New Indications for Existing Drugs – Implications for Drug Development and Clinical Practice

B. H. SMITH*
New York, U.S.A.

Abstract – *Optimization of the use of available resources for health is a necessity for both the developing and developed world because both are faced with a significant disparity between needs and resources. Better use of existing therapeutic agents, which are cost-effective, readily available and easy to use represents a critical element in the overall effort.*

Using the unusual case of the drug phenytoin as an example, this paper explores the value of new indications for existing drugs and describes a system for evaluating such indications and expanding the appropriate use of these agents. Emphasis is placed on the leadership role of developing countries in this process and on crucial elements of any such program such as knowledge of local / national needs and priorities; innovative approaches to clinical research in a range of clinical settings from rural primary health care clinics to tertiary care centers; and the establishment of national and multinational teamwork and more effective two-way communication.

INTRODUCTION

On a world with rapidly shrinking economic resources, the goal of achieving 'Health for All by the Year 2000,' as set by the World Health Organization, seems remote. Both industrialized and developing nations face severe challenges to their health efforts. In the developing world, especially in rural areas, the need to build basic infrastructural components of a good-health system and to provide the necessary logistical support and maintenance is just one of many pressing concerns including adequate nutrition, clean water, sanitation and restoration of polluted environments.

The availability of suitable, cost-effective pharmacologic agents for the treatment of diseases and the relief of symptoms is an important component of any health system. One clear point is that, with respect to drug development, the resources required to bring a new chemical therapeutic entity through a U.S.-type pharmaceutical regulatory maze to approval for marketing and general use are just too great to make such efforts practical in the developing world[1,2].

What can and should be done in the developing world with respect to drug development and regulation? Does all drug development have to be left to

* Director, The Health Foundation, New York, N.Y. 10021, U.S.A.

the industrialized countries? No. As stated in the accompanying article, there are many things that can be done in the developing world[1]. In fact, the optimization of the use of available health resources is an area in which the developing nations can take a strong leadership role, teaching the developed world how to do things better.

A PRACTICAL APPROACH

One very practical approach is the optimization of the use of already available, often inexpensive, drugs. What steps can be taken to achieve this? The first step for a physician, other health care professional, clinic, hospital, or nation, is to identify health needs clearly. Existing data should be reviewed for their adequacy and inadequacy. Proper epidemiologic studies may be needed, but simpler surveys of the qualitative and quantitative health problems seen at each level of the health care system from rural primary health care center to tertiary care facility within a major medical center should be carried out first.

As a second step, the list of health needs must be matched against a list of available resources. In the case of therapeutic agents (such as phenytoin, see below) lists of indications can be compared to the symptoms and disorders that need to be treated. If an inexpensive, easy-to-use, and readily available drug, can be used to treat several symptoms and disorders, so much the better.

Being presented with a list of reported therapeutic uses of a drug, of course, does not solve the problem of determining which to recommend to physicians and other health professionals. Critical review of the available literature (database) is an essential third step.

Once the list of indications has been reviewed and trimmed or augmented as indicated, health professionals need to be informed as to how to better use the agent. In other words, effective and reliable systems of communication and education need to be established.

The fifth and final step is the establishment of a monitoring or reporting system enabling health professionals to report their experience with therapeutic agents or approaches to symptoms and diseases to the central data bank and health promotion coordinating facility. Feedback is essential to the continuing improvement of the total health system.

THE PHENYTOIN STORY

To elucidate this topic and illustrate some important associated issues, the story of the drug phenytoin is very relevant. It shows how additional research inputs can define new indications for existing drugs. At the same time, it illustrates how good clinical research carried out in places as disparate as rural primary health care centres, hospitals and major academic medical centers can come together to contribute to better health and health-care delivery. Good clinical care and good clinical research are not antithetical, but mutually reinforcing.

Phenytoin (PHT) has been in clinical use for more than fifty years. Originally synthesized in 1904 by a German chemist, Heinrich Biltz, it was found by Putnam and Merritt to be an extremely effective anticonvulsant[3,4]. In fact, phenytoin revolutionized the care of epileptic patients because it was not only effective in preventing seizures, but also not sedative, enabling epileptic patients to lead normal lives.

As important as phenytoin's use in seizures has been, and continues to be, it is just the beginning of the phenytoin story. Since 1938, clinical investigators and practising physicians around the world have reported it useful for a wide variety of symptoms and disorders (see Table 1).

