Chilton and colleagues hope that they have overcome this problem by combining GLA with the Δ-5-desaturase inhibitor, EPA. The two-step production of arachidonic acid in the liver from GLA requires the molecule to be first elongated to produce the structural analogue of arachidonic acid, dihomo-γ-linolenic acid (DGLA), and then desaturated by Δ-5-desaturase (Fig. 1)[1]. However, immune cells such as neutrophils do not contain Δ-5-desaturase and consumption of high quantities of GLA therefore leads to a build-up of DGLA in these cells[2]. 'This fatty acid competes with arachidonic acid resulting in an inhibition of the synthesis of the important inflammatory mediators such as LTB_4', explains Chilton. Anti-inflammatory metabolites, including the cyclooxygenase product prostaglandin E_1, are also generated from DGLA (Ref. 2).

Early studies

Studies in human hepatocarcinoma cells (HepG2) – a model for investigating fatty-acid metabolism in the liver – confirm that EPA inhibits Δ-5-desaturase and causes a build-up of DGLA, thus inhibiting the increase in arachidonic acid levels[1]. Studies in volunteers taking a combination of GLA and EPA also show that EPA prevents a build-up of arachidonic acid in the serum. Moreover, in the presence of EPA, DGLA builds up in immune cells without an accompanying build-up of arachidonic acid from the liver, thus maximizing the anti-inflammatory effects of GLA without the adverse effects associated with increased production of arachidonic acid[1,2].

'More recently, our work has addressed the minimal daily dosage of GLA required to obtain a maximum benefit as well as the contribution that other dietary fatty acids with proven anti-inflammatory action might have on these indices of inflammation,' explains Chilton. 'Another trial identified the minimal effective dose of (*n*-3) fatty acids. This dose will define concentrations in the final product,' he adds.

Studies in asthma

The next step will be to test the safety and efficacy of different dosages of the fatty-acid combination in people with asthma; 'a forthcoming trial in people with asthma will evaluate the effect of the product on key biomarkers of lung inflammation,' explains Chilton.

The safety consequences of dietary supplements are of crucial importance and are exemplified in the potential cardiovascular risks of taking GLA alone. Indeed, Chilton and colleagues highlight this point in their recent study: 'As the nutraceutical industry continues to experience explosive growth, it will be increasingly important to understand the safety profiles of dietary supplements'[1]. If Pilot's studies are successful, Chilton anticipates that the supplement will be available early in 2001.

REFERENCES

1 Barham, B.J. *et al.* (2000) Addition of eicosapentaenoic acid to γ-linolenic acid-supplemented diets prevents serum arachidonic acid accumulation in humans. *J. Nutr.* 130, 1925–1931

2 Johnson, M.M. *et al.* (1997) Dietary supplementation with γ-linolenic acid alters fatty acid content and eicosanoid production in healthy humans. *J. Nutr.* 127, 1435–1444

Sharon Dorrell

News in brief

Autoimmune diseases committee to sit within NIH Director's Office

An Autoimmune Disease Coordinating Committee is to be created to sit permanently within the Director's Office of the National Institutes of Health (NIH), reported the American Autoimmune Related Diseases Association (AARDA) recently. The committee, created by legislation that is part of the Children's Health Act, will oversee all autoimmune research carried out by NIH facilities and will co-ordinate these activities with other relevant Federal agencies, such as the Centers for Disease Control and Prevention and the Food and Drug Administration.

The diseases of the autoimmune process are highly diverse (type 1 diabetes, lupus and multiple sclerosis) and it is hoped that effective coordination of research and knowledge will yield improved results and new ways to secure funding. One of the major questions to be addressed is why autoimmune diseases disproportionately affect women as autoimmunity is one of the ten leading causes of death among women aged 65 and under. Other research will examine the biomedical, psychosocial and rehabilitative issues associated with these diseases.

Public would prefer to know if genetically predisposed to cancer

If given the choice, at the age of 30, of knowing whether you are predisposed to develop cancer at the age of 55, 78% of people said they would prefer to know, reports a survey recently conducted by Roche UK. Four-fifths of the questioned group went on to state that, if found predisposed to developing cancer, they would then take preventative measures to reduce that risk, such as quitting smoking or drinking alcohol. The survey also enquired into people's attitudes to ageing. Although 30% of

 1359-6446/00/$ – see front matter PII:S1359-6446(00)01591-9

people questioned said they would be happy with the thought of living past 100, the majority would rather live a natural lifetime. Finally, 10% said that if they could, they would consider having their first baby at 60 years of age.

