardige wantoestande en wat oortappinge vereis, kandidate wees. Manlike homoseksuele is alreeds genoem, en weens die veneriese oordrag van die virus sal die seksuele maats van HBsAg-positiewe persone by die vaksien baat vind. Huisgenote van HBsAg-draers, die suigelinge van HBsAg-positiewe moeders asook kinders in endemiese areas moet vir inenting oorweeg word. Laastens mag die personeel wat in 'n hepatitis B-endemiese area werksaam is, inenting benodig. Daar word gehoop dat, met die inentingstrategie wat die bogenoemde kategorieë van persone insluit, die aantal draers uiteindelik geëlimineer sal word en dat die bedreiging van hepatitis B (met sy uitvloeisels van chroniese lewersiekte en lewerkarsinoom) grootliks verminder sal word.

1. Alter HJ. The evolution, implications, and applications of the hepatitis B vaccine. *JAMA* 1982; **247:** 2272-2275.
2. Krugman S. The newly licenced hepatitis B vaccine. *JAMA* 1982; **247:** 2012-2015.
3. Mulley AG, Silverstein MD, Dienstag JL. Indications for use of hepatitis B vaccine, based on cost-effectiveness analysis. *N Engl J Med* 1982; **307:** 644-652.

Acquired immunodeficiency syndrome (AIDS)

In an editorial in the *SAMJ* of 27 February 1982[1] we prophesied that the apparently new syndrome mainly affecting male homosexuals in New York and Los Angeles, and now designated as the acquired

immunodeficiency syndrome (AIDS), would sooner or later appear in South Africa. This prophecy has now been fulfilled. The deaths of 2 White men on 26 August 1982 and 1 January 1983 in H. F. Verwoerd Hospital, Pretoria, apparently from AIDS, have received widespread publicity in the media and provoked a somewhat hysterical reaction among those sections of the community most at risk, the male homosexuals and the drug abusers.

Two things should be emphasized at the outset. AIDS is not a specific diagnosis but a convenient term for a syndrome of unknown origin manifesting itself in a variety of ways. Secondly, although the overwhelming majority of cases have been in male homosexuals a few cases have been reported in heterosexual men, women, persons of Haitian origin, and haemophiliacs.

In the 2 South African cases, there was a history of contact with persons in New York, and lung biopsies revealed pneumonia due to *Pneumocystis carinii*. Cytomegalovirus was isolated from one patient and the other was serologically positive for the virus and had marked lymphocytopenia. All these features have been recorded in the USA.

Interest in this syndrome was aroused in the USA when, in about June 1981, an increase in the occurrence of Kaposi's sarcoma, *P. carinii* pneumonia and other serious opportunistic infections was recorded by the Central Surveillance Unit of the Center for Disease Control, Atlanta, Georgia. A task force was formed to undertake surveillance and to further investigate the condition.

The syndrome is characterized by a severe loss of natural immunity and lymphocytopenia, in which the usual ratio of T-helper cells to T-suppressor cells of roughly 5 : 3 is reversed. Cell-mediated immunity is consequently grossly reduced, leaving the victim wide open to opportunistic infections. In the USA alone more than 750 cases have been reported in the period June 1981 to November 1982. In about 90% of these patients either Kaposi's sarcoma or *P. carinii* pneumonia or both were found; 95% of patients have been males and 75% of these were either homosexual or bisexual. The age group affected is usually 25-44 years and the disease has been found in all race groups. The mortality rate is high, varying between 20% and 70%. The disease model most closely resembling that of AIDS appears to be hepatitis B infection. About 60 cases have also been found in countries of Western Europe.[2] With very few exceptions, all these patients reported recent contact with persons in the USA, or with Americans in Europe. About half the American cases were in New York City and a further 20% in California.

The aetiology of the disease in unknown. Hypotheses being explored include: (*a*) infection with blood-borne virus (cytomegalovirus or one yet to be identified); (*b*) inhalation of amyl nitrite or similar stimulant; (*c*) a factor found in semen which suppresses cell-mediated immunity and which is absorbed *per rectum* but not *per vaginam*.

