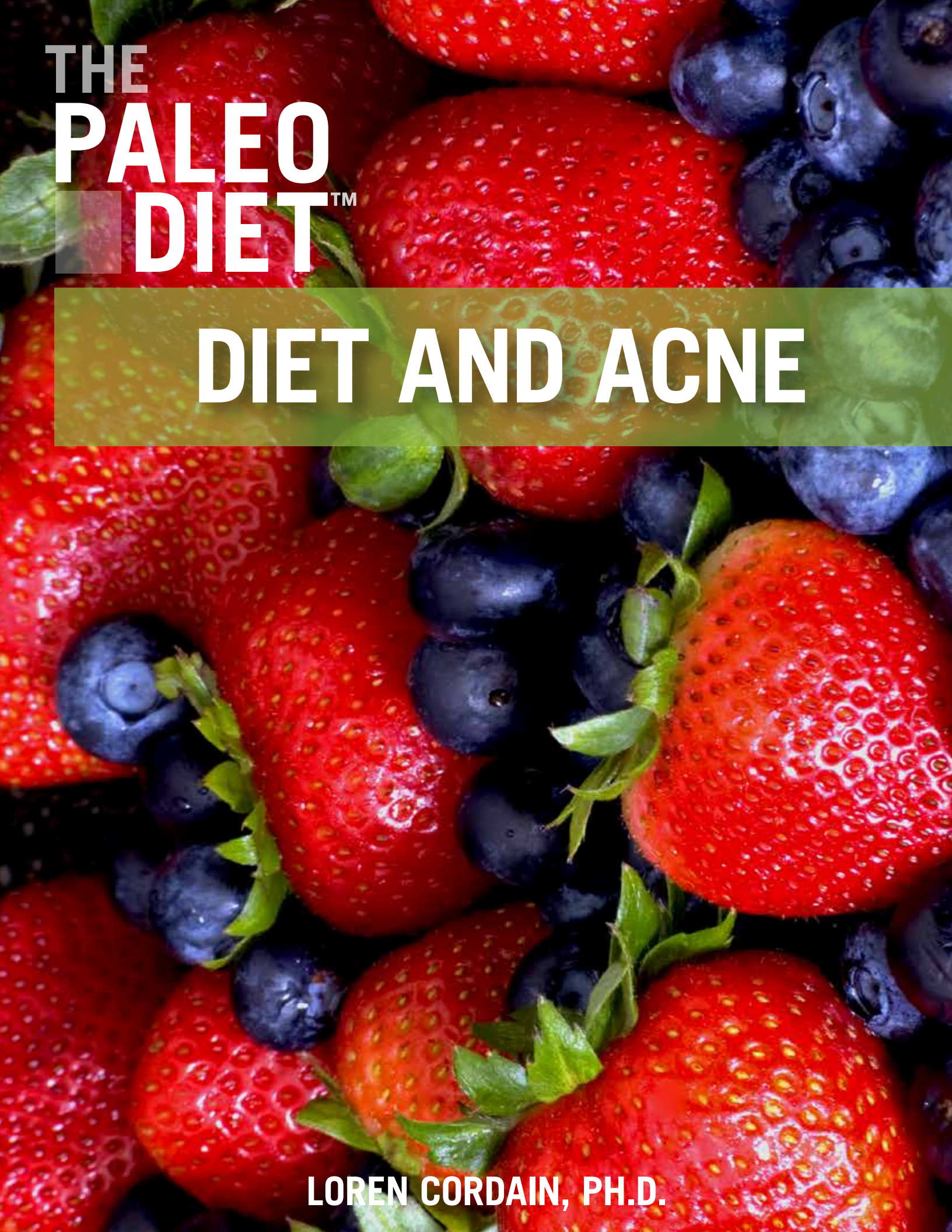

THE PALEO DIET™

DIET AND ACNE

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By Loren Cordain, Ph.D., Professsor