Early treatment with Avonex delays onset of MS

A recent report has demonstrated that early treatment with Biogen's (Cambridge, MA, USA) interferon β1a (Avonex®) significantly postpones the onset of clinically definite multiple sclerosis (rate of development of MS reduced by >44% compared with placebo). These studies were conducted in 'high risk' individuals[1], who have not been diagnosed with MS but have experienced one symptom (i.e. the onset of a first acute demyelinating event such as optic neuritis, incomplete transverse myelitis or brainstem/cerebellar syndrome). Further, a relative reduction in the number and volume of brain lesions examined through MRI scans were reported after treatment.

This Phase III clinical trial, known as the CHAMPS study (controlled high-risk subjects Avonex multiple sclerosis prevention study), was randomized, double blind, placebo-controlled and involved 383 patients who were at a high risk of developing MS, as determined by brain MRI changes and clinical events consistent with MS. Patients received weekly intramuscular injections of either 30 μg Avonex or placebo; although the trial was intended to last three years, it ended early to enable patients in the placebo group to benefit from treatment.

'To date, there are no accepted guidelines for treating patients who have experienced a single MS-like attack but who have not yet developed clinically definite MS,' said Lawrence Jacobs, Head of the Department of Neurology at the Buffalo General Hospital (Buffalo, NY, USA) and principal investigator. 'This study is extremely important because it indicates that initiating therapy with Avonex at the first indication that a patient might have MS can significantly delay the development of the disease.'

'This study will contribute to changing the treatment paradigm for early MS from "watch and wait" to "diagnose and treat early"', said James Mullen, President and CEO of Biogen.

1 Jacobs, L.D. (2000) Intramuscular interferon β1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *New Engl. J. Med.* 343, 898–904

More stability predicted for biotechnology companies

A major new phase of growth in biotherapeutics has been predicted by Decision Resources (Waltham, MA, USA), fuelled by a stream of receptor-based targets (especially for proteins and peptides) from genomics research. The report, entitled *The Global Biotechnology Industry in 2010*, suggests that as the new technologies and techniques become less experimental, there should be better opportunities for long-term investments, which should in turn enable the industry to discover and develop novel drugs in a more predictable financial environment.

The perception that biotechnology companies are difficult to value and are always a long way from earning profits is thought to be fading, although they are still more volatile than other hi-tech industry segments. However, true stability in the industry is unlikely to occur until the intellectual property issues with regard to genomic information have been resolved. Without the ability to convince potential investors that it can conduct business in a secure legal framework, provided by securing and defending intellectual property rights, a start-up biotechnology company could have difficulty in raising significant capital.

NDA for anticancer drug refused approval

The New Drug Application (NDA) for Aptosyn (exisulind) for familial adenomatous polyposis (FAP) has been orally refused approval by the Food and Drug Administration (FDA), according to its developers Cell Pathways (Horsham, PA, USA). A formal letter outlining the deficiencies the FDA found in the NDA is expected by the company, upon which they anticipate requesting a meeting to discuss the future of Aptosyn.

Aptosyn is one of a novel class of compounds called selective apoptotic anti-neoplastic drugs (SAANDs) that inhibit a novel form of cGMP phosphodiesterase and selectively induce apoptosis in abnormally growing precancerous and cancerous cells. In addition to FAP, Aptosyn is also being studied as a single agent, or in combination with conventional chemotherapeutic drugs, for treating a variety of other cancers and precancerous indications. Cell Pathways' second SAAND compound, CP461, has recently completed Phase Ib clinical trials as a single agent.

Potential beneficial effects of HE2200 on inflammatory bowel disease

Hollis-Eden Pharmaceuticals (San Diego, CA, USA) have concluded that HE2200, a second-generation immunomodulator, acts as a potent immunosteroid with immunoregulatory and anti-inflammatory properties in a preclinical model of inflammatory bowel disease.

An experimental animal model of inflammatory bowel disease was used, and distal colitis was induced by intracolonic instillation of 2,4-dinitrobenzenesulfonic acid (DNBS). Animals were administered with placebo, sulfazalazine (administered orally for 7 days) or HE2200 (2 mg per day subcutaneously for 5–6 days). All animals receiving placebo or sulfazalazine had diarrhoea, but only two out of nine animals receiving HE2200 had diarrhoea. HE2200 and sulfazalazine-treated animals had reduced colon-to-body weight ratios compared with placebo animals; the former two groups also had reduced intestinal

adhesions and colon ulcerations relative to placebo-treated animals. These results indicate that HE2200 might be beneficial in treating inflammatory bowel diseases and related gastrointestinal disorders.