The symptoms of AIDS are nonspecific: fever, loss of appetite, weight loss, extreme fatigue and enlargement of lymph nodes. Histologically these resemble angio-immunoblastic lymphadenopathy.

On 7 January 1983 the Department of Health and Welfare called a meeting of representative specialists to formulate a surveillance and containment strategy. All contacts of the 2 deceased patients will be traced as far as possible and fully investigated. A group considered to be at particularly high risk will be screened forthwith, using, for a start, a full blood count and selected skin tests as indicators. A third working group will make contact with a larger group also regarded as at risk. Details of the protocol to be followed in respect of the latter will be worked out shortly. Records of suspects and cases will be forwarded to a central processing unit. The question of making AIDS a notifiable condition under the Act was considered, but this decision has been held in abeyance.

General practitioners are urged to be on the alert for further cases. Pointers in this regard can emerge from a well-taken history. Does the patient belong to any of the at-risk groups? Has he recently been in New York, San Francisco or Los Angeles? Has he recently had a blood transfusion or has he habitually sniffed amyl or butyl nitrite? What is his pattern of sexual behaviour? A history of intravenous drug abuse may also provide a clue. Clearly the symptoms mentioned above are all relevant and the physical examination of the patient may reveal swollen glands and/or skin lesions suggestive of Kaposi's sarcoma. The most useful test for screening purposes appears to be a full blood count; patients with a lymphopenia should be referred for further investigation to a pathologist, who might consider skin testing for cell-mediated immunity, cytomegalovirus serology, extended virus serology (hepatitis B, herpes simplex), the T4 : T8 (helper : suppressor T-lymphocyte) ratio, total circulating T and B lymphocytes and several other tests. In the light of the limited and highly specific groups at risk, the most important task of general practitioners is to allay the fears of the general public by appropriate health education.

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2. Gerstoft J, Malchow-Møller A, Bygbjerg I *et al.* Severe acquired immunodeficiency in European homosexual men. *Br Med J* 1982; **285:** 17-19.

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Coronary vasospasm

Atherosclerotic ischaemic heart disease (IHD) remains the most significant affliction of the White population in South Africa today. It is therefore of paramount importance that the underlying pathophysiological mechanisms be understood, looked for and counteracted therapeutically. For more than a century thinking on IHD has been clouded by the acceptance of the concept of 'anatomical' obstruction to coronary blood flow as represented by fixed atherosclerotic lesions. However, the past decade has provided a wealth of information which has brought to the fore the significance of a 'functional' component to coronary blood flow and has thus witnessed the resurgence of the concept of coronary vasospasm. This would not have been possible without the availability of

sophisticated equipment, coronary arteriography and interventional drugs. Historically, Heberden (1792) appears to have been the first to suggest that 'a strong spasm be the true cause of this disorder' (referring to angina pectoris), and Latham (1896) and then William Osler (1910) postulated that coronary vasospasm was of paramount importance in the pathogenesis of angina. Wilson and Johnson (1941) were the first to notice transient ST-segment elevation during episodes of angina but did not appreciate the possible underlying mechanism. It thus remained for Prinzmetal *et al.*[1] to describe the entity of 'variant angina', i.e. angina at rest associated with transient ST-segment elevation with varying degrees of underlying coronary atherosclerosis, which they directly attributed to coronary vasospasm. Subsequent to this description prominent researchers in this field such as Oliva, Maseri, Conti, Chahine, Théroux, Yasue and MacAlpin have provided additional documentation of its importance in IHD.*

