

Swine Flu Pandemic - Drugs or Nutrients?

On June 11th the World Health Organization declared the first global flu epidemic in 41 years and moved the world to Phase 6, the agency's highest alert level. "The world is moving into the early days of its first influenza pandemic in the 21st century," said Head of WHO Margaret Chan, "the virus is now unstoppable."

She was quick to stress that it did not mean the virus was causing more deaths or had increased in severity, but the omens are worrying. Flu epidemics normally emerge late in the year, and those few which – like swine flu – start in the spring, have historically been much more serious. The so-called 'Spanish flu' started in the spring, with the first known case (thought to be an US army cook called Albert Gitchell) occurring in March of 1918. Initially a mild disease, by the autumn it had become something much worse; over the next year and a half it went on to kill vast numbers of people.

Estimates of the total death count vary considerably, from 1% of the world's population to as much as 3% (Johnson & Mueller '02, Ansart et al '09). Extrapolations to today's larger global population are, therefore, equally fuzzy. Some suggest a total of 62 million deaths (Murray et al '06). My own belief is that given the weakness of our innate immune systems today, caused by our over-sanitised food chain and evidenced by our abnormally high incidence of allergy (ie Baran et al '07), the death toll could be very much higher.

The WHO has not recommended that any national borders be closed or that restrictions on the movement of people and goods are currently necessary, because these precautions are effectively redundant. Instead, we must take medical precautions. Unfortunately, to our drugs-obsessed Department of Health, that means vaccinations and Tamiflu.

I wouldn't like to imply that our D of H could ever get it wrong, but here they have made a series of potentially catastrophic errors. Vaccinations can only be made up after the antigenic strain of the virus has been identified – it takes 4 months or so to get vaccine production up to speed – but the flu virus is genetically very unstable. By the time we have made vaccine for one strain the next viral wave will be just about to hit us. We will always be one step behind

Ansart S et al. **Mortality burden of the 1918-1919 influenza pandemic in Europe**. Influenza Other Respi Viruses. 2009 May; 3(3):99-106.

Baran J et al. **Oral beta-glucan adjuvant therapy converts nonprotective Th2 response to protective Th1 cell-mediated immune response in mammary tumor-bearing mice**. Folia Histochem Cytobiol. 2007;45(2):107-14.

Beebe DP et al 1983. Neutralization of influenza virus by normal human sera: mechanisms involving antibody and complement. J Immunol 130:1317-1322 Biothera 2004. Data on file.

Carr J et al. Influenza virus carrying neuraminidase with reduced sensitivity to oseltamivir carboxylate has altered properties in vitro and is compromised for infectivity and replicative ability in vivo. Antiviral Res. 2002 May;54(2):79-88. Cheng PK et al. Oseltamivir- and amantadine-resistant influenza viruses A (H1N1). Emerg Infect Dis. 2009 Jun;15(6):966-8.

Gooskens J et al. Prolonged influenza virus infection during lymphocytopenia and frequent detection of drug-resistant viruses. J Infect Dis. 2009 May 15;199(10):1435-41. Gubareva LV et al. Selection of influenza virus mutants in experimentally infected volunteers treated with oseltamivir. J Infect Dis. 2001 Feb 15;183(4):523-31.

Hurt AC et al. Susceptibility of human influenza viruses from Australasia and South East Asia to the neuraminidase inhibitors zanamivir and oseltamivir. Antiviral Res. 2004

- or as our Yankee friends put it, a day late and a dollar short.

Tamiflu is just a bad joke, albeit a very profitable one. Senior people I have spoken to admit that Tamiflu is being purchased and stockpiled primarily so that our political masters can tell us they're 'doing something'. They don't expect it to be effective, and neither do I. Remember the problems with antibiotic resistance? The same thing happens with anti-virals, only even more rapidly.

The two main anti-viral drugs Zanivir (Relenza) and Oseltamivir (Tamiflu) were launched in US in 2000.

Experimental resistance was demonstrated in 2001 (Gubareva et al '01). Clinical resistance emerged a couple of years later (ie Carr et al '02, Hurt et al '04) and subsequently spread widely and rapidly (Gooskens et al '09, Vicente et al '09).