TABLE 1. Partial List of Reported Clinical Uses of PHT (based on literature survey, 1938–1990).

- Grand mal and local motor seizure disorders
- Anxiety
- Episodic dyscontrol/irritability
- Stuttering and speech disorders
- Bulimia
- Cardiac arrhythmia, especially ventricular and digitalis induced
- Angina
- Atherosclerosis (raises high density lipoproteins)
- Choreiform disorders
- Continuous muscle fiber activity syndrome (Isaacs Syndrome)
- Other myotonic disorders
- Singultus (hiccups)
- Tetanus
- Trigeminal and other neuralgias
- Migraine headache
- Neuropathic pain
- Wound healing (periodontal, decubitus, diabetic, trophic leprosy post-infection ulcers, and burns)
- Pruritus Ani
- Scleroderma
- Epidermolysis bullosa
- Asthma
- Irritable bowel syndrome
- Hypoglycemia reactions
- Syndrome of inappropriate antidiuretic hormone
- Fever/transfusion reactions
- Rheumatoid arthritis

First obstacles

Virtually every physician knows of phenytoin's use in seizure disorders and some, of its usefulness for cardiac arrhythmias, and for trigeminal neuralgia. Many of its other reported applications are unknown. Why is this?

There are several reasons, all of which are germane to any discussion of how to improve health through the optimization of the use of available resources. First, the reports of phenytoin's usefulness in a range of symptoms and disorders are scattered in some 250 medical journals and are written in at least 15 different languages. No one physician could be expected to see even a small fraction of the reports. The same could be said of many aspects of medicine. Extensive knowledge on a particular topic can be scattered and therefore hidden in the enormous world of medical literature. In developing countries, especially in rural areas, the problem is made worse by the fact that libraries may be non-existent or woefully inadequate. You can't optimize the use of resources if you don't know about the resources.

Established misconceptions of medicine form a second obstacle to the optimal use of available resources. Goodwin and Goodwin call this 'the tomato effect'[5]. 'Generally accepted' ideas about disease pathophysiology or therapeutic agent usefulness have often led physicians to reject clear evidence that the truth is otherwise.

Phenytoin is a 'double tomato'. After its synthesis, it was tested for its sedative properties since it was (incorrectly) assumed that effective antiseizure agents had to be sedatives. Because phenytoin had no sedative effect, it was put back on the shelf for twelve years until Putnam and Merritt tested it in a cat model of epilepsy and found it to be effective and, remarkably, non-sedative[3,4]. In other words, it was not put into clinical use sooner because of a faulty assumption used to screen all potential antiepileptic compounds. The second 'tomato effect' occurred when phenytoin's broader uses, well-described in the literature, were ignored, in part because everyone knew that it was an anticonvulsant. Under the guiding axiom of a 'single drug for a single disorder', phenytoin shouldn't be useful for anything else. We now know that diseases don't define drugs; rather it is the basic mechanisms of action of a drug that define where it may be useful.

Optimizing the use of phenytoin

To better use phenytoin we need to not only overcome the above obstacles (which, fortunately, we can control and systematically apply the five principles or steps outlined earlier). As stated previously, there are reports of numerous successful applications of phenytoin in a variety of disorders (see Table 1). As physicians in country X, we would like to explore these to see if we might make better use of this drug.

A good starting place for the review of indications for a medication is with its basic mechanisms of action. Although such mechanisms will not always tell us exactly how a drug may be achieving a particular therapeutic effect, they offer a general background against which to measure the likelihood that the drug could have such effects.

Mechanisms of action

The structure of phenytoin (5, 5-diphenylhydantoin, DPH, MW 252) is shown in Figure 1. It is a lipid-soluble, membrane-active agent. Phenytoin appears to act at the interface between membrane lipids and integral proteins altering the function of the latter. In the case of the sodium channel, phenytoin prolongs the recovery time of activated, voltage-dependent Na^+ channels[6,7,8,9]. By doing this, it limits the rapid reuse of the channel and thus selectively reduces or prevents repetitive firing of Na^+-dependent action potentials.