Following our 2002 publication in *The Archives of Dermatology*[1] demonstrating that acne was not present in two non-westernized populations, there has been renewed interest in the role that diet may play in the pathogenesis of this disease. In the past two years, there have been many studies that now support the link between diet and acne.[2-5] Although these reports will need to be followed up by more extensive experiments, they are important for two reasons: 1) they represent the only well controlled, modern studies of diet and acne that have been published in more than 35 years[6], and 2) they are contrary to the long held belief that acne is not caused by diet.[7-9]

RANDOMIZED CONTROL TRIALS

In addition to our ecologic study demonstrating the absence of acne in the Kitavan islanders of Papua New Guinea and the Ache hunter gatherers of Paraguay[1], two recent observational epidemiological studies also support the notion that diet is linked to acne.[2,3] In a retrospective cohort of 47, 355 women, after accounting for age, age at menarche, body mass index, and energy intake, Adebamowo and colleagues found a positive association between acne incidence and total and skim milk intakes.[2] In a prospective cohort of 6,094 girls, aged 9-15 years studied from 1996 to 1999 milk drinking of all kinds (total, whole, low fat and skim) was positively associated with acne.[3] These two observational experiments are important in that they are the first evidence in westernized populations to show that diet (and milk in particular) is associated with acne. In order to establish causality, future randomized controlled trials, in which milk is either added to or excluded from the diet and acne symptoms assessed, will be needed to confirm these preliminary epidemiological observations.

Mann and colleagues recently completed a more powerful randomized controlled trial evaluating the effect of a low glycemic load, high protein diet upon acne symptoms in 43 male acne patients aged 18. 3 +/- 0.4 years.[4,5] Subjects were randomly assigned to either an experimental group with a diet consisting of 25% energy from protein and 45% energy from low glycemic index carbohydrates or to a control group consuming their usual diet. Following the 12 week dietary intervention, total and inflammatory lesion counts decreased significantly in the treatment group compared to the control group 4. The hormonal profile of the treatment group improved concomitantly with the reductions in acne lesion counts as measured by significant declines in dehydroepiandrosterone sulfate and the free androgen index 5. Milk and dairy products were a component of the treatment diet in this study, hence it is unclear if further improvement in lesion counts would have occurred had these foods been excluded.

UNDERLYING PHYSIOLOGICAL MECHANISMS

Acne results from the interplay of six proximate factors: 1) increased proliferation of basal keratinocytes within the pilosebaceous duct, 2) delayed keratinocyte apoptosis, 3) incomplete separation of ductal corneocytes from one another during desquamation via impairment of desmosomal disintegration and subsequent obstruction of the pilosebaceous duct 4) androgen mediated increases in sebum production, 5) colonization of the comedone by Propionibacterium acnes, and 6) inflammation both within and adjacent to the comedone.[10-14] Despite the wholesale dismissal of diet as a potential environmental factor underlying the development of acne[7-9], a large body of evidence now exists which demonstrates how certain foods and food substances may adversely influence hormones and cytokines that influence five (1-4, 6) of the six previously listed proximate causes of acne.[1, 6, 15]

THE DIETARY GLYCEMIC INDEX

The glycemic index, originally developed in 1981, is a relative comparison of the blood glucose raising potential of various foods or combination of foods based upon equal amounts of carbohydrate in the food.[16] In 1997, the concept of glycemic load (glycemic index x the carbohydrate content per serving size) was introduced to assess blood glucose raising potential of a food based upon both the quality and quantity of dietary carbohydrate.[17] Refined grain and sugar products nearly always maintain much higher glycemic loads than unprocessed fruits and vegetables. From an endocrine perspective, the importance of the glycemic index and load is that they are closely related to the insulin response.[19] An exception to this general rule is dairy products, which exhibit low glycemic indices and loads, but paradoxically elicit high insulin responses similar to white bread.[20] Highly glycemic and insulinemic foods are ubiquitous elements in western diets and comprise 47.7 % of the per capita energy intake in the U.S.[21]