Once Tamiflu started being used to treat H5N1 (bird flu) in 2003/4, resistant strains of the virus cropped up within months (Le et al '05). Tamiflu-resistant strains of swine flu virus have emerged ALREADY (Cheng et al '09, Hurt et al '09). It looks increasingly likely that the anti-viral drugs will be little more than an expensive distraction.

There is an alternative, namely 1-3, 1-6 beta glucan, a natural ingredient extracted from baker's yeast. This compound enhances the innate immune system and has been shown to protect against influenza virus in rats (Irinoda et al '92, Biothera '04) and in pigs (Jung et al '05).

It is not known if the beta glucan can protect against all flu viruses, but we do know that it is effective against pathogens that activate an innate immune mechanism, whereby they bind something called complement. Critically, the H1N1 virus binds complement (Beebe et al '83, Jayasekera et al '07). 1-3, 1-6 beta glucan is the main active ingredient in **ImmunoShield**.

Apr; 62(1): 37-45

Hurt AC et al. Emergence and spread of oseltamivir-resistant A(H1N1) influenza viruses in Oceania, South East Asia and South Africa. Antiviral Res. 2009 Jul;83(1):90-3. Irinoda K et al. Stimulation of microbicidal host defence mechanisms against aerosol influenza virus infection by lentinan. Int J Immunopharmacol. 1992 Aug;14(6):971-7.

Jayasekera JP et al. Natural Antibody and Complement Mediate Neutralization of Influenza Virus in the Absence of Prior Immunity. J Virology, Apr 2007,3487-3494, 81-7 Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. Bull Hist Med. 2002 Spring; 75(1):105-15

Jung K et al. Antiviral effect of Saccharomyces cerevisiae beta-glucan to swine influenza virus by increased production of interferon-gamma and nitric oxide. J Vet Med B Infect Dis Vet Public Health. 2004 Mar;51(2):72-6.

Le QM et al. Avian flu: isolation of drug-resistant H5N1 virus. Nature. 2005 Oct 20;437(7062):1108

Murray CJ et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. Lancet. 2006 Dec 23;368(9554):2211-8.

Vicente D et al. Rapid spread of drug-resistant influenza A viruses in the Basque Country, northern Spain, 2000-1 to 2008-9. Euro Surveill. 2009 May 21:14(20)

Sunshine, shadows and showers: the dangers of living in glasshouses

Vitamin D is actually NOT a vitamin, but a hormone.

A very few foods contain this compound, but most of us produce most of our own vitamin D ourselves in our skin, when it is exposed to sunlight. In Britain, however, we don't expose much skin to sunlight after the end of September, and we don't take our shirts off again until May at the earliest. This is why most Brits are depleted in D for most of the year, a pattern that has been worsened by the blizzard of anti-sunshine PR from a Department of Health that seems hell-bent on convincing us that sunlight is dangerous and unnatural.

This campaign was started partly as a result of input from a well-known cancer specialist, whose Scottish patients were showing an increasing incidence of melanoma. The Department of Health jumped on board and soon, in the public's mind, the link between sunlight and melanoma was established. We all had to wear hats, UV-blocking clothing, tons of sunscreen, and not even venture into the midday sun.

Lessons from the Victorians

Seen from an historical perspective, of course, this is all rubbish. We were 'designed' to be outdoor animals, and the very idea that sunlight is somehow dangerous for us shows just how ignorant of history many scientists (and of course politicians) are. In the mid-Victorian period, when – as regular readers will know, life expectancy equalled or exceeded our own – rural workers laboured in the fields from dawn to dusk, throughout the spring, summer and autumn. And yet, despite the shocking absence of sunscreen, cancer was very rare indeed; it occurred at about 10% of today's levels (Clayton & Rowbotham '09).

Today, however, when more and more of us work indoors, and are less exposed to sunlight than ever before, the incidence of melanoma continues to climb. It has doubled since 1950, and is continuing to increase (Purdue et al '08, Montella et al '09); to the point where this once rare condition is now the leading cancer in young British women (Cancer Research UK '09). Part of the increase in melanoma is probably due to increased sunbed use, but this cannot be the only factor.