Calcium channel function is also modulated by phenytoin[10,11]. The net effect is a reduced entry of

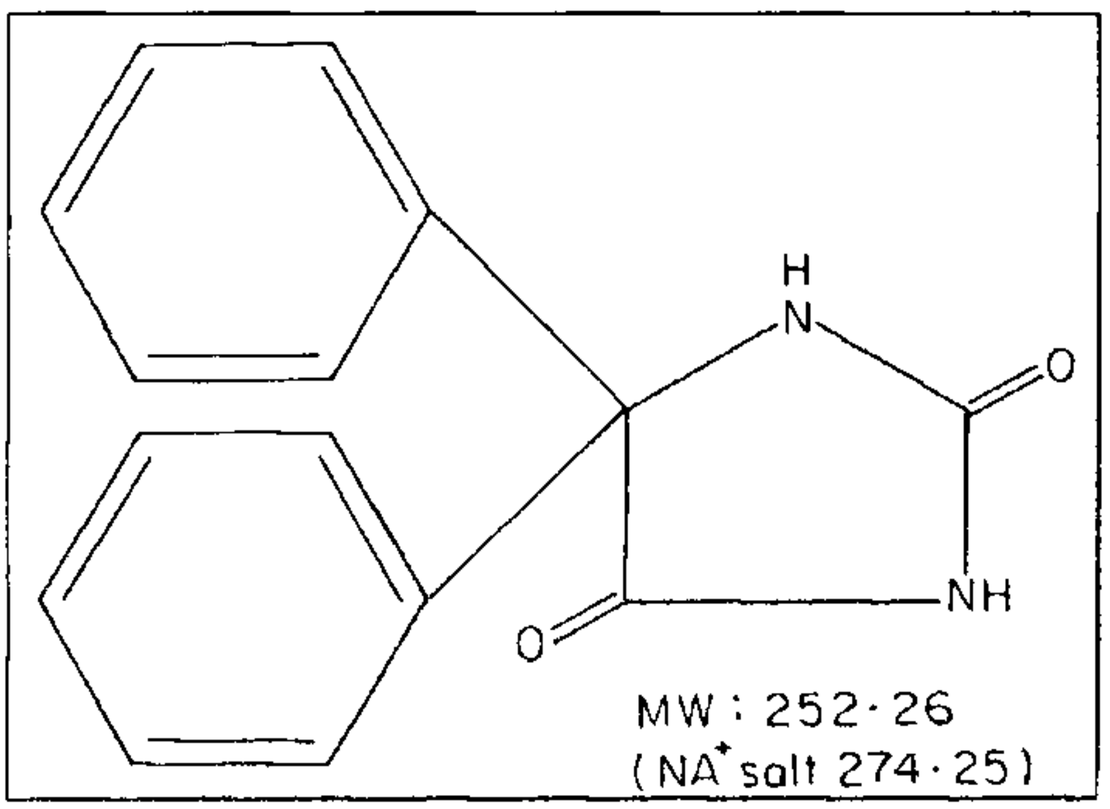

FIGURE 1. Molecular Structure of Phenytoin.

Ca^{2+} into the cell. Consequently, both pre- and post-synaptic neuronal function is affected. A summary of phenytoin's actions is presented in Figure 2. In non-neuronal cells, such as glia, the activity of $Na^+ - K^+$ ATPase is stimulated, resulting in extrusion of Na^+ from the cell in exchange for K^+ [12].

