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Early dietary exposures and feeding practices: role in pathogenesis and prevention of allergic disease?

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ABSTRACT

Immune dysregulation has become a hallmark of the modern era. This has led to an epidemic of disease states that result from failed immune surveillance and inappropriate or maladaptive immune responses to self-antigens (autoimmunity) and environmental antigens (allergy). Although environmental change is clearly implicated, the specific causes are still unconfirmed. Any hope to reverse such immune dysfunction must be based on a clearer understanding of the causal pathways and the environmental factors that may be driving the concerning surge in disease rates. This review explores the role of modern dietary changes that, through their known documented immune effects, may play a role in either promoting or preventing disease. Food allergen avoidance has been largely unsuccessful, and most expert bodies no longer recommend delayed complementary feeding or the avoidance of any specific allergenic foods, unless symptoms develop and allergy is confirmed. Rather, focus has shifted to other factors that may influence the ability to develop immune tolerance. There is now evidence that specific nutrients, such as folate, have the capacity to promote an allergic phenotype by epigenetically altering gene expression during early development. A number of other dietary factors including n-3 polyunsaturated fatty acids, oligosaccharides, probiotics, vitamin D, retinoic acid and other antioxidants may also clearly influence immune function and immune development. This review summarises the current evidence, recommendations and future directions in the context of allergy, with the aim of highlighting the need to further investigate the role of diet and nutrition in disease pathogenesis and prevention.

The escalating prevalence of allergic disease^{1 2} is of urgent concern, particularly as the underlying cause of this “epidemic” remains uncertain. Although there is compelling evidence of a hereditary component in the pathogenesis of allergic diseases, the undisputed increase and the magnitude of geographical variations in prevalence cannot be explained primarily by genetic factors.^{1 3 4} This has therefore generated intense interest in the environmental changes that must be responsible. Curiously, the same environmental changes may also be implicated in the parallel rise in many other immune disorders (namely autoimmune diseases) during the same period. This further suggests that these environmental effects may impair common immune regulatory pathways, thereby allowing a wide range of inappropriate immune responses to go unchecked. The multifactorial nature of these diseases has made it difficult to identify specific individual factors that are contributing to the rise in disease.

As there are wide variations in the allergic phenotype, it is likely that different environmental

factors interacting with genetic predisposition contribute to the pattern of expression. Typically, the earliest manifestations of the allergic phenotype, often evident in infancy, are eczema and food allergy. Many such affected children go on to develop subsequent inhalant allergies and associated asthma and allergic rhinitis, in what is often referred to as the “atopic march”. However, this pattern is not seen in all individuals. Although different environmental factors at different developmental stages may contribute to disparate patterns of disease expression, this is still not known.

ENVIRONMENTAL CANDIDATES IN THE ALLERGY EPIDEMIC: ROLE OF DIET?

Although there have been considerable lifestyle changes over the past few decades, several leading candidates have been implicated in the rise in allergic disease because of clear epidemiological associations coupled with evidence of plausible immune mechanisms. These include changes in microbial exposure, environmental pollutants and complex dietary modifications. In contrast, there is little evidence that changes in allergen exposure play a significant role in the increase in allergic disease. Thus, the search for allergy prevention strategies has gradually shifted from allergen avoidance, which has been generally unsuccessful, to other environmental factors with immunomodulatory potential.

It is logical that environmental changes must be exerting effects very early in life, as allergic disease is often manifest in young infants. Thus exposures (or lack thereof) in utero and in infancy are presumably increasing susceptibility to the subsequent development of disease.⁴ Although declining microbial exposure has become one of the most popular theories for the increase in immune disease,⁵ there is also evidence that dietary factors can also have a significant effect on immune function and disease predisposition. In the prenatal period, maternal dietary factors (including fatty acids,⁶ antioxidants⁷ and folate⁸) can have significant effects on fetal immune development. In the postnatal period, the gut is arguably the most critical interface between the infant and its new environment. It is the site of highest exposure to microbial products, potential allergens and a broad range of dietary nutrients with immunomodulatory properties. These complex dietary exposures play a major role in the maturation of the mucosal immune system and have major implications for the success or failure of subsequent tolerance to foods. There is intense interest in how exposure to these oral exposures can be optimised to promote tolerance and prevent allergic disease.