HE2200 is a candidate for clinical trials in 2001, and is licensed from Roger Loria (Virginia Commonwealth University, Richmond, VA, USA).

University hires contract research company to meet FDA standards

The University of Pennsylvania (Philadelphia, PA, USA) has entered into an agreement with the contract research management and development organization Covalent Group (Wayne, PA, USA) to help the University meet new Food and Drug Administration standards for human clinical research. Covalent will also assist in the training of key personnel on clinical research compliance issues.

The new standards, for laboratories that conduct human trials, already apply to corporate research outfits but have now been extended to cover all research entities, including academic institutions. The training in Good Clinical Practices (GCP) guidelines is expected to be completed by mid-2001, and could define the model for research studies conducted in humans that could then serve as a prototype for future relations between the FDA and academic medicine.

New targets for HIV vaccine development

A recent study has reported that the key viral proteins that are predominant early in the viral life cycle might be attractive targets for HIV vaccine development[2]. Researchers from Epimmune (San Diego, CA, USA) and the University of Wisconsin (USA) showed that replacement of amino acids with key viral proteins (Tat, Rev and Nef) in rhesus monkeys infected with simian immunodeficiency virus (SIV) enables the virus to escape the immune response. Furthermore, mutations of the dominant Tat epitope was associated with an inability of Tat-specific killer T cells to recognize and kill virus-infected cells. The researchers therefore suggest that the Tat-specific killer T cells could play a significant role in controlling the virus in the early stages of infection, making it an ideal target for epitope-based vaccines. Epimmune hope to enhance the immunogenicity of this epitope by altering its amino acid sequence.

2 Allen, T.M. *et al.* (2000) Tat-specific cytotoxic T lymphocytes select for SIV escape variants during resolution of primary viraemia. *Nature* 407, 386–390

Positive results for α1-antitrypsin study in cystic fibrosis patients

PPL Therapeutics (Edinburgh, Scotland) has announced positive results for their transgenic α1-antitrypsin (tgAAT) in a one-year safety study in patients with cystic fibrosis (CF). All patients received daily aerosol administration by nebulizer of 250 mg tgAAT. No drug-related serious adverse events were recorded in any of the patients, and all had a stable lung function throughout the study.

This safety study followed, and involved patients from, an earlier six-month placebo-controlled trial that indicated that 250 mg of tgAAT administered by nebuliser to patients with CF resulted in a 50% reduction in the frequency of exacerbations (reported in February 1999).

Further, the one-year safety study indicated that sustained and prolonged tgAAT therapy might offer an additional benefit because CF patients showed a lower frequency of exacerbation in the second six months of the study than the first.

PPL are to collaborate with Bayer to develop nebulized AAT medication for CF and AAT-deficient patients. In AAT-deficient patients, Phase III clinical trials are due to start before the end of this year; subsequently, Bayer and PPL will establish the most effective combination of nebulizer technology and trial design, which will then be taken forward into Phase III clinical trials for CF.

Fungal market expected to grow

The international market for anti-fungal therapeutics is expected to grow over the next ten years because populations are becoming increasingly susceptible to severe fungal infection (SFI) and increasingly treated using drugs. These are the predictions in a forthcoming Decision Resources (Waltham, MA, USA) study entitled *Strategic Overview of Severe Fungal Infections*.

During this time period, drug-resistant pathogens and previously rare fungi are expected to emerge as novel sources of human infection. In addition, the rate at which the HIV and AIDS epidemics spread throughout the population will have a major effect, as infected individuals will be markedly more prone to developing SFIs.

Changes in medical practice and the launch of novel, safer and broader-acting drugs are expected to increase sales in the seven major pharmaceutical markets (US, France, Germany, Italy, Spain, UK and Japan). Three novel azoles – voriconazole (Vfend, or UK109496; Pfizer), posaconazole (SCH56592; Schering-Plough) and ravuconazole (BMS207147; Bristol-Myers Squibb) – are in late-stage development and offer improved potency and a wide spectrum of activity.

A new class of agents, the candins, comprising caspofungin (Cancidas or MK0991; Merck), micafungin (MK463; Fujisawa) and anidulafungin (V-echinocandin or LY303366; Versicor) are also eagerly anticipated. Finally, Aronex is developing Nyotran, a novel liposomal formulation of nystatin, while a new class of protein synthesis inhibitors, the sodarins, is in preclinical development by Glaxo SmithKline.

Positive Phase II results for the antifungal V-echinocandin

An open-label, randomized Phase II clinical trial of V-echinocandin (VEC;

Versicor, Toronto, Canada), the antifungal compound, showed positive safety and efficacy results for the treatment of oesophageal candidiasis. This disease is common in immunocompromised patients such as in AIDS or during chemotherapy treatment.