The net effect of these and various other actions

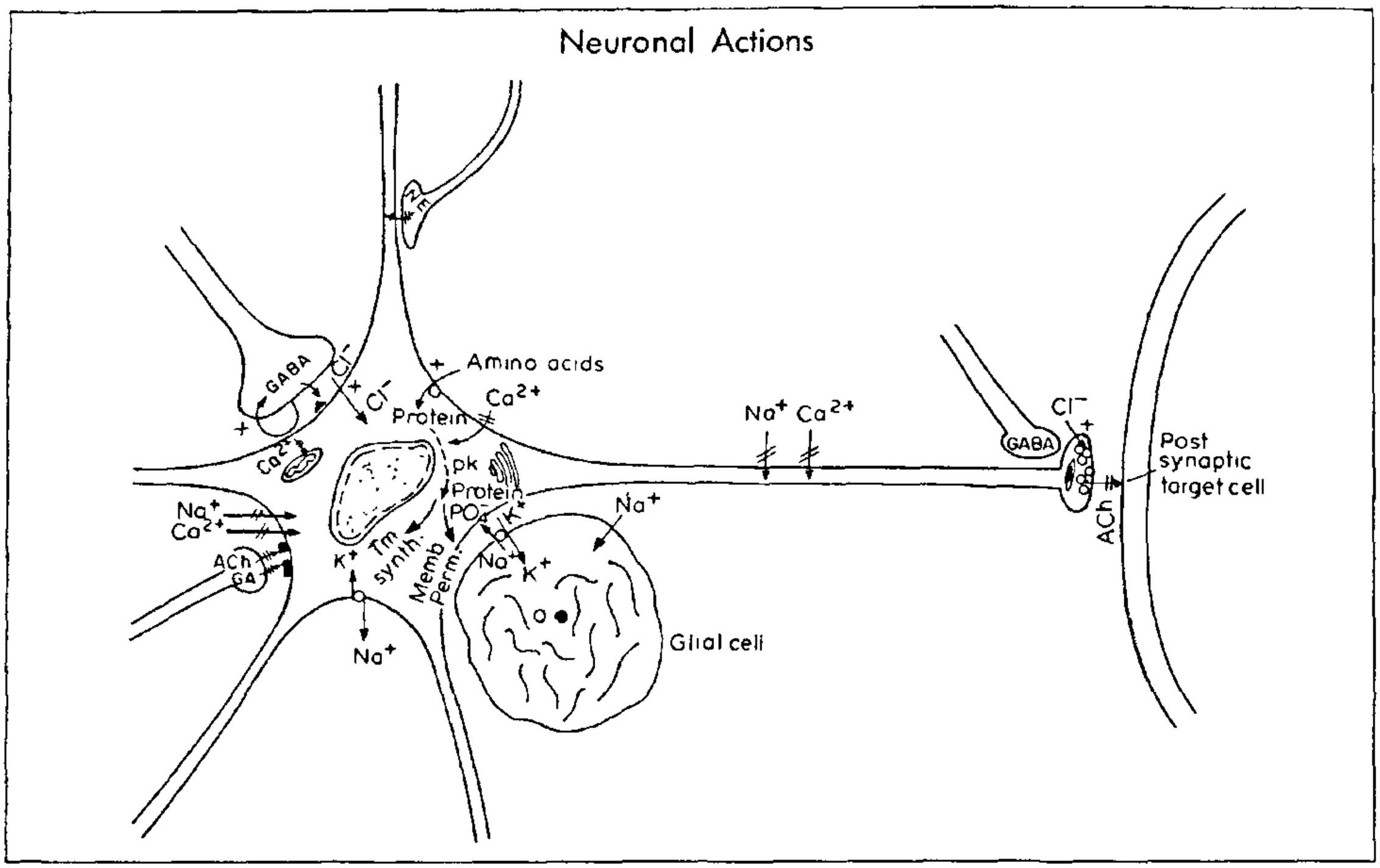

FIGURE 2. Phenytoin's Actions on the Neuron.