The mid-Victorians provide us with one valuable clue. They ate huge amounts of fruits and vegetables, which contain a range



of compounds that migrate into the skin, give it a golden colour, and protect it against solar damage (ie Stahl & Siess '07, Dinkova-Kostova '08, Kowalczyk et al '09). Due to our less physical lifestyles and our drastically reduced food intakes, our skins do not receive the same level of dietary protection. This is one major reason why we are more vulnerable to skin cancer. If, in addition, you eat a terrible diet – such as is routinely eaten

References

Adams JS, Clemens TL, Parrish JA, Holick MF. Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and vitamin-D-deficient subjects. N Engl J Med. 1982 Mar 25; 306(12):722-5

Clayton P, Rowbotham J. How the mid-Victorians worked, ate and died. Int J Environ Res Public Health. 2009 Mar;6(3):1235-53.

Dinkova-Kostova AT. Phytochemicals as protectors against ultraviolet radiation: versatility of effects and mechanisms. Planta Med. 2008 Oct; 74(13): 1548-59. Epub 2008 Aug 11. Review Garland CF. Symposium in Print on the Epidemiology of Vitamin D and Cancer. Ann Epidemiol. 2009 Apr 1. North of the Border – levels of these protective compounds in the food and in the skin will be even lower. I say this from personal experience, as I was raised in Scotland; the reason why so many Scots are so pale is not only because they have Celtic blood, but also because the only vegetable that many of them eat is the chip. The resulting lack of dietary protection in their skin makes them very pale, and leaves their skin very vulnerable.

The problem with sunlight through glass

The other reason for the increase in melanoma is that more and more of us work under glass. By that I mean that we



mostly see sunlight through windows, rather than exposing ourselves to the sunlight directly. Sunlight through glass is a very different animal from direct sunlight, and while glasshouses may be good for strawberries, evidence is accumulating that they are not good for us. This is because glass lets the UV-A component of sunlight through, but blocks UV-B; a doubly dangerous combination because UV-A is potentially dangerous, and we need UV-B.

UV-A vs UV-B

UV-B is a higher-frequency component of sunlight, and it is UV-B that triggers vitamin D synthesis in the skin. Vitamin D has a range of anti-cancer properties, and we would therefore expect the overall effect of moderate exposure to UV-B to be cancer-protective, especially if the skin is also protected with dietary compounds. In the last month alone, three major papers have been published making a very strong case for vitamin D being extremely cancer-protective (Garland '09, Grant et al '09, Yin et al '09); In one of these, Professor Cedric Garland of the University of California said a 50mcg dose of vitamin D daily would prevent an estimated 200,000 cases of breast cancer and 250,000 of bowel cancer worldwide.

More vulnerable skin from fewer fruits and vegetables

The rural mid-Victorians were exposed to long periods of direct sunlight, with plenty of UV-B, and as a result had far higher levels of vitamin D than we do today. In addition, their high intakes of fruit and vegetables meant that they had outstanding dietary skin protection. As a result of these two factors, they had very little cancer of any kind.

We are in exactly the opposite situation. We eat far less fruit and vegetables, and have more vulnerable skin as a result. To make matters worse, our glazed offices and conservatories mean that we are bathed in UV-A. UVA can cause cancerous mutations, and it breaks down any vitamin D that had been

Godar DE, Landry RJ, Lucas AD. Increased UVA exposures and decreased cutaneous Vitamin D(3) levels may be responsible for the increasing incidence of melanoma. Med Hypotheses. 2009 Apr; 72(4):434-43.

Montella A, Gavin A, Middleton R, Autier P, Boniol M. Cutaneous melanoma mortality starting to change: A study of trends in Northern Ireland. Eur J Cancer. 2009 Apr 15.

Grant WB, Cross HS, Garland CF, Gorham ED, Moan J, Peterlik M, Porojnicu AC, Reichrath J, Zittermann A. Estimated benefit of increased vitamin D status in reducing the economic burden of disease in western Europe. Prog Biophys Mol Biol. 2009 Mar 4.