The study examined 29 patients with oesophageal candidiasis following 14–21 days of intravenous VEC. Endoscopy revealed an 80–85% efficacy of VEC with no serious drug-related adverse events. VEC is an inhibitor of cell wall synthesis in fungi. The company is now planning Phase III trials.

The results of the study were presented at the *40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy*. The company also presented positive interim Phase I trial results for the second-generation anti-bacterial glycopeptide, V-glycopeptide, which is related to vancomycin, showing it is safe and well tolerated. Phase II studies are planned for early 2001.

Peanuts stave off hunger with no increase in weight

Peanuts have been shown to be an effective way of controlling hunger without any associated weight gain[3]. The study showed that 12 male and 12 female healthy subjects of normal weight who snacked on peanuts or peanut butter self-adjusted their calorie intake, and their hunger was reduced for 2.5 h. By contrast, after typical portions of other snacks (such as rice cakes, chestnuts, chocolate), hunger returned within half-an-hour. Additionally, their overall fat profile improved while consuming peanuts, as their mono- and polyunsaturated fat levels increased while their saturated fat levels decreased, supporting previous long- and short-term studies that regular consumption of peanuts reduces the risk of heart disease and does not promote weight gain.

3 Kirkmeyer, S.V. and Mattes, R.D. (2000) Effects of food attributes on hunger and food intake. *Int. J. Obesity* 24, 1167–1175

Same principle used to develop both herpes and HIV/AIDS vaccine

A preventive HIV/AIDS vaccine, AIDSVAX®, which is currently in large-scale Phase III clinical trials, was developed using the same principle as that used to develop the first successful herpes vaccine. These vaccines were co-invented by Philip Berman, Senior Vice-President of R&D at VaxGen (Brisbane, CA, USA), and were developed by the cloning of key surface or envelope proteins of the viruses. The cloned envelope proteins do not cause infection, but they prime the human immune system to produce antibodies against the viruses.

The herpes vaccine was shown to be >70% successful in preventing genital herpes in women with no previous exposure, which could extensively reduce the spread of this virus. 'These results are very encouraging,' said Berman. 'This is evidence that a vaccine based on envelope proteins can be effective against sexually transmitted viruses.'

The VaxGen vaccine, AIDSVAX, is in two Phase III clinical trials, one in North America and Europe (5400 participants) and one in Thailand (2500 participants). If analysis indicates that this vaccine is at least 30% effective, VaxGen will stop the trial and apply for regulatory approval. If not, the trial will continue until the end of 2002.

Rebecca N. Lawrence, Ben Ramster and Annabel Hinde

Collaborations…

De Novo Pharmaceuticals Ltd (Cambridge, UK) have announced their collaboration with **Aventis Pharmaceuticals** (Parsippany, NJ, USA) under De Novo's Drug Design Partnership Program. In return for a technology access fee and 12 months research funding, De Novo will provide Aventis with novel patentable small-molecule leads for its research program. De Novo's expertise and platform of proprietary computer algorithms will be used to convert information from structural genomics and medicinal chemistry into new chemical designs. This partnership will build on the existing TeknoMed collaboration in drug design technology development between Rhone-Poulenc Rorer (now part of Aventis) and Cambridge University (Cambridge, UK).

Genzyme General (Cambridge, MA, USA) and **Cambridge Antibody Technology** (CAT; Melbourn, Cambridge, UK) have announced a collaboration to develop and commercialize human monoclonal antibodies directed against TGF-β. Primarily, the aim is to develop a treatment for diffuse scleroderma, a life-threatening disorder caused by excess production of collagen, which leads to scarring of the skin and internal organs, for which there is currently no effective therapy. Genzyme has received an exclusive global license to CAT's anti-TGF-β antibodies for all clinical applications, including post-surgical scarring, fibrosis of major organs and certain forms of cancer, but the agreement excludes ophthalmic use. Furthermore, Genzyme has received a non-exclusive global license from CAT for non-antibody antagonists to TGF-β in exchange for milestones and royalties. R&D and commercialization activities will be funded jointly and profits will be shared. CAT will receive significant credit for initial contributions to the collaboration and its future profit share will be calculated accordingly. Genzyme will make a US$20 million equity investment in CAT, which will give Genzyme an ~1% equity stake in the company. Genzyme will be responsible for the clinical and regulatory development of products, global marketing and sales, and CAT will be responsible for antibody optimisation, in addition to the codevelopment of antibodies with Genzyme.