BOOKS: MEDICINE

Unexpected Effects

Esther M. Sternberg

The Powerful Placebo. From Ancient Priest to Modern Physician. ARTHUR K. SHAPIRO and ELAINE SHAPIRO. Johns Hopkins University Press, Baltimore, 1997. xiv, 282 pp. $39.95. ISBN 0-8018-5569-1.

This thought-provoking book forces us to reconsider the worthlessness of the lowly placebo—usually measured against proven medical treatments and found wanting. A placebo, the authors state, is any treatment "used for its ameliorative effect on a symptom or disease but that is actually ineffective or not specifically effective for the condition being treated." This broad definition encompasses concoctions of all sorts (including substances mixed with oil, wine, alcohol, or hot water), applied topically or introduced through various orifices. The term placebo also applies to countless psychological processes ranging from magic and laying on of hands to prayer and modern psychotherapy. Nevertheless, the placebo can help heal; the authors note "the nonspecific, as yet mystifying, but very powerful therapeutic potential of the placebo effect." Inescapable after reading this book is the thought that perhaps we should consciously utilize the placebo effect in our legitimate medical armamentarium.

Arthur Shapiro, late clinical professor of psychiatry at New York's Mount Sinai Medical School, was preparing this synthesis of his long and abiding interests in the history, explanation, and therapeutic value of the placebo effect at the time of his death. *The Powerful Placebo* was completed by his colleague and wife Elaine Shapiro. The Shapiros present a historical view of medical treatment through the prism of the placebo effect, which at times makes the book seem forced through the narrow opening of a placebo vial. But a wealth of fascinating detail supports their perspective. For example, theriac—a mixture of 33 to over 100 substances that takes up to six months to prepare—was developed before 100 B.C. and was still available after World War II. Originally an antidote to poisons and venoms, theriac was later used for a plethora of ills including epilepsy, "tightness of breath," and "all pestilences." In a footnote running nearly half a page, the authors list the ingredients for Galen's recipe from the second century A.D., including: "gentian, 4 ounces … rape seeds, agaric, 12 ounces each; … opium 24 ounces … myrrh, oliganum, turpentine, 6 ounces each; … castor, 2 ounces; … trochiscs of squill 48 ounces; of vipers, of sweet flag 24 ounces each." It is hard to imagine how this repulsive mixture, and others like it detailed by the authors, could not have killed, let alone how it might have healed. The Shapiros repeatedly suggest, however, that throughout medical history non-medicinal placebo treatments have succeeded because they allow healing while not harming.

But the authors go so far as to claim that until nearly modern times all medicinal treatments were placebos. This extreme extension of their ideas ignores the very real possibility that many of these concoctions, made from herbs and extracts of animal parts, contained biologically active ingredients. At the right dose, in the right vehicle, and for the right illness, these so-called placebos might actually have cured. (Although at the wrong dose or for the wrong illness, they also could have killed.) For example, aphrodisiacs are among the many examples considered under "Bizarre Placebos." The authors' list of substances used, for centuries and still, to enhance libido or sexual performance includes oil in which an ass's verge has been macerated, "gander's foot … placenta of newly foaled mare … mixture of mother's and daughter's milk, bulls' balls … and powdered skink flesh from the genital area drunk with wine." Although these prescriptions seem bizarre to our modern ears, they may well have been effective. Oil and alcohol extracts of such tissues could contain large enough quantities of active hormones to have had significant biological effects, in addition to their placebo effects. After all, Premarin was first isolated from pregnant mare's urine, and testosterone is present in testes in large concentrations.

Other examples abound in which the therapeutic value of these mixtures could have been based at least in part on their chemical content rather than—as the authors contend—on their placebo effects. Theriac's rape seed contains therapeutic quantities of phytoestrogens, and its squill (*Drimia maritima* of the Liliaceae family) contains a variety of cardioactive glycosides (including Proscillaridin, a cardiotonic drug). Frog skin contains antibiotic peptides called maganins. The poppy *Papaver somniferum* is, as the authors describe, the source of opium. Alcohol at low doses is a psychological stimulant and at higher doses a depressant.