Kowalczyk MC, Walaszek Z, Kowalczyk P, Kinjo T, Hanausek M, Slaga TJ. Differential effects of several phytochemicals and their derivatives on murine keratinocytes in vitro and in vivo: implications for skin cancer prevention. Carcinogenesis. 2009 Mar 27.

formed in skin after outdoor UVB exposure. This is an imbalance of effects that would be expected to raise the incidence of cancer in indoor workers – and this is exactly what we see today.

The opposite effects of UV-A and UV-B on vitamin D levels form a protective mechanism, which prevents prolonged sun exposure from causing Vitamin D overdose.

More fruit, vegetables - and sun!

The way to better health is to eat more fruit and vegetables, and get the midday sun on your back – just enough to cause slight reddening, and no more. This will produce up to 200 mcg of D in your skin (Adams et al '82), and this dose is the right amount to keep not just your bones healthy, but also to reduce your risk of cancers such as breast and colon cancer. It makes a mockery of the government's decision to keep the RNI of vitamin D at 10 mcg/day, which was set long ago when it was thought that the only impact of vitamin D was on bone; especially as this low level of intake is strongly associated with ill health.

This sad story is yet another example of the dangers of medical specialism, and doctors who know everything about drugs but little about anything else. The cancer specialist who initiated the anti-sun campaign was (rightly) concerned about skin cancer. Unfortunately the lack of any awareness of history or nutrition led to ill-advised and counter-productive advice about staying out of the sun, which has lowered vitamin D levels across the nation; did nothing to reduce skin cancer; and caused many unnecessary cancer deaths.

Don't shower the vitamin D off straight away with soap

One last note. I mentioned showers in the title, and now it turns out that showers may also be contributing to the increase in melanoma and other cancers. You might think this is crazy, but bear with me ... I make no bones about having first seen this in Dr Mercola's column. I am sceptical about him because he will often go far further than the science permits, but recently he raised an interesting point.

Vitamin D is a steroid hormone, and like all steroids it is lipid soluble. When it is formed in the upper layers of the skin, after exposure to UV-B, it doesn't get into the blood stream right away. It remains in the lipid layers of the skin (such as the sebum) for some time before it can be absorbed into the deeper layers of the skin, and then passed into the bloodstream. This is a slow process of diffusion, and is not completed for up to 8 hours (Umemura et al '08) or even longer (Yamaguchi et al '07). If you de-grease your skin by washing with soap before that time, you will wash away a considerable part of the freshly formed vitamin D. Better leave the protective sebum on the skin until the next morning, and wash before (or after) breakfast.

Oh, and if you are still scared of the sun, here are the best food sources of this sunshine 'vitamin'.

To get you off to a really good start, **NutriShield** provides **20mcg** Vitamin D per daypack.

	mcg D	% RNI
Cod liver oil, 1 tablespoon	36	360
Salmon, cooked, 3.5oz/90g	90	900
Mackerel, cooked, 3.5oz/90g	80	800
Tuna fish, canned in oil, 3.5oz/90g	50	500
Sardines, canned in oil, drained, 1.75oz	60	600

Purdue MP, Freeman LE, Anderson WF, Tucker MA. Recent trends in incidence of cutaneous melanoma among US Caucasian young adults. J Invest Dermatol. 2008 Dec; 128(12):2905-8. Stahl W, Sies H. Carotenoids and flavonoids contribute to nutritional protection against skin damage from sunlight. Mol Biotechnol. 2007 Sep; 37(1):26-30. Review

Umemura K et al. Cutaneous pharmacokinetics of topically applied maxacalcitol ointment and lotion. Int J Clin Pharmacol Ther. 2008 Jun; 46(6):289-94.

Yamaguchi K et al. Analysis of in vitro skin permeation of 22-oxacalcitriol from ointments based on a two- or three-layer diffusion model considering diffusivity in a vehicle. Int J Pham. 2007 May 24;336(2):310-8. Yin L et al. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. Aliment Pharmacol Thre: 2009 Apr 16.