MECHANISMS OF DIETARY AND OTHER ENVIRONMENTAL EFFECTS ON DISEASE PREDISPOSITION: EPIGENETIC EFFECTS?

"Epigenetic" regulation is essential to all aspects of development and allows genetically identical stem cells to produce a range of lineages with major differences in morphology and function. There is now firm evidence that environmental factors can influence the epigenetic pathways that control normal developmental programming and subsequent gene expression and physiological and metabolic adaptations. Changes in the methylation of DNA and histones, and histone acetylation alter the degree of DNA accessibility for gene transcription, regulating gene expression and/or silencing. Although this has been best studied in the context of cardiovascular⁹ and metabolic disease,¹⁰ the epidemic rise in both allergic and autoimmune diseases also highlights that epigenetic programming of immune development may also be susceptible to modern environmental influences.^{11 12}

It is well established that immune development and differentiation is under epigenetic regulation. For example, methylation of the interferon (IFN) γ gene promoter is the main epigenetic control of type 1 T helper cell (Th1) and regulatory T cell (Treg) expression, with progressive demethylation corresponding to postnatal increases in Th1 IFN γ ¹³ and Treg^{14 15} activity. In contrast, Th2 gene expression is associated with increases in histone acetylation, which opens chromatin structure for enhanced gene transcription.¹⁶ Expression of genes that lead to differentiation of proinflammatory Th17 cells also appears to be controlled by similar pathways.¹⁴

There is also now emerging evidence that environmental exposures in utero can alter the risk of subsequent allergic disease through epigenetic effects. Variation in maternal diet, exposure to cigarette smoke and microbial exposure have all been associated with changes in allergy risk. The most notable example of a clear epigenetic effect is evident in an animal model that clearly demonstrates that folate supplementation in pregnancy increases gene methylation (silencing) and the risk of allergic airways disease (as discussed further below). This provides clear support for a role of dietary factors in the pathogenesis and, potentially, prevention of allergic disease (as discussed further below).

ROLE OF GENETIC POLYMORPHISMS AND GENE-ENVIRONMENTAL INTERACTIONS

Variations in gene sequence can also have subtle effects on the function of some genes, and may account for individual differences in disease susceptibility. Asthma has been most extensively studied in this context, with associated genetic polymorphisms described in a number of pathways (reviewed elsewhere¹⁷). However, associations appear to vary significantly between populations, and none has been shown, as yet, to have a clear causal role. More recently, genetic associations have been described for atopic dermatitis. Specifically, mutations in the filaggrin gene have been implicated in altered skin permeability and disease susceptibility.¹⁸ Moreover, there is also speculation that increased "penetration" of allergens (including inhaled allergens) may be implicated in the pathogenesis of systemic sensitisation¹⁹ and other diseases.²⁰

The complexity of gene-environmental interactions is also becoming more apparent. Some environmental exposures may only be relevant in individuals with functional genetic polymorphisms in related pathways. Similarly, the effects of genetic polymorphisms may only be relevant in certain environments. One of the best known examples of this is the

observation that functional genetic polymorphisms in microbial recognition pathways (Toll-like receptor (TLR) 2) can confer protection from allergic disease, but only in the context of high bacterial exposure.²¹ This may explain apparent inconsistencies between studies conducted under different environmental conditions. Genetic differences may also explain some of the differences in the effectiveness of dietary interventions with microbial products (eg, probiotics) between individuals and populations. Functional polymorphisms have also been identified in the metabolic pathways of a number of other dietary candidates, including folate metabolism²² and fatty acid metabolism.^{23 24} Genetic variants of the fatty acid desaturase 1 fatty acid desaturase 2 (FADS1 FADS2) gene cluster are associated with variations in the polyunsaturated fatty acids (PUFAs) in cell membranes²³; however, at this stage the relationship to allergic disease needs to be further investigated. Similarly, the effect of variations in folate metabolism conferred by the MTHFR (C677T) genotype are not clear, with one study suggesting an association with allergic disease²² and another unable to confirm this.²⁵ These genetic polymorphisms could potentially alter the relationship between environmental exposure and biological effects.