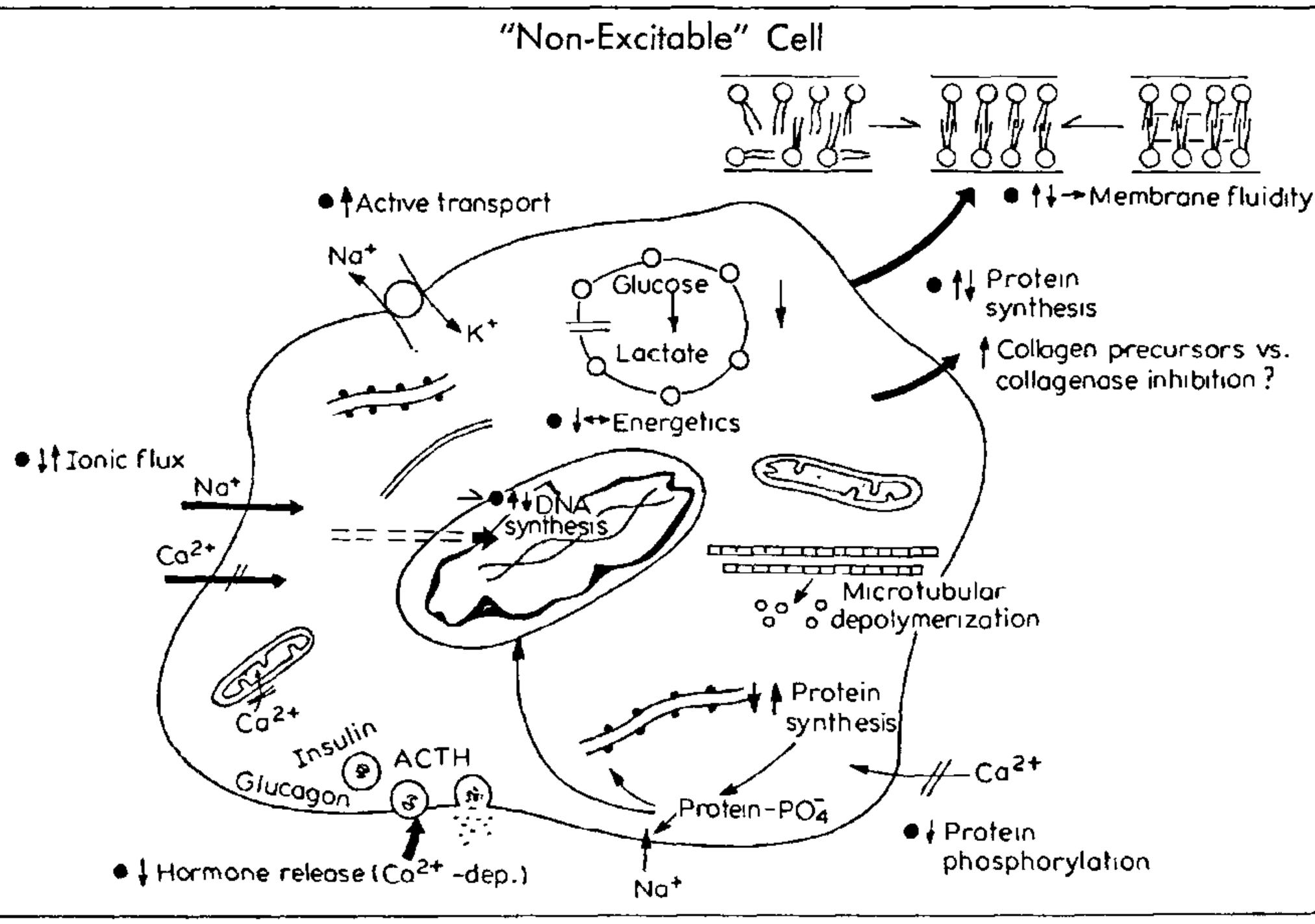

FIGURE 3. Phenytoin's Actions on the 'Non-excitable' Cell.

(which cannot be discussed here because of space limitations) is a stabilization of membranes and decreased abnormal neuromatic (or muscle) excitability. Importantly, single or low-frequency activity is not affected.

As a membrane-active agent, phenytoin should also affect the function of cells other than neurons or muscle cells (so-called 'non-excitable') cells. Such effects have been well documented and range from expected alterations in the Ca^{2+}-dependent release of hormones such as insulin from pancreatic beta cells[13,14] to stimulation of $Na^+ - K^+$ ATP use and modulation of cell mitosis in part because of alterations in cytoskeletal function (microtubule assembly) and protein synthesis[15]. A summary of some of these actions is presented in Figure 3.

Given both the pervasive influence of phenytoin on the nervous system which effects physiological function, as well as phenytoin's direct modulatory effects on the functions of non-neural systems, there is a clear basis for phenytoin to affect multiple body systems and functions.

Reviewing the Clinical Literature

With this background in mind, we need to consider the evidence that phenytoin is useful in various clinical symptoms and disorders. Only a few can be presented here, but are useful as examples of the practical process of analyzing existing data (i.e., reviewing the published literature) prior to making recommendations about the broader, more efficient use of any drug.

In reviewing existing literature, one has to deal with a wide variety of types of evidence. There are data from case reports; open trials involving small and large numbers of patients; controlled series comparing one drug to another or to placebo; on-off-on studies in which the therapeutic agent is instituted, withdrawn and reinstituted; and the randomized, double-blind trials favoured today. The problem confronting the analyst is how to put all the evidence together in a meaningful, accurate way. Reviews continue to be useful resources, but are necessarily imprecise and not always relevant to local problems. Techniques such as meta-analysis have been developed to assess the evidence from different studies, but thus far have limited capabilities[16,17]. The realistic problems facing analysts in developing countries are not going to wait for sophisticated new methodology or idealized studies, as valuable as they both may be. Analyses and decisions have to be made on the basis of available data, application of real-life probability assessments, simple risk-benefit analyses, and common sense. Given the proper care and diligence such methods can work.