The elucidation of the exact mechanism initiating coronary vasospasm has proved exceptionally difficult. Nevertheless, most workers would agree that there is an underlying 'hypersensitive' coronary vasculature (possibly due to chronic hypoxia or cholesterol deposits) which interacts with a multitude of precipitating factors. A popular suggestion has been that of an imbalance between thromboxane A_2 (the platelet-derived smooth-muscle vasoconstrictor) and prostacyclin (the intima-produced potent vasodilator). This concept has been discredited, since aspirin-induced reduction of thromboxane A_2 has proved to be ineffective in reducing the frequency of angina at rest. Furthermore, the administration of prostacyclin intravenously did not prevent ischaemic episodes thought to be secondary to coronary vasospasm. Other substances such as histamine,[2] methacholine and ergonovine[3-5] have provoked coronary vasospasm in susceptible subjects, and serotonin causes severe vasoconstriction in the hypercholesterolaemic rabbit aorta, as well as being a mediator of constriction secondary to ergonovine. Documentation of precipitation of variant angina by stimuli such as iced-water intake, alcohol consumption, food, and rapid dextran infusion suggests a role for neural, humoral and mechanical stimuli. Catheter-induced spasm, particularly of the right coronary artery, is well known and occurs in some 1-3% of patients undergoing coronary angiography.[6] This form of spasm is usually benign in that it does not cause angina or give rise to electrocardiographic (ECG) features of ischaemia. Recently, coronary vasospasm occurred during an anaphylactoid reaction to iodine-containing radiographic contrast material, although these substances usually cause coronary vasodilation.[7] The role of α-adrenergic receptors in coronary artery spasm is controversial, since phentolamine (an α-adrenergic blocking agent) has been documented as abolishing cold-pressor-induced spasm by some workers,[8] while others failed to show abolition of ischaemic episodes precipitated by cold-pressor or ergometrine with infusion of the drug.[9] Yasue *et al.*[10] have favoured the involvement of the α-adrenergic nervous system and have documented a circadian rhythm in the precipitation of vasospasm, in that coronary artery tone is greater from midnight to the early morning hours and significantly less in the afternoon. These researchers also demonstrated that hyperventilation in the presence of tris-buffer infusion decreased the hydrogen ion concentration, resulting in less calcium ion antagonism with subsequent coronary artery spasm. Cardiac transplantation has provided material for studying epicardial human coronary arteries, and the presence of spontaneous calcium-dependent contractions, increased by potassium and noradrenaline solution and decreased by nitroglycerin, verapamil and calcium-free solutions, has been demonstrated *in vitro*. These findings provide evidence of a potential mechanism of coronary vasospasm in the absence of the α-adrenergic receptor system.

Continuous haemodynamic and ECG monitoring has demonstrated that many ischaemic episodes can be completely asymptomatic,[11] in that ECG evidence of ischaemia was not preceded by an increase in myocardial oxygen demand such as a rise in systolic blood pressure and an increase in heart rate. Furthermore, a rise in end-diastolic pressure and a fall in systolic pressure and peak dp/dt preceded or occurred simultaneously with the ischaemia. The symptom of angina is usually only a relatively late indication of myocardial ischaemia. Maseri *et al.*[12] have documented the varying ECG features accompanying coronary vasospasm. Thus, severe transmural myocardial ischaemia, as occurs with classic Prinzmetal's angina, gives rise to ST-segment elevation and a large transmural defect is evident on thallium-201 scanning. ST-segment depression and pseudonormalization of inverted T waves is a manifestation of non-transmural (subendocardial) ischaemia; on thallium-201 scanning a diffuse regional reduction of perfusion is seen. A further sophisticated method to detect myocardial ischaemia secondary to reduced coronary blood flow is the thermodilution technique. Recently, Nademanee *et al.*[13] described the use of an analogue method applied to a semi-automated analysis of 24-hour Holter ECG recordings which should allow for more accurate assessment of myocardial ischaemia occurring at rest.

Selective coronary angiography has enabled direct visualization of vasospasm — whether this be spontaneous, catheter-induced or provoked pharmacologically. Ergonovine (ergometrine) maleate, given in graded intravenous boluses, has become the accepted standard drug for the provocation of coronary spasm in patients with suspected variant angina.[4] This drug is usually given at the time of coronary angiography, but it has also been safely used on an outpatient basis to detect ECG evidence of transient myocardial ischaemia accompanied by chest pain.[14] Spasm is usually superimposed upon underlying coronary atheromatous lesions of varying severity, although it may occur in the absence of any underlying fixed obstruction.[15] A single vessel, either the right coronary artery or left anterior descending coronary artery, is usually involved, but multiple vasospasm has been encountered.[16] Provoked spasm is usually rapidly relieved with either sublingual nitrates,[17] intracoronary nitrates,[18] sublingual nifedipine (Adalat) or intracoronary nifedipine.[19] Although reactions such as heart block, severe arrhythmias and hypotension may occur with use of the latter, acute myocardial infarction and death are rare.

