Box 1. The formulation of Bile Beans in the 1940s [1]

Aloes Barb.	6.67%
Res. Podophyllum	4.42%
Res. Scammony	8.85%
Leptandrin	3.30%
Pulv. Ext. Jalap	8.85%
Pulv. Ext. Colocynth	2.67%
Ext. Gentian	17.75%
Cascarin	6.67%
Cardamom	2.67%
Zingiber	10.67%
Saponis Cast.	1.65%
Ol. Menth. Pip.	4.42%
Ol. Res. Capsicum	0.75%
Ol. Res. Zingiber	4.42%
Excipients to:	100%

in the 1960s, the product was then taken over by Fisons of Loughborough (England) who continued its manufacture until its withdrawal in the mid 1980s. During this time the formulation was standardized as shown in Box 2 [2].

It is interesting to note that, in this formulation, liquorice is listed as an active ingredient. Unfortunately, the claims were not given with this formulation but no doubt they were certainly expurgated (I make no apologies for the pun) in the light of the then current Medicines Acts.

The question remains as to why this product had such a long lifespan. No doubt, like all proprietary medicines, it must have had its devotees who swore by its effect on them and purgation is not a difficult effect to identify. The date of its withdrawal is interesting because the 1980s would have seen the death of the majority of those born when the product was at its height in the early part of the 20th century when there was an obsession with purgation and inner cleanliness. Thank goodness that is now at an end!

Box 2. The standard formula of Bile Beans in the 1980s [2]

Cascara dry extract	17.8 mg
Jalap resin	3.09 mg
Peppermint oil	0.89 mg
Ginger oleoresin	1.57 mg
Powdered ginger	12.59 mg
Capsicum oleoresin	0.79 mg
Extract of colocynth	4.97 mg
Powdered aloes	23.4 mg
Cardamom fruit	1.82 mg
Ipomoea resin	4.38 mg
Sodium tauroglycocholate	11.24 mg
Powdered gentian	5.11 mg
Extract of gentian	10.37 mg
Powdered liquorice	14.81 mg

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Synthetic polymers in 21st century therapeutics: the way forward ▼

We are delighted to see that our recent perspective review [1] has generated numerous responses with markedly diverse points of view. Our article provided selected examples on the nature of therapeutic polymers and their wide range of effects on the immune system and cellular machinery. The intention was to stimulate research into the understanding of the molecular basis of such interactions and associated responses, as the basis of a paradigm shift in thinking in this area of research. Such studies would provide us with the necessary scientifically derived rational information for the successful design and engineering of polymers for use in medicine. Parallel to this there is a need for technological advancement in polymer synthesis, characterization and separation of these materials if this desirable objective is going to be achieved. We applaud the comments of Pardridge [2] and Phillips [3] for their further emphasis on the importance of these issues.

Some of the respondents [4,5] have suggested that the pharmaceutical industry has been performing toxicity tests on a wide range of macromolecular materials. Although this might be a fundamental process to ultimately fulfil regulatory requirements, it is distinct from

 1359-6446/03/$ – see front matter PII: S1359-6446(03)02605-9

conducting a thorough scientific investigation into underlying causal factors and omits new issues that have come to light through recent advances in immunology, as well as molecular and cellular biology [6].

For example, poly(ethylene glycol), PEG, is generally accepted as a pharmaceutically safe polymer however, recent work [7] has demonstrated the inhibitory effect of PEGs on P-glycoprotein (Pgp). PEG is known to prolong the circulatory profile of proteins, which is perceived to provide clinical advantage [4]; therefore, it might trigger deleterious effects on the function of protective biological barriers and underlying tissues in the systemic circulation, for example Pgp expressed on the brain endothelium [8,9]. Furthermore, recent studies also indicate that grafting of PEG to liposomes [10], and even red blood cells, further enhances complement activation [11]. Another concern is the precise role for the linkage chemistry in the generation and modulation of polymer toxicity, which could be highly pertinent to polymer-conjugated-drug or polymer carrier technologies.

Another example is recent work from our laboratory [12], which has confirmed that poloxamer-induced complement activation is an intrinsic property of these macromolecules and not the contaminants as suggested by Davis [4]. Furthermore, complement-mediated pseudoallergic responses are unpredictable. The molecular basis of this characteristic remains unknown, although it seems to be dependent on the genetic profile of the individual [12,13]. Unfortunately, some investigators [4,14] do not appear to perceive these issues as important, yet in our view they are fundamental.

