advertising slogan that it 'fortifies the over forties' is Phyllosan, manufactured throughout the second half of the 20th century by Beechams. At the height of its popularity in the 1970s and 1980s, each tablet comprised 65 mg Ferri Phosphas (a mixture of hydrated ferrous phosphate and ferric phosphate) although this was replaced by 35 mg ferrous fumarate in the early 1980s; 8.5 mg nicotinic acid; 0.166 mg thiamine hydrochloride; 0.333 mg riboflavine and 5 mg ascorbic acid.

'Life begins at forty?'

How the slogan originated is open to debate but the product itself had already been on the market for many years. During World War II, it had an altogether different formula, comprising 10 mg chlorophyll, 10 mg Ferri Phosphas, 100 mg sucrose and 50 mg dibasic calcium phosphate. The inclusion of chlorophyll is somewhat of a mystery until one realizes that the material had an official monograph in the 1934 British Pharmaceutical Codex where its uses were listed as 'possessing blood forming properties particularly when given with iron'. The product, then manufactured by Natural Chemicals (London, UK) was claimed 'to revitalize the blood and fortify the heart, relieve arterial tension, improve the circulation, strengthen the nerves, stimulate metabolism and increase the vital forces' [5]. Ideal for the ravages of age!

Final words

Two centuries after Confucius, Mencius, another Chinese philosopher wrote [7]:

'At forty I attained an unperturbed mind'.

Surely, for all you pre- and post-40 youngsters, this is worth waiting for. Throw away the Phyllosan and enjoy life!

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Polymers – a synthetic or natural choice? ▼

The recent paper in *Drug Discovery Today* by Hunter and Moghimi [1] highlighted many issues –biological and pharmacological activity together with immunotoxicity – that are related to synthetic polymers and polymer conjugates, which are a consuming concern. This paper suggests that the quality of the work that we apply to these issues could be raised, and the resultant 'benefit' to the patient is a mutual objective.

However, any interventive procedure, surgical or pharmacological, is subject to detailed and continual risk–benefit evaluation. Synthetic polymers seem to be presented negatively in this article, although the issues raised are significant, the 'benefit' to patients that polymers offer with respect to drug delivery is largely ignored. Indeed, Peginterferon a-2a plus ribavirin is linked to a lower rate of troublesome side effects – depression, flu-like symptoms (chills, headache and fever) – than the standard interferon and ribavirin treatment in the care for chronic hepatitis C patients [2].

It is stated that, in opposition to polydisperse synthetic polymers, endogenous biopolymers, when synthesized *in vivo*, are monodisperse with an absolutely defined structure, biological function and fate. This statement appears to neglect that polymers *in vivo* are synthesized as a process and, hence, many intermediate forms of the monodisperse end-product are also present in biological systems. We should not ignore the numerous mechanisms (e.g. glycosylation, phosphorylation, sulfation, deacylation,

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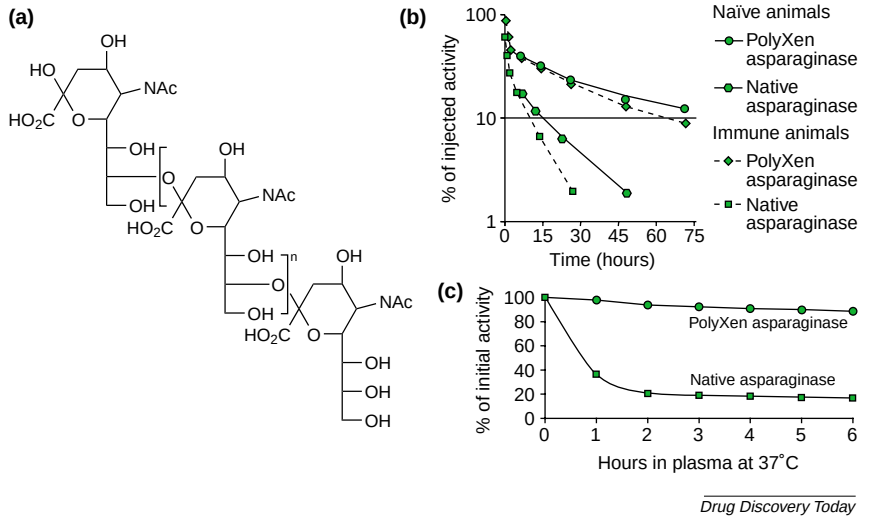

Figure 1. (a) The biopolymer polysialic acid (PSA) **(b)** extends half life (solid line) and reduces antigenicity (broken line) **(c)** and retains activity of conjugated drug .

deamidation and oxidation), that can result in heterogeneity of a monodisperse product. The issue of heterogeneity in biological materials is identified as a challenging and controversial problem facing the World Health Organization biological standardization program [3]. I agree in principle that biological materials, including biopolymers, do posses a defined structure, biological function and fate, but I am not confident that we posses all the facts in relation to either polymers or biopolymers.

Perhaps biopolymers do offer a greater potential for exploitation than synthetic polymers; biopolymers might be able to avoid the many chemical contaminates that have been suggested to exert immunotoxicity, cited by Hunter and Moghimi. Numerous groups, including Gregory Gregoriadis [4], have advocated and demonstrated the value of biopolymers in relation to drug delivery (Fig. 1). Polysialic acids (PSAs) are naturally occurring hydrophilic polymers of sialic acid, which are known to be biodegradable with non-toxic catabolic products. PSAs are used by bacteria to escape recognition by the immune system of the host and are evolved to be immunologically evasive. Although a substantial number of issues raised also need to be addressed by workers using biopolymers, the list might not be as large as for synthetic polymers.

Hunter and Moghimi suggest a paradigm shift in relation to synthetic polymer thinking; I would like to add that immunotoxicity is not all bad. This statement is supported by a recent paradigm, that of the danger model [5] introduced into the field of immunology, and has implications related to vaccine products in my own area of interest.

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Polymer therapeutics – what is missing? ▼

The recent review by Hunter and Moghimi [1] covers a broad area; polymer therapeutics, polymers used in new chemical entity (NCE) formulation and polymer–drug conjugates – I will restrict my comments to the third class of polymer. A limited range of (homo)polymers is listed by the US regulatory authorities as being biologically inert (http://www.fda.gov/cder/drug/iig), although the FDA make the point that this might not always be the case. Few of these homopolymers are listed for parenteral use and most have simple and uncharged residues.

Success for polymer therapeutics can only be judged by clinical success, which is most likely to be achieved by industrial rather than academic organizations. All of the concerns raised in the review article have been considered by companies in depth (there are pegylated drugs on the market), but they have not been effectively communicated to academia, where much of the primary research is conducted. It is easy to make a polymer conjugate but the knowledge of how to convert it into a marketable drug is often missing (compared with NCEs). The analytical burden of many polymer systems described in the literature would make them non-viable as drug candidates.

The regulatory authorities and corporate analytical departments prefer chemistries where the regiochemistry is defined and there are specific points of attachment of drugs. Bear in mind that all impurities have to be identified down to a few percent in a manufacturing process and that few reactions go to completion. Low molecular weight impurities can be quantified readily, but drugs with a polydisperse core are particularly troublesome. Techniques for analyzing the drug metabolism and pharmacokinetics (DMPK) of such polymers *in vivo* are also essentially