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induced angina is probably less, but the frequency is unknown. The exact role of coronary vasospasm in the causation and extension of acute myocardial infarction is particularly difficult to ascertain, although the fact that it can cause infarction is undisputed.[20] The frequency of this occurrence will most probably be more accurately established with the recent introduction of intracoronary thrombolysis, and preliminary data suggest that it may not be very frequent. The role of coronary spasm in the genesis of sudden death appears to be a most important one. Potentially lethal arrhythmias such as ventricular tachycardia and fibrillation have been documented during episodes of vasospasm and disappeared on reversal of the transient myocardial ischaemia by calcium-blocking drugs[21] and nitrates.[22] Acute thyrotoxicosis has been shown to be associated with coronary vasospasm, with resultant ventricular fibrillation.

In this issue of the *SAMJ* (p. 103) Przybojewski reports a case of multiple coronary vasospasm giving rise to atypical ventricular tachycardia (*'torsade de pointes'*) with ensuing syncopal episodes which responded satisfactorily to long-acting nitrate and nifedipine treatment. Complete atrioventricular heart block has also been known to occur secondary to coronary vasospasm, particularly in association with ST-segment elevation. The role of this pathophysiological mechanism in non-atheromatous coronary artery disease found in subjects working with nitroglycerin explosives is fascinating. Lange *et al.*[23] were the first to establish angiographic evidence of spasm during the withdrawal period and this feature was subsequently confirmed by Klock.[24] (In a forthcoming issue of the *SAMJ* Przybojewski and Heyns will document a patient with repeated attacks of angina at rest during withdrawal from industrial nitroglycerin who responded favourably to oral nitrates and nifedipine therapy, as well as to removal from the explosives environment.) Sudden 'Monday morning' death, well described in the explosives industry, may be due to coronary vasospasm with ensuing fatal ventricular arrhythmias.[25]

Hellstrom[26] proposed the 'injury-spasm hypothesis' to explain all the events occurring in IHD, especially the genesis and propagation of coronary atherosclerosis. An intriguing problem is that of vasospasm occurring within saphenous vein bypass grafts,[27] but its importance in postoperative failure of bypass grafts has still to be elucidated.

Acceptance of the entity of coronary artery spasm determines the therapeutic approach in each individual case. Detailed history-taking is crucial in establishing whether there is a variable threshold of exertional angina, which indicates a probable underlying vasospastic factor. The mainstays of therapy are the nitrates, because of their relaxant effects on vascular smooth muscle and intramyocardial tension, as well as the slow calcium antagonists nifedipine,[28] verapamil[21] and diltiazem.[29] Beta-blockers are contraindicated in definite vasospasm, especially if there is no additional angina on exertion to indicate an increase in myocardial oxygen demand.[30] The danger of ß-blockers in this clinical situation is that the ß-adrenergic receptors in the epicardial coronary arteries (vasodilatation) no longer oppose the vasoconstrictor action of the α-adrenergic receptors, giving rise to more severe vasoconstriction with its deleterious consequences. This aspect should be taken into consideration in view of the current suggestion that all patients should be placed on prophylactic ß-blocker therapy after a myocardial infarction. As with the 'propranolol withdrawal syndrome', rapid withdrawal of nifedipine might cause rebound coronary vasospasm. Bypass surgery in patients with fixed coronary artery obstruction plus coronary artery spasm is not as successful as it is in those without, and would seem to be primarily indicated to prevent acute myocardial infarction rather than to control episodes of variant angina. More aggressive forms of surgical intervention such as complete denervation of the heart (autotransplantation) and incomplete denervation (plexectomy) combined with bypass surgery are successful to varying degrees.

J. Z. Przybojewski

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