Mahuang, a Chinese cure since 2600 B.C., contains ephedrine and other related alkaloids. According to the Shapiros, a Chinese dispensary of 1596 recommended it as a circulatory stimulant, diaphoretic, and sedative for the coughs of asthmatic bronchospasm. When combined with fermented milk and honey (a mixture producing alcohol), Mahuang was used as an exhilarating stimulant. Topically, it was used to staunch bleeding. To suggest that its effects other than for bronchospasm were exaggerated romanticism, based largely on a placebo effect, is overreaching. Variations in effectiveness related to collection, production, and storage do not eliminate the biological effects of this potent plant chemical. Mahuang, sold in American health food stores today under a variety of names, has been associated with hundreds of cardiac side effects (including arrhythmias) and several deaths—hardly effects attributable entirely to placebo.

The idea that "natural" and age-old cures can do no harm is today a widely held misconception, one that fuels the rapidly expanding, multi-billion dollar food supplement industry, which supports peoples' desperate search for elixirs of life, love, and youth. The authors correctly outline the many complexities of deriving and prescribing such ancient drugs. A plant's content of biologically active chemicals can vary with different geographical sources, seasons, years, and plant parts. The chemicals themselves are also variable and labile, properties that depend heavily on collection, extraction, and storage methods. Additional variations in effectiveness are related to dose-response curves, therapeutic-toxic windows, and half-lives—factors that apply to biologically active chemicals whether they are administered in pure synthetic form as drugs, or in complex unpurified mixtures of herbs or animal parts.

Two chapters trace the histories of clinical trials and the double-blind, placebo-controlled, method (today's gold standard for separating placebo from pharmacological effects of any drug therapy). To the uniniti-

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Pricey placebo. Unicorn horn sold at ten times its weight in gold at the height of its popularity in the 16th century. The cost declined following Ole Wurm's conclusion that the horns are the teeth of narwhals (1638), but ground horn is still being dispensed in Japanese herbal shops.

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ated, placebo-controlled trials may appear to do little except limit one's freedom to choose tried and true remedies. But these methods actually provide the consumer greater control over the risks and efficacies of ancient and modern preparations, many of which undoubtedly contain both powerful biological and placebo components.

The authors have tackled a timely subject, contrasting ancient testimonials and histories of use with modern controlled approaches for determining efficacy and risks of complex therapeutic mixtures. The former perspective forms the rationale for the current laws governing dietary supplements; the latter the premise for pre-market safety and efficacy approval by the U.S. Food and Drug Administration. One is left wondering whether, after understanding these principles, so many consumers would still rather return to the seemingly simpler, but clearly riskier, old methods—methods that do not distinguish placebo from therapeutic or potentially toxic effects.

ORGANISMAL BIOLOGY

Developmental Diversity

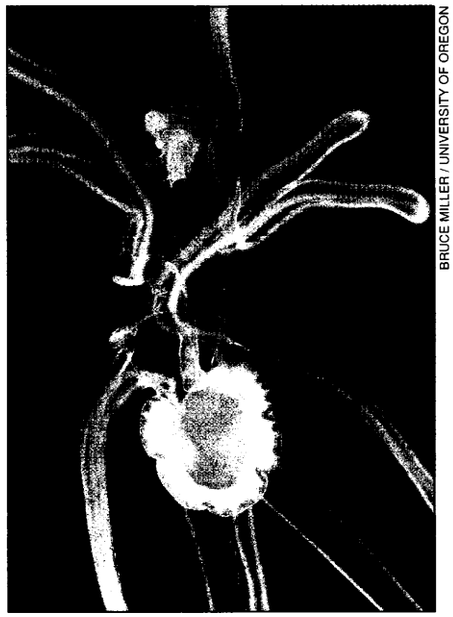
Richard Emlet

Embryology. Constructing the Organism. SCOTT F. GILBERT and ANNE M. RAUNIO, Eds. Sinauer, Sunderland, MA, 1997. xii, 537 pp., illus. $69.95. ISBN 0-87893-237-2.