Glucosamine does not cause hepatitis

There have been a lot of anti-supplement stories lately, many of them sponsored by the drugs industry. One of the most stupid of these was the story, put about by a group of industry stooges, that glucosamine might cause hepatitis.

Glucosamine, of course, is a widely sold supplement that can be quite helpful in arthritis. It does not work in every patient, because many other nutritional factors are needed to make cartilage; but considering that 90% of medical drugs only work in 30 to 50% of patients (Roses '03), that is no reason to condemn glucosamine. (Unless, of course, you represent a drug company that makes the rather toxic NSAIDs).



This hepatitis scare was never very plausible because glucosamine is produced in the body, and taking a glucosamine supplement merely tops up levels of endogenous glucosamine.

There were a couple of cases of people who took glucosamine and who subsequently developed liver damage, but oddly enough the headlines omitted any reference to other factors which might have contributed such as allergy, iron overload and alcohol intake! This was an obvious smear job, and to its credit the FSA's Committee on Toxicology (COT) has concluded after examining existing evidence that glucosamine is vanishingly unlikely to cause liver damage.

A word of caution. If you take or are planning to take glucosamine, ensure that it is not the sulphate form. This has been linked to an array of gastro-intestinal problems, some of which are potentially very serious indeed (Gibson et al '93, Bullock et al '04). The glucosamine in **NutriShield** and **JointShield** is the hydrochloride form.

References

Bullock NR, Booth JC, Gibson GR. Comparative composition of bacteria in the human intestinal microflora during remission and active ulcerative colitis. Curr Issues Intest Microbiol. 2004 Sep;5(2):59-64.

COT statement: http://cot.food.gov.uk/pdfs/cotstatementgluco200901.pdf Gibson GR, Macfarlane GT, Cummings JH. **Sulphate reducing bacteria and hydrogen metabolism in the human large intestine**. Gut. 1993 Apr; 34(4):437-9. Review.

Roses, Allen. Worldwide vice-president of genetics at GlaxoSmithKline (GSK), statement 8.12.03

Anti the anti-supplementers

"There is nothing more powerful," said the French poet Victor Hugo, "than an idea whose time has come." Some commentators have taken this to mean that the truth must, eventually, out – but this is a Panglossian reading. The idea doesn't have to be a good one. What life actually teaches us is that there is nothing more powerful than a delusion whose time has come, whether this is Stalinism, Fascism or – to turn back to my own lathe – pharmaceutical medicine.

Pharmaceutical medicine is, of course, the dominant medical model today. One of the largest sectors of the entire global economy (along with arms and illegal drugs), Big Pharma has infiltrated the regulatory and political systems, the medical curricula and the clinical research establishments. Most invidiously, it has colonised the way that medics and medical scientists think. The poor things are taught at medical school that the key to health is pharmacology (it is), but that the only pharmacology that matters is pharmaceutical pharmacology – which is, of course, the big lie. So big, in fact, that most doctors today are completely incapable of thinking beyond it.

They merrily keep on prescribing statins, anti-hypertensives and anti-diabetic drugs as per their instructions (which were drawn up by committees heavily influenced by the drug companies), blithely ignoring, for the most part, the rising tide



of degenerative disease that floods their surgeries twice daily. All the perfumes of Araby, and all the drugs in their pharmacies, have no effect on the pandemics of diabetes, cancer, dementia, osteoporosis, gout, auto-immune disease, arthritis and allergy that are wrecking so many lives, and costing us so dear.

They search blindly, obstinately, for answers in the pharmacopeia, while ignoring the mountain of evidence that shows with absolute clarity that the way to a healthier population and reduced health care costs is through the food chain. Countless studies of the contemporary Mediterranean diet show an improved diet leads to improved health, with up to 15% reductions in the incidence of heart disease, cancer and dementia (ie de Lorgeril & Salen '08, Scarmeas et al '06, Scarmeas et al '08). And we can do better than this. The 'super-Mediterranean' diet consumed in mid-Victorian Britain reduced heart disease and cancer by a staggering 90% (Clayton & Rowbotham '09).