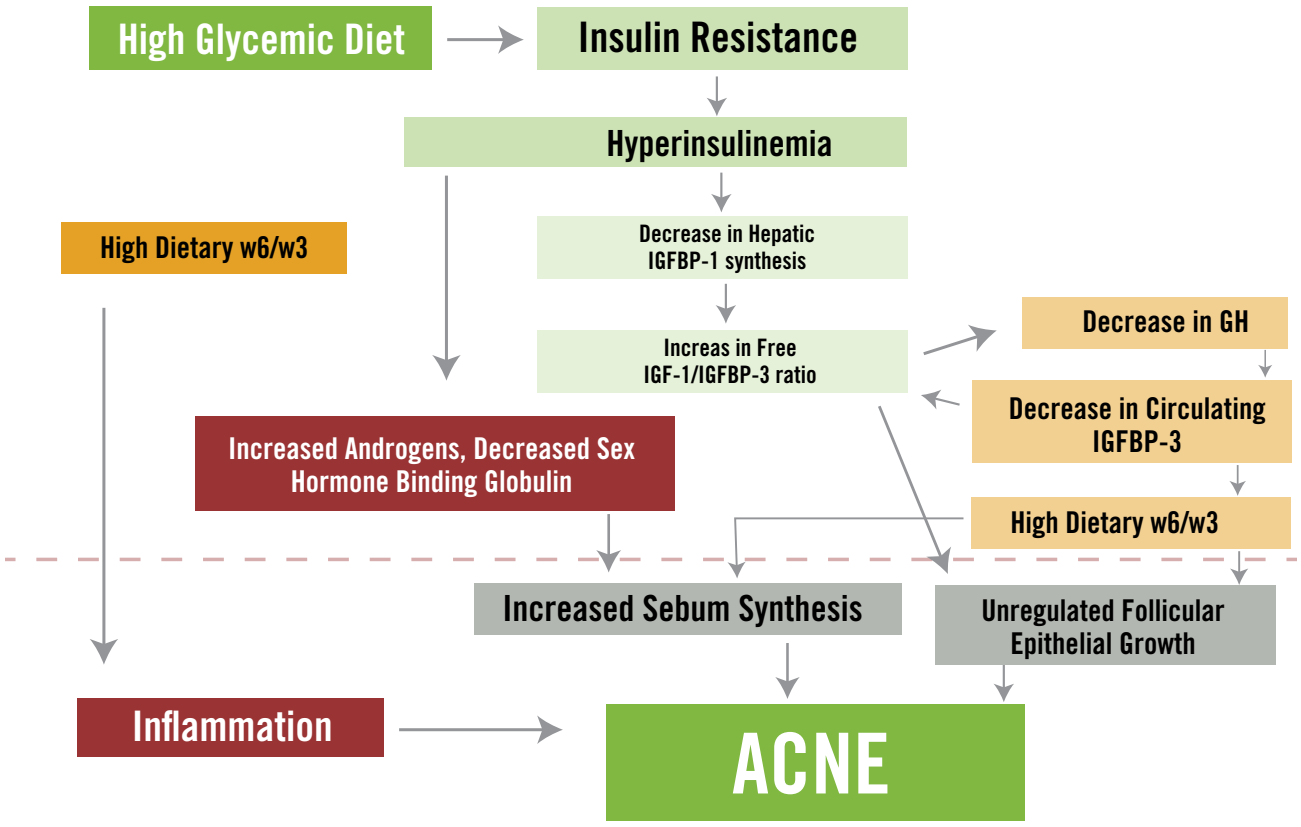
Figure 1 shows how high glycemic and insulinemic foods including dairy products set off a hormonal cascade that may ultimately result in acne.