A converse approach has been argued by Bacon [15] as a partial answer to circumventing problems associated with synthetic polymers, such as polydispersity and the activity of unknown catabolic products, he suggests the use of biologically derived polymers such as the polysialic acids. However, this suggestion negates the possible immunological responses associated with such camouflage [16]. For instance, $\alpha(2\rightarrow8)$-polysialic acids B and K1, derived from pathogenic micro-organisms, are well known to elicit poor immunogenicity [16,19]. As suggested by Bacon [15] these materials exhibit stealth property in rodents and hence can be used for drug delivery purposes. However, the immunogenicity of sero group B capsular polysaccharide conjugate vaccines in mice is well known [17]. The binding of $\alpha(2\rightarrow8)$-linked polysialic acid antibodies to certain host antigens in mammals has raised concern about the safety of such conjugated vaccines in humans [18]. Recent studies by Devi *et al.* [19] have conclusively demonstrated that such conjugated systems are immunogenic and show T-cell-dependent properties in juvenile rhesus monkeys. Antibodies were elicited against both the spacer molecule as well as the whole complex. In addition, the authors [19] concluded that the safety profile was insufficient to justify clinical trials in man. On the basis of this evidence caution must be observed before such strategies are employed for the purpose of intravenous drug delivery.

Another concern is the possible binding of such polysaccharides to sialic acid binding receptors that are expressed by immune cells (e.g. sialoadhesin and siglec-5). These receptors function primarily as ligands, in signalling as well as recognition events [20,21]. This again highlights the fundamental importance of understanding the possible molecular interactions between polymers and host and the associated responses before they can be applied for drug delivery purposes. We are pleased to see that Bacon has the same view with regard to the application of certain polymers in vaccination protocols as indicated by us in our previous article [1].

In summary, what seems necessary is a clear understanding of how the polymeric materials induce immunotoxicity and interact with cellular machinery. Understanding these events will open avenues for the intelligent design and, hence, widespread use of polymeric materials in 21st century medicine, as opposed to limiting oneself to the currently available materials as suggested by Davis [4].

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The use of combi chem, high-speed analog chemistry and HTS in drug discovery ▼

Over the past decade, research groups in both the pharmaceutical industry and academia have used combi chem and high-speed analog chemistry (HSAC) as tools in the drug discovery process. When coupled with HTS, these approaches have led to the discovery of a significant number of lead structures, clinical candidates and marketed compounds. In a recent issue of *Drug Discovery Today* [1], a timely review describes the use of combinatorial chemistry to discover active matter at signal transduction targets.

Although the review focuses on one strategy (comb chem), I believe that it is necessary to re-emphasize the distinction between combi chem and HSAC. These are distinct chemical synthesis strategies; however, the terms describing them are sometimes used interchangeably. The field of combi chem has focused on the preparation of a limited number of the 10^{100}–10^{200} potential structures that can be made that do not violate the Lipinski 'rule of five' [2]. Variations of this combinatorial strategy include 'diversity oriented synthesis' approaches. Although compounds with excellent potency and specificity can be made, combi chem approaches have typically resulted in libraries of compounds with high logP values, low hit rates and poor ADME characteristics [2,3]. These liabilities truly become magnified (and highly costly) in moving from HTS hits to clinical candidates, where optimized ADME properties are crucial.

By contrast, HSAC focuses on the synthesis of compounds around a common scaffold. When the scaffold is chosen correctly, these densely populated analog expansions typically result in libraries of compounds with better hit rates and good ADME/Tox characteristics. Moreover, analogs derived from carefully chosen 'preferred' scaffolds with demonstrated good 'drug-like' properties would be predicted to have a better chance of delivering a clinical development candidate in a timely and more cost efficient fashion. For example, analogs based on the benzodiazepine template (a 'preferred' scaffold), have resulted in compounds with activities against GPCR, ligand-gated ion channel and kinase targets [4,5]. An inherent benefit of the HSAC approach is that most of the resulting compounds already possess good drug-like properties. Therefore, it should require less time and resources to bring an HTS hit to a clinical development candidate.

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 1359-6446/03/$ – see front matter PII: S1359-6446(03)02597-2