Although the details of a practical literature analysis system are beyond the scope of this paper, a check list of useful elements to consider is given in Table 2. In the sections that follow, these points will be applied in a summary fashion to the example being used in this paper, phenytoin.

TABLE 2. Elements to be Considered in a Medical Literature Review

Questions asked	◊ Question/Hypothesis to be tested • Is it clearly stated with precise endpoints? • Can it be answered?
Materials and methods	◊ Study Design: Open, Controlled, Double-Blind? ◊ Patient Selection: • Randomized? • Homogeneous? • Precise inclusion/exclusion criteria • Patient numbers adequate? ◊ Treatment • Groups/Arms • Well-matched/comparable? • Nature of control/cooperative treatment • Duration of treatment sufficient? • Can treatments be compared? ◊ Assessment • Number/frequency adequate? • Observations/measurers/endpoints? ◊ qualitative/quantitative ◊ subjective/objective ◊ observer bias • Follow-up adequate? ◊ duration ◊ observations • Drop outs/fail to complete?
Results	◊ Data • Clear and sufficient presentation? • Internally consistent? • Error measurer? ◊ standard deviation ◊ error of the mean • Analysis adequate? ◊ proper statistics? ◊ common sense test? • What 'holes' are there in the data? • Adverse results?
Conclusion	◊ Do data justify? ◊ Is one treatment better/worse than another? • Do we know enough? • Do we need more evidence? ◊ Is treatment applicable to my patients? • Is treatment safe? • Is treatment cost-effective?

CLINICAL INDICATIONS FOR PHENYTOIN

Central Nervous System Disorders

Observed very early in phenytoin's use for seizures was the fact that, with seizure control, came improvements in patients' sense of well-being, mood and behaviour[4,18,19]. These same changes were also seen in non-epileptics with mood and behavioural disorders given phenytoin. Since then, phenytoin has been reported to be useful in anxiety[20,21,22], episodic dyscontrol and violence[23,24], alcohol and drug withdrawal[25,26,27,28], and attention deficit disorders[29,30,31], to name just a few.

How good is the evidence? As pointed out above, the first question we may want to ask is whether it makes sense that phenytoin should be valuable in mood and behavioural disorders. The answer must be 'yes,' since phenytoin acts to regulate excess neuronal activity or hyperexcitability states in the central nervous system. Episodic dyscontrol and outbursts of violence, as well as the dramatic state of heroin withdrawal, reflect excess neuronal activity.

Consistency with the theoretical basis does not mean clinical effectiveness. We must look at the clinical data. Taking violent behaviour and episodic dyscontrol as a first case, we can identify 30 published studies or reports of clinical experience including anger and related emotions (see reference 32 for citations) commenting on phenytoin's usefulness. Seven are double-blind; 8 involve large numbers of patients (more than 100 on average). Taking into account the variety of conditions represented and assigning even very modest probability figures (10 in 11 for the double-blind studies; 5 in 6 for the large studies; and 1 in 2 for the remaining 15 studies) that these studies are correct (including both positive and negative results), the probability that phenytoin is useful for episodic dyscontrol and/or violent behaviour is high (J. Dreyfus, personal communication).

Recently, very carefully controlled studies being carried out by the University of Texas Medical Branch at Galveston and the Texas Department of Corrections have shown significant reductions of episodes of violent behaviour and tension-anxiety measures in a high-risk prison population[33,34]. Put to this rigorous test, the rough probability assessment made above has held up well.

Neuromuscular Disorders

The nature of the evidence for the effectiveness of phenytoin in neuromuscular disorders is different from that for mood and behavioural disorders. The theoretical basis, however, is clearly parallel since both neurons and muscle cells are 'excitable'.

For disorders such as the continuous muscle fiber activity syndromes, the database is inevitably smaller because the conditions are so rare. Under the diagnostic category of neuromyotonia, Isaacs syndrome, and/or other continuous muscle fiber activity disorders[32,35,36,37], there are 40 papers reporting 60 cases. Phenytoin is clearly of value in 50. Sometimes combination with carbamazepine has been of value. Useful controls include the failure of other medications, the worsening of symptoms after PHT withdrawal, and the correlation of electromyographic measurements of the myotonic discharges with or without phenytoin.