ROLE OF SPECIFIC DIETARY FACTORS IN DEVELOPMENT OR PREVENTION OF ALLERGIC DISEASE

A number of dietary elements have clear potential to influence immune development and the risk of allergic disease.

Food allergens

The only established strategy for dietary allergy prevention has focused on avoidance of food allergens. This traditional approach has been largely unsuccessful (even detrimental), and a number of studies²⁶⁻²⁹ have led to speculation that prolonged attempts to avoid food allergens may not reduce the risk of allergic disease. Although there is also emerging evidence that prolonged avoidance of specific allergenic foods such as fish,³⁰ cow's milk,³¹ wheat²⁶ and egg²⁸ may actually be associated with higher risk of food allergy and atopic dermatitis/eczema, this is not conclusive. The relatively few studies addressing this issue have been retrospective, making them vulnerable to both recall bias and reverse causation.

Further research is needed to establish what effect (if any) delaying the introduction of solids, in general, and allergenic foods, in particular, into the infant diet has on allergic disease such as eczema and food allergy. A number of new studies are underway to address this, including the well-publicised "LEAP" study (<http://www.leapstudy.co.uk>) and the "EAT" study (<http://www.eatstudy.co.uk>), which are prospective randomised controlled trials of infant feeding. These studies are based on the concepts that oral tolerance is an antigen-driven process that depends on regular oral exposure to foods and other antigens (reviewed by Lack³²). Furthermore, there is evidence that additional favourable exposures, such as optimal gut colonisation,³³ breast milk³⁴ and/or other immunomodulatory factors,^{6 35} may also be important for promoting oral tolerance. With the evidence that changes in these factors rather than allergen exposure may be contributing to the allergy epidemic, there has been a shift in interest from allergen avoidance to the role of these other dietary and environmental exposures that may promote tolerance.

Breast milk

Breast milk is arguably the most important dietary exposure in infancy. It contains a complex array of immunologically active compounds, including immunoglobulins, lactoferrin, lysozymes,

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oligosaccharides, long-chain fatty acids, cytokines, nucleotides, hormones, antioxidants and maternal immune cells. In addition to protection from infection, these factors are also likely to have other effects on immune development including oral tolerance. A landmark study in *Nature Medicine* recently demonstrated that tolerance to allergens is dependent on cytokines such as transforming growth factor (TGF) β in maternal milk.³⁴ Maternal milk promotes regulatory T cells in the developing gut, and the addition of TGF β to formula increases tolerance.³⁶ Although a systematic review of 12 prospective studies (8183 infants)³⁷ found that exclusive breast feeding in the first months of life is associated with reduced rates of subsequent asthma (odds ratio 0.70; 95% CI 0.60 to 0.81), a number of later studies have failed to support this, and there are inherent limitations in studies addressing the effects of breast feeding on allergy, including the inability to randomise and blind. There is some evidence that continued breast feeding during the introduction of complementary foods is important for promoting tolerance, although this is limited to coeliac disease.³⁸ Breast feeding is strongly encouraged for many reasons, although the specific role in allergy prevention is not clear. Although more studies are needed, it seems logical to encourage continued breast feeding in conjunction with the introduction of "solid" food.

Dietary immunomodulatory factors

Observational studies examining the role of individual nutrients can be difficult to interpret because of correlations and complex inter-relationships between individual nutrients. One approach has been to investigate effects of common dietary "patterns" such as the "Mediterranean diet" on disease outcomes. Several recent studies have suggested that the "Mediterranean diet" may protect against wheezing in early childhood,^{39 40} and that this effect is largely due to dietary effects in pregnancy.⁴⁰ In a large population-based UK birth cohort, some dietary patterns were associated with eczema, IgE, lung function and asthma; however, none had any effect after other environmental confounders had been allowed for.⁴¹

Another approach to examining the effects of specific nutrients has been to perform randomised controlled intervention studies. In pregnancy, this must be approached with some caution, particularly as some nutrients proposed to be protective against allergic disease (such as vitamins E, A and D) also have the potential to increase disease or have other adverse effects (as reviewed by Shaheen⁴²).