How a fertilized egg turns into a functional individual is among the most fascinating and greatest of never-ending stories. Moreover, new organismic and evolutionary approaches and expanding molecular and optical techniques have revitalized a centuries-old interest in development of the diverse organisms inhabiting earth. Gilbert and Raunio have coordinated the efforts of selected experts to produce a comprehensive textbook describing current knowledge of animal development that even includes a chapter on development in flowering plants.

The editors' goals include presenting comparative information on development (at a level comprehensible to college sophomores), encouraging creation of new embryology courses, and providing details of structural pattern for additional upper level training in developmental biology. Given the tremendous variation among the more than 30 animal phyla and their classes, the modern explosion of knowledge about development in model organisms, the tightness of undergraduate biology curricula, and that such a comprehensive effort has not been made since the end of the last century, the authors face formidable challenges.

Two introductory chapters provide the basics on the structure and organization of eggs and embryos, body symmetry, larval function and ecology, and the evolutionary analysis of traits. The remaining chapters on different phyla or subphyla (16 on invertebrates and 4 on vertebrates) proceed as "stand alone" presentations. They are grouped into sections that represent levels of increasing



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Late stage larval sea star. The bilaterally symmetric brachiolaria larva of *Pisaster ochraceus* drifts in the plankton, capturing unicellular algae along the cilia-lined arms projecting from its body. After metamorphosis, the pentamerous juvenile (surrounding the orange larval stomach) develops into an adult that lives on the sea floor.

structural complexity. Each chapter includes an overview of adult body plans, gametogenesis, fertilization, cleavage and gastrulation, larval structure, experimental embryology (when available), and some comments on evolution and development. Illustrations throughout are well done and extremely useful in portraying morphology, embryonic fate maps and structure, and often complex experimental manipulations and their results. A minor but recurrent problem is that symbols in some figures are not defined in the caption or explained in the text.

Many chapters will be valuable sources for developmental and evolutionary biologists; however, college undergraduates lacking knowledge of anatomy and function of animals and plants will experience considerable difficulties assimilating all the information. The wide variation in content and focus of individual chapters has as much to do with the authors and their freedom of choice as it does with the information available on the organisms covered. Particularly well presented chapters are those on ctenophores (Martindale and Henry), nemerteans (Henry and Martindale), echinoderms (Wray), tunicates (Jeffery and Swalla), and fishes (Langeland and Kimmel). After describing patterns of development, these chapters recount experimental analyses in particularly clear and compelling ways. Some chapters are more narrowly focused than their titles suggest: "Annelids" covers mainly the leeches (1 of 3 classes); "Echinoderms," mainly sea urchins (1 of 5 classes); and "Fishes," only the zebra fish, a teleost. Several large or phylogenetically important taxa (including bivalve and cephalopod mollusks, many crustaceans, and hemichordates) are not even considered in the book.

General patterns of development (as well as those within related groups covered in different chapters) are obscured by the lack of cross-referencing among chapters. Summaries for each of the book's sections could have been added to synthesize the comparative information across taxa and to identify gaps in knowledge. Although descriptive and experimental (surgical) approaches to developmental analysis are well covered, there is no full explanation of how genetic analyses of developmental mutants are carried out and why these are so informative when they can be completed. Expanding the introductory section to include definitions of indirect and direct development and generalized descriptions of spermiogenesis, oocyte maturation and cytological organization, and fertilization would also help demystify these subjects for many readers.

The book is especially important because of increased interest in the evolution of, and evolutionary implications of, development. By providing a modern, highly readable compendium of developmental patterns in many different phyla, it should lead new generations of biologists to explore the diversity of developmental mechanisms. Such explorations will uncover many new traits and advance our understanding of developmental transitions, and so provide new perspectives on the evolution of life on Earth.

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