DAIRY PRODUCTS AND ACNE

In addition to having a potent insulin response, similar to eating a slice of white bread[20], a recent dietary intervention showed that a high milk diet for only seven days caused insulin resistance in a group of 24 eight year old boys.[22] Insulin resistance in turn may promote acne via the hormonal cascade depicted in Figure 1.

Milk is essentially filtered blood and as such contains the full complement of hormones which are also present in blood.[23] Traditional theory held that consumption of cow milk would not result in the transfer of cow hormones into human circulation for a number of reasons. First, in industrialized countries, milk is usually consumed many hours or days after it is initially procured. Many hormones such as the insulin secretagogues (GIP, GLP-1) have very short half lives (< 10 min)[24] and simply would not be present in commercial milk. Secondly, the heat of pasteurization (149 ° F for 30 min) may degrade or inactivate

Figure 1. Hormonal changes elicited by high gylcemic load diets which promote acne.[6]



thermally labile hormones. Further, the acidity of the stomach and peptidase enzymes in the small intestine would also make it difficult for any peptide hormones in cow's milk to reach the intestines intact with full biological activity. Finally, the most daunting task of all would be for intact peptide hormones to cross the gut barrier which normally prevents intact proteins and large peptides from entering the epithelial cells lining the gut.

THE EPIDERMAL GROWTH FACTOR RECEPTOR

Only 12 short years have elapsed since the discovery that humans bear a hormonal receptor in their gastrointestinal tract called the epidermal growth factor receptor. This trans-membrane, hormonal receptor is very unusual in that it is expressed luminally – meaning that it faces the gut contents rather than the bloodstream.[25, 26] The location of the EGF receptor puzzled scientists for years – why was it expressed luminally and what was its function?[27] Since, hormones always arrive at tissues from the circulation, why should the EGF receptor face the gut contents, which in effect are outside the body?

It turns out that the primary function of the luminally facing EGF receptor is to stimulate healing and maintain the integrity of the cells lining the gastrointestinal tract.[26,28] In humans, the primary source of the hormone (EGF) which binds to the EGF receptor in the gut comes from saliva.[29] Hence by swallowing saliva, the residual EGF contained in saliva helps to maintain the integrity and promote healing of the epithelial cells lining the gut.

The EGF receptor is a promiscuous receptor in that it doesn't just bind a single hormone (EGF), but rather binds a large family of hormones including betacellulin (BTC).[30] Cow's milk contains no EGF, but does contain high concentrations of BTC, amounting to 1,930 ng/liter.[31, 32] Additionally, BTC is quite stable and survives the pasteurization process and is even found in high concentrations in cheese.[32] Further, a low ph, such as may be found in the gut, does not impair or prevent BTC from binding its receptor.[33] Finally, bovine

Figure 2. Route by which bovine BTC reaches systemic circulation in humans.