Pain

Phenytoin has been used since the 1940s for the control of various types of pain including trigeminal neuralgia, migraine and other types of headache, painful neuropathies, tabes, post-stroke pain, cancer pain, herpes zoster and post-herpetic neuralgia, angina, and, recently, in rheumatoid arthritis[32]. It is also being used topically to relieve the pain of various types of wounds and ulcers. Space limitations prevent us from examining the evidence for all these types of pain. Accordingly, our discussion must be limited to trigeminal neuralgia and cancer pain.

Phenytoin was first tried in trigeminal neuralgia in 1942 by Bergouignon[38]. A summary of the studies since then indicates that 265 of 483 patients treated with phenytoin have responded with significant relief (see Table 3; see reference 32). The initial success rate with oral phenytoin is quite high (60%), especially considering the history of therapeutic refractoriness in this disorder. Reviewing the literature further we find that intravenous phenytoin can be used in cases of trigeminal neuralgia refractory to oral phenytoin or to carbamazepine[39]. This adds another dimension to its usefulness.

Mention of carbamazepine raises a different kind of question. The data indicate that carbamazepine is more effective than phenytoin initially in trigeminal

TABLE 3. PHT in Trigeminal Neuralgia*

Pts.	Response	%
265	Complete Relief	55
114	Partial Relief	24
24	Slight Relief	5
80	No Response	16
483	Total	100

* Data collected from the section on trigeminal neuralgia in *The Broad Range of Clinical Use of Phenytoin* (Smith *et al*, 1988a).

neuralgia[40,41,42]. Both drugs have a substantial failure rate with time. Since resources are limited, should we choose just one of the two drugs for our antineuralgic armamentarium? As far as cost is concerned, phenytoin is a far cheaper drug. It also offers an intravenous form, which carbamazepine currently does not. However, since there are cases where one is effective and the other is not, or where one is tolerated, but the other is not, then we probably should have both available (likely in any case since both are essential to antiseizure therapy).

Terminal cancer pain is currently the subject of a WHO program because it has not been adequately treated in the past[43]. A major problem in rural India is the difficulty of obtaining opiates for the relief of malignant cancer pain. Recognizing this need, and mindful of the reports that phenytoin is useful as an analgesic or as an analgesic adjuvant[44], we can easily argue that trials of phenytoin in terminal cancer pain should be carried out. Three recent and/or current trials in India support the effectiveness of phenytoin[45,46,47].

Wound Healing

A final example of the optimization of phenytoin's usefulness as an available, cost-effective resource for health is that of wound healing. In 1958 Shapiro found that periodontal surgery patients pretreated with phenytoin not only healed faster, but had less pain[48]. Subsequently, his findings were confirmed and extended to topical phenytoin use[49,50,51,52].

In the early 1980s a team of physicians in Mexico decided to examine the use of both oral and topical phenytoin in the healing of a variety of wounds including chronic skin ulcers and burns. They found phenytoin to be much more effective than their standard therapies in relieving pain and promoting healing[53,54].

Given the encouragement of these findings, the then-Dreyfus Medical Foundation (now The Health Foundation) decided to carry this message to physicians in other parts of the world. If the findings were correct, phenytoin was a valuable resource for wound healing all over the world.

To put together a phenytoin-wound healing program, further discussions were carried out in Brazil, the Dominican Republic, Ghana, India, Iran, Iraq, and Mexico. Various types of skin wounds were identified as targets – decubitus ulcers, trophic leprosy ulcers, diabetic ulcers, abscess cavities, traumatic wounds, and second- and third-degree burns. The initial evaluations were quite positive, and so more formal trials were planned and carried out. Again, the data indicated that phenytoin was effective in promoting wound healing in comparison to the standard therapies used in the different regions or countries. These new data were submitted to peer review and found to hold up well, with manuscripts accepted for publication by first-rank international journals such as the *British Journal of Surgery, Diabetes Care,* and *The International Journal of Dermatology.* Selected references are given so that the reader can study the data[55,56,57,58,59,60].

Uniformly commented upon by the multinational team of investigators (all working independently) was the fact that phenytoin's clinical usefulness in promoting wound healing was greatly enhanced by its availability almost everywhere in the world, its ease of use, its low cost, and its apparent safety.