It is obvious that better nutrition dramatically improves health (as any farmer already knows), and as a pharmacologist I can assure you that it doesn't matter if the critical nutrients are

References

Clayton P, Rowbotham J. How the mid-Victorians worked, ate and died. Int J Environ Res Public Health. 2009 Mar; $6(3){:}1235{-}53$

de Lorgeril M, Salen P. The Mediterranean diet: rationale and evidence for its benefit. Curr Atheroscler Rep. 2008 Dec; 10(6):518-22. Review.

Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson JE, Sesso HD, Buring JE. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2009 Jan 7; 301(1):52-62.

Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM and 25 other authors. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer

given in food, functional (fortified foods) or supplements. So why, when some medics are so keen on giving (out-dated) advice about diet, is the establishment so consistently hostile about supplements? And why are there so many scientific publications about the uselessness and dangers of supplements?

I'll start with an editorial published in the esteemed Journal of the Federation of American Societies for Experimental Biology (FASEB) last month (Weissman '09). Weissman complained, "Dietary supplement are nostrums ... you see so many claims for supplements that promote 'joint health', 'breast health', or 'male vigor' rather than more precise claims that would have to be validated by the FDA in regard to ethical pharmaceuticals."

He's right. Most supplements are designed around the latest fashionable nutrient, or to a price point, and from the formulations it's sadly apparent that they have little to do with science. The unfortunate truth is that too many supplement companies sell little more than contemporary versions of Tono-Bungay, the toxic cure-all in H G Wells' Edwardian satire. That, of course, is not an argument against <u>well-designed</u> supplements.

It is also true that the results of the latest intervention studies of 'antioxidants' make up a long list of failures (ie Sesso et al '08, Gaziano et al '09, Lippman et al '09). But when you look at the bizarre and ignorant combinations of (often synthetic) nutrients that are used, it is not hard to see why the results are often negative. The question then arises, why were these trials so badly designed? There are two possible explanations.

The kindest one is that clinical scientists are still so obsessed with the Pharma model (one drug in, one variable measured), that they genuinely don't understand the futility of mono- or oligo-therapy. They fail to see that most of their trial subjects are, like the scientists themselves, depleted in most micro- and phytonutrients; and that the only rational way to enhancing their health prospects is to provide wide-spectrum nutritional support.

The other, more malignant idea is that Big Pharma really does get it. They know that better nutrition would create vastly improved public health, and vastly reduced revenues for themselves. And they are fighting a very clever, legalistic and methodological long game to prevent that disaster from ever coming to pass.

A nutritional programme (*Nutriplete*) has just been approved for Medicaid reimbursement in several US states, where it is available on prescription. It contains 29 active ingredients, and is a rational and well-designed formulation. The reimbursement issue was fought tooth and nail by the drug companies, but this product eventually won through. This is a vital development, as the anti-retroviral drugs used to treat HIV/AIDS are toxic, and fast losing their effectiveness as viral resistance continues to increase.

NutriShield, of course, was also designed not for existing chronic disease, but as a comprehensive nutritional supplement to support and help prevent degenerative disease in the first place.

Prevention Trial (SELECT). JAMA. 2009 Jan 7;301(1):39-51.

Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol. 2006 Jun; 59(6):912-21.

Scarmeas N, Luchsinger JA, Mayeux R, Schupf N, Stern Y. **Mediterranean diet and** mortality in a US population. Arch Intern Med. 2008 Sep 8;168(16):1823-4 Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson

Sesso HD, Buring JE, Christen WG, Kurth I, Belanger C, Machadyen J, Bubes V, Manson JE, Glynn RJ, Gaziano JM. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2008 Nov 12;300(18):2123-33.

Weissmann G, **The Atlanta Falcon and Tono-Bungay: Dietary Supplements as Subprime Drugs**. The FASEB Journal. 2009;23:1279-1282

The Paul Clayton Newsletter describes developments in the new field of pharmaco-nutrition, where nature and science are combined to offer non-drug solutions to degenerative disease. The Newsletters are intended to increase knowledge and awareness of health issues and are for information only. No health claims for specific products are made or intended and the information should not be used as a substitute for medical advice.