Folate

Perhaps one of the most intriguing recent developments has been recognition of the epigenetic effects of dietary folate in the development of asthma. A recent animal model demonstrated that supplementation with folate (a dietary methyl donor) during pregnancy induces hypermethylation (suppression) of regulatory genes in lung tissue, leading to the development of allergic airways disease and associated systemic allergic responses.⁸ Notably, this effect was also transmitted to subsequent generations. The significance in humans is not yet clear. Although one recent study has reported that folate supplements in pregnancy are associated with increased childhood wheezing,⁴³ another found the opposite relationship,⁴⁴ and there is now an urgent call for further studies to address the role of folate further in this context.^{12 45}

Polyunsaturated fatty acids

Fish oil (n-3 PUFAs) supplementation has been extensively investigated and appears to be safe in pregnancy (reviewed by

Sala-Vila *et al*⁴⁶). Observational studies have suggested that maternal consumption of fish oil in pregnancy has protective effects on the development of allergic sensitisation,⁴⁷ eczema⁴⁸ and asthma,⁴⁹ although this has not been seen in all studies.⁵⁰ A recent long-term (16-year) follow-up of a pregnancy fish oil supplementation study (providing 2.7 g n-3 PUFAs in the active group) suggested that the risk of asthma was subsequently reduced compared with the placebo group (receiving olive oil).⁵¹ Another more recent intervention study⁵² has also shown a significant reduction in both food allergy and IgE-associated eczema in fish oil-supplemented children (compared with a placebo group). There have also been reports that fish oil supplementation in pregnancy was associated with increased maternal and cord blood TGF β mRNA expression and lower expression of Th2-related molecules (interleukin 4, interleukin 13 and CCR4).⁵³ The outcomes of other current intervention studies designed to assess the role of fish oil in allergy prevention are awaited with great interest.

Oligosaccharides (prebiotics)

It is known that non-digestible, fermentable oligosaccharides can selectively stimulate the growth and activity of bacteria in the colon and improve host health, but, so far, studies of the role of prebiotics in allergy prevention are limited. There has really only been one study specifically designed to assess the effects of prebiotics on allergy prevention.^{54 55} This reported lower cumulative incidences for possible allergic outcomes such as atopic dermatitis, recurrent wheezing and allergic urticaria in the intervention group compared with the placebo group. However, at this stage more studies are needed before recommendations can be made.

Probiotic supplements

A growing number of studies have investigated the effects of probiotic supplementation on the risk of allergy. We have reviewed them in more detail elsewhere.⁵⁶ Briefly, although some studies have shown that various combinations of prenatal and postnatal probiotics may reduce the risk of eczema, many other studies have shown no benefit. There is little evidence of benefits on other allergic outcomes. The effects (or lack thereof) are likely to depend on the strain, other environmental factors that affect colonisation, and host genetic factors (as indicated above). Considerably more research is needed in this area to understand how best to optimise early colonisation.

Antioxidants and other micronutrients

Recent dietary changes also include declining intakes of antioxidants (such as vitamin C, vitamin E, beta-carotene, zinc and selenium). Although there is no evidence that these trends are "causally" associated, epidemiological associations have been found between lower intake of antioxidant-rich foods (such as fresh fruits and vegetables) and allergic outcome in both adults⁵⁷ and children.^{58 59} The immunological properties of antioxidants also support this hypothesis.^{60 61} Although associations have been found between maternal antioxidant status in pregnancy and cord blood immune responses⁷ and reduced risk of developing wheeze, asthma and/or eczema in childhood,^{62–65} there is reluctance to explore this with supplementation studies in pregnancy because of concerns over paradoxical effects.⁶⁶ Concentrations of other vitamins, including vitamin D, which can promote immunoregulation through Treg differentiation,⁶⁷ have also been found to be associated with a reduced risk of infant wheezing.⁶⁴ Although some epidemiological associations have been found between vitamin D and allergy (reviewed by

Box 1 Key points underlying changes in complementary feeding practices

- ▶ There is little evidence that delaying the introduction of complementary solid foods beyond 6 months reduces the risk of allergy, and there have been some suggestions that delaying introduction of foods may actually increase (rather than decrease) allergy.
- ▶ There is insufficient evidence to support previous advice to specifically delay or avoid potentially allergenic foods (such as egg, peanuts, nuts, wheat, cow's milk and fish) for the prevention of food allergy or eczema. This also applies to infants with siblings who already have allergies to these foods.
- ▶ More research is needed to determine the optimal time to start complementary solid foods. On the basis of currently available evidence, many experts across Europe, Australia and North America recommend introducing complementary solid foods from around 4–6 months.
- ▶ Based on Infant Feeding Advice of the Australasian Society of Clinical Immunology and Allergy (http://www.allergy.org.au/images/stories/pospapers/ascia_infantfeedingadvice_oct08.pdf).