The data obtained were reviewed at a meeting attended by several U.S. wound healing experts in New York in December of 1988 (ref. 61). The U.S. physician-investigators in attendance were sufficiently impressed by the data presented by their colleagues from the Dominican Republic, Ghana, Iran, Iraq, India, and Mexico that new U.S. trials were undertaken with the approval of the U.S. Food and Drug Administration. As the data spread in publications and at national and international meetings, more new trials were stimulated in a number of other countries. Efforts to obtain official approval for routine use of phenytoin in wound healing are now being made in several nations.

The story of phenytoin in wound healing makes several important points:

- Good clinical research data can be generated even under difficult circumstances by a wide range of investigators in many different settings ranging from rural health care clinics to tertiary care centres. In fact, data gathered under difficult conditions in a rural clinic, for example, can be very valuable because they represent tests under real-life conditions.
- Work done in the developing world can influence what physicians in the developed world do. The many creative, innovative, and cost-effective solutions to health problems now existing in the developing world can, and should be, brought to the attention of the rest of the world. Two-way communication is not only desirable, it is essential, if we are to optimize the use of available resources for health.
- There is tremendous potential value in the examination of new indications for old, inexpensive and safe medications. More such efforts need to be made.
- Multinational team efforts can bring new indications for 'old' drugs to improve patient care quickly and effectively. Good communication is a vital supplementary ingredient.

- The networks or 'teams' established for one effort, such as that described for phenytoin, can be used repeatedly for parallel therapeutic agents or modalities.

CONCLUSION

Optimization of the use of available resources for health is a necessity for the developing and developed world, as both are faced with shrinking resources for health. Better use of existing therapeutic agents, which are cost-effective, readily available, and easy to use represents a critical element in the overall effort. Developing countries can and should take a leadership role in this effort. The story of phenytoin, especially in relation to wound healing, makes this clear. The opportunities are great; the potential for human benefit, enormous.

REFERENCES

1. Smith B H. Drug Development and Health – How Relevant is the U.S. Model? *Curr Sci* 1990; **60(4):** 237–41.
2. Cato A E. The Challenge of the Clinical Development of Drugs. *Clinical Drug Trials and Tribulations*, Marcel Dekker, Inc., New York, 1988; 1–16.
3. Merritt H H and Putnam T J Sodium diphenylhydantoinate in the treatment of convulsive disorders. *JAMA* 1938, **111:** 1068–73.
4. Putnam T J and Merritt H H. Experimental determination of the anticonvulsant properties of some phenyl derivatives. *Science* 1937, **85:** 525–26.
5. Goodwin J S and Goodwin J M. The tomato effect: Rejection of highly efficacious therapies *JAMA* 1984, **251:** 2387–90.
6. Adler E M, Yaari Y, David G and Selzer, M E. Frequency-dependent action of phenytoin on lamprey spinal axons *Brain Res* 1986; **362(2):** 271–80.
7. McLean M J and Macdonald R L. Multiple actions of phenytoin on mouse spinal cord neurons in cell culture. *J Pharmacol Exp Ther* 1983, **227(3):** 779–89.
8. Perry J G, McKinney L and DeWeer P. The cellular mode of action of the anti-epileptic drug, 5-diphenylhydantoin *Nature* 1978; **272:** 271–3.
9. Willow M, Kuenzel E A and Catterall W A. Inhibition of voltage-sensitive sodium channels in neuroblastoma cells and synaptosomes by the anticonvulsant drugs diphenylhydantoin and carbamazepine. *Mol Pharmacol* 1984; **25(2):** 228–35.
10. Messing R O, Carpenter C L and Greenberg D A. Mechanism of calcium channel inhibition by phenytoin: Comparison with classical calcium channel antagonists *J Pharmacol Exp Ther* 1985; **235(2):** 407–11.
11. Pincus J H and Weinfeld H M Acetylcholine release from synaptosomes and phenytoin action. *Brain Res* 1984; **296:** 313–17.
12. White H S, Yen-Chow Y C, Chow S Y, Kemp J W and Woodbury D M Effects of phenytoin on primary glial cell cultures. *Epilepsia* 1985; **26(1):** 58–68.
13 Pace C S and Livingston E. Ionic basis of phenytoin sodium inhibition of insulin secretion in pancreatic