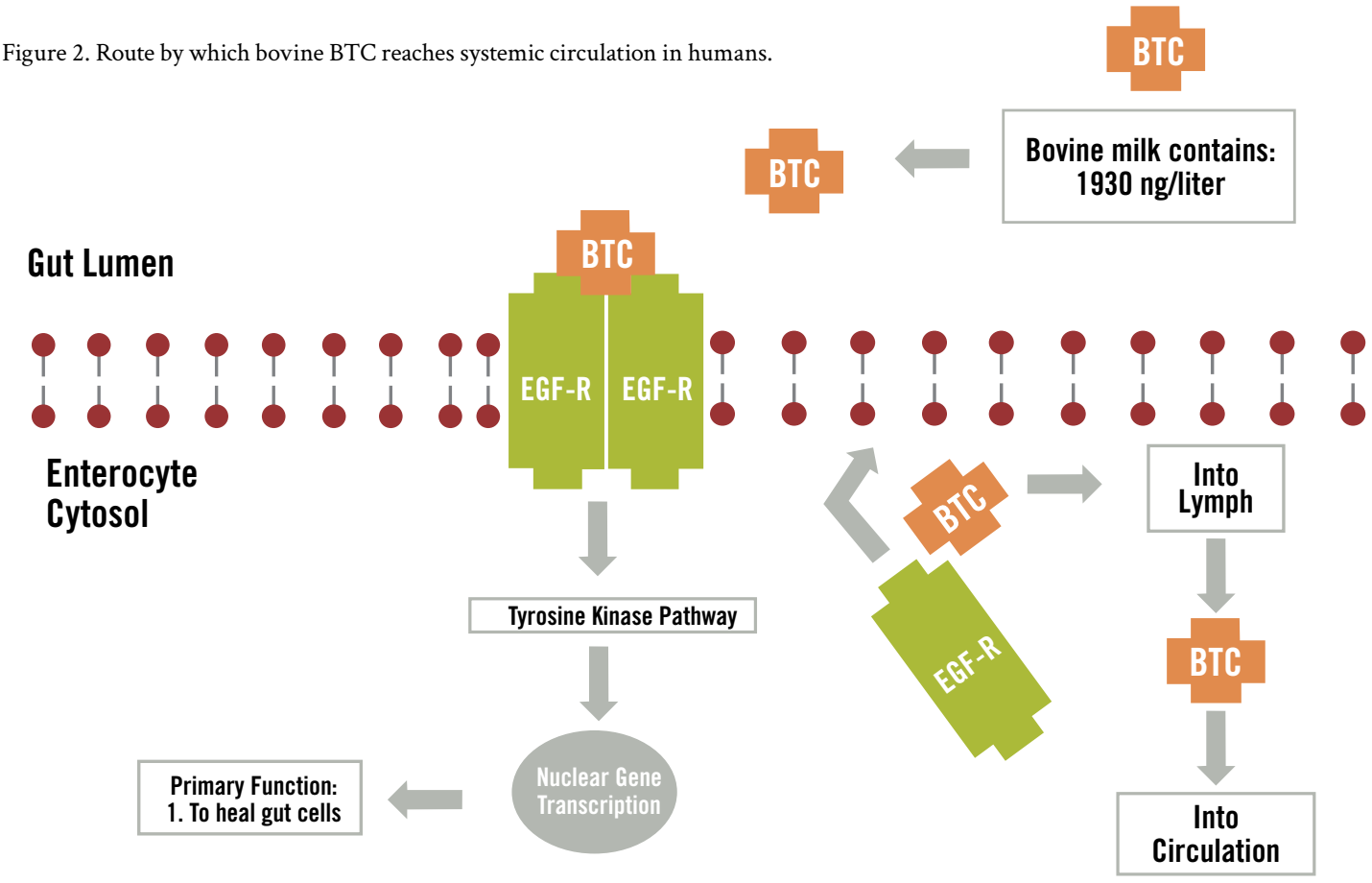
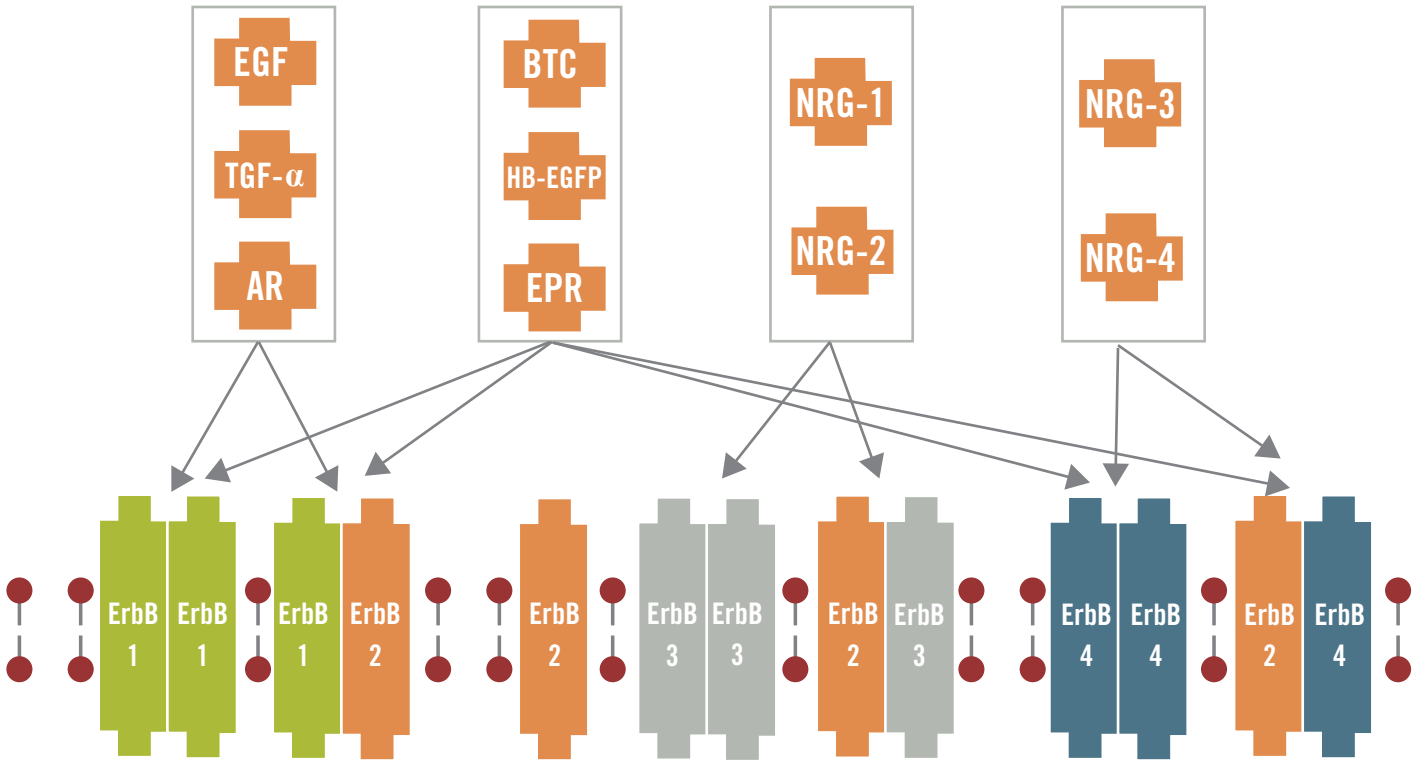