Litonjua and Weiss⁶⁸), they are largely indirect (such as distance from the equator and level of sunlight exposure) and not conclusive. Again, it is premature to make recommendations, so while the potential role of these factors is unclear, it is best to advocate a healthy balanced diet rather than specific vitamin supplementation.

CURRENT DIETARY RECOMMENDATIONS FOR ALLERGY PREVENTION

Although there has been some recent controversy over feeding guidelines, a degree of consensus is emerging in industrialised countries.^{35 69–71} Revised guidelines are based on the current available evidence, but this has highlighted the paucity of conclusive data in this field and the need for more studies to provide a basis for recommendations.

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Table 1 Feeding advice based on current evidence (as at September 2008)

	Current advice
Target population	All children, including those with siblings who already have allergies or children affected by eczema (even though these children are at higher risk of allergies).
Breast feeding	Breast feeding is recommended for at least 6 months and is encouraged for as long as the mother and infant wish to continue, without any maternal dietary restrictions. This is for the many nutritional and non-nutritional benefits of breast feeding for both the mother and infant. It is thought that continuation of breast feeding at the time foods are first introduced may help prevent the development of allergy to those foods.
Infant formulas before 4 months	If complementary formula is required before solid foods are started, recommendations vary. Where there is no family history of allergic disease in the infant's parents or siblings, a standard cow's milk formula may be used. Infants with a family history of allergy (parents or siblings) should be started on a partially hydrolysed cow's milk formula (usually labelled "HA" or hypo-allergenic). For known cow's milk allergy, these formulas are not suitable; elemental formulas are used instead. Soy milk and other mammalian milks (eg, goat's milk) are not recommended for allergy prevention or for infants with known cow's milk allergy.
Starting complementary foods	From 4–6 months onwards. When a child is ready, parents should consider introducing a new food every 2–3 days, according to what the family usually eats (regardless of whether the food is thought to be highly allergenic). In this way, reactions can be more clearly identified and the food excluded (or continued) as a part of a varied diet. Infants are unlikely to develop a new allergy to any food that is already tolerated, if it is given regularly. Breast milk or an appropriate infant formula should remain the main source of milk until 12 months of age, although cow's milk can be used in cooking or with other foods.
Allergenic foods	There are no particular allergenic foods that need to be avoided. Some children will develop allergies, but there is no way of accurately predicting who. If there is any reaction to a food, parents should exclude that food until the child is reviewed by a medical practitioner with experience in food allergy.

Based on Infant Feeding Advice of the Australasian Society of Clinical Immunology and Allergy (http://www.allergy.org.au/images/stories/pospapers/ascia_infantfeedingadvice_oct08.pdf).

Previous approaches

For many years feeding guidelines in industrialised countries have recommended delaying introduction of complementary foods until at least 6 months of age and prolonging avoidance of "allergenic" foods for up to 3–4 years. The original rationale for delayed feeding and avoidance of allergenic foods was that young infants have relatively immature mucosal immunity and greater gut permeability, which may increase the risk of systemic allergic responses. However, there is very little evidence to support this beyond the first 4 months of age.^{35 69–71} Despite this, prolonged avoidance of specific foods, including cow's milk protein (until 1 year), eggs (until 2 years) and nuts and fish (until at least 3 years), is still contained in many guidelines. There is preliminary evidence that, in addition to the logistic pressures and stress that restrictive diets place on families, infants on prolonged allergen avoidance diets are at increased risk of sensitisation.^{35 69–71} However, as indicated above, it is also well recognised that more research is needed to understand if the timing of the first complementary feeding is an important factor in the development of allergic disease.