Figure 3. The four families of the epidermal growth factor receptor (ErbB1, ErbB2, ErbB3 and ErbB4). Each of the four receptors combines to form a pair with a different receptor (a heterodimer) or itself (a homodimer). The 10 hormones which can bind the various receptors are depicted in boxes above the receptors. Their binding specificities are indicated by the arrows.[30]



milk contains peptidase inhibitors which prevent human gut enzymes from degrading EGF receptor ligands.[34] In summary BTC maintains all the physical characteristics needed to arrive in the gut intact and with full biological activity. But more importantly, it can breech the gut barrier and enter circulation by the transcellular EGF-R route as depicted in Figure 2.

Once within circulation BTC then has the capacity to bind EGF receptors bound in all epithelial cells, including keratinocytes. BTC can bind the specific receptors depicted in Figure 3.[30] BTC from ingested bovine milk may contribute to the pathogenesis of acne by its ability to increase keratinocyte cell proliferation and to decrease keratinocyte apoptosis.[35] Further, BTC up-regulates its own receptor[30], thereby causing additional signaling through the EGF receptor pathway. In support of the notion that increased flux through the EGF receptor pathway by exogenous BTC from milk may promote acne is the observation that EGF receptor blocking pharmaceuticals cause non-comedonal acne in most patients who are administered these drugs.[36, 37]

Future studies will be able to clarify these issues, and the myth that "diet and acne are unrelated" will one day be relegated to the bin of false medical dogma.

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