Revised approaches

On the basis of the available literature, opinion leaders in Europe,^{69 71} the USA⁷⁰ and Australia³⁵ have independently concluded that there is no scientific evidence to support delayed introduction of complementary "solid" foods beyond 4–6 months of age or avoidance of any specific "allergenic" foods. The

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Key learning points

- ▶ Modern environmental changes are associated with a rise in a wide range of diseases associated with failure of immune tolerance.
- ▶ These effects are likely to occur very early in development, and dietary exposures are a significant influence during this period.
- ▶ More research is needed to understand the specific environmental factors that influence immune tolerance and how they can be modified for disease prevention.

rationale for this, together with an example of specific feeding advice for parents, is shown in box 1 and table 1.⁷²

At this stage, until further research has been completed, there are no specific recommendations for the use of dietary supplements (ie, probiotics, prebiotics, fatty acids, vitamins and other micronutrients). A nutritionally balanced diet therefore remains the best approach.

FUTURE DIRECTIONS

A number of randomised controlled trials are now being carried out examining if early introduction of specific “allergenic” foods such as peanut and egg will actually promote specific oral tolerance to these foods and reduce the risk of specific allergies.⁷² Other studies are investigating the age of first feeding (in general rather than for specific foods). These approaches are aimed at earlier oral exposure to induce tolerance before sensitisation occurs through cutaneous or respiratory routes (reviewed by Lack³²). The outcomes of these studies are awaited with enthusiasm, and it is possible that the results could further modify feeding guidelines.

The results of a series of studies examining the postulated allergy-protective effects of n-3 PUFAs should be available in the next few years. The role of probiotic and prebiotic supplements remains unclear. Despite initial reports that these may reduce the risk of allergic disease, there is insufficient evidence to recommend their use. Similarly, further studies are needed to determine the role of folate supplementation in pregnancy (for preventing neural tube defects) in the rise of allergic disease.

CONCLUSIONS

Diet in pregnancy and the early postnatal period is of fundamental importance for all aspects of infant growth and development. There is now clear evidence that dietary elements have the capacity to alter immune development and the risk of subsequent allergic disease. A better understanding of these pathways is important for the delineation of disease pathogenesis and disease prevention strategies.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. Concerning allergen avoidance

- A. Avoidance of specific allergenic foods (such as peanut, milk and egg) is an effective measure for preventing allergic disease
- B. Introduction of complementary feeding before 3-4 months of age has been associated with increased allergic disease
- C. The use of hydrolysed infant formulas reduces the development of allergic disease in children at high risk of allergy, compared with standard cows' milk formulas
- D. Delayed introduction of allergenic foods has been associated with increased risk of allergic disease

2. Concerning gene–environmental interactions

- A. Environmental exposures can induce epigenetic changes that can be heritable from one generation to the next
- B. Demethylation of the interferon gene promoter is associated with gene silencing
- C. The effect of an environmental exposure can vary significantly according to functional genetic polymorphisms
- D. The disease risk conferred by a specific genotype can vary according to environmental exposures

3. Concerning immune development

- A. The rise in immune disease is believed to be due to environmental changes that are promoting Th2 development and inhibiting Th1 development
- B. Environmental exposures in utero can induce variations in neonatal immune function
- C. It is well established that immune development is under epigenetic control
- D. The parallel rise in both autoimmune and allergic disease implicates environmental effects on common regulatory pathways

4. Concerning the current knowledge of environmental exposures

- A. Breast milk is a natural source of prebiotic oligosaccharides
- B. Folate is a methyl donor which can alter gene expression through epigenetic effects
- C. Colonisation of the gut is critical for oral tolerance
- D. Fish oil supplementation in pregnancy can be recommended for reducing the risk of allergic disease

5. Concerning the allergic phenotype

- A. Atopic dermatitis has been associated with filaggrin gene defects, and changes in skin permeability
- B. Transcutaneous sensitisation has been implicated in the progression to inhalant allergic diseases
- C. The “atopic march” refers to the progression from atopic dermatitis and food allergy to asthma and allergic rhinitis, and generally applies to all children with the atopic phenotype
- D. Dietary exposures in utero may influence the risk of allergic disease

See page 99 for answers

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ANSWERS

1. (A) F; (B) T; (C) T; (D) T; 2. (A) T; (B) F; (C) T; (D) T; 3. (A) F; (B) T; (C) T; (D) T; 4. (A) T; (B) T; (C) T; (D) F; 5. (A) T; (B) T; (C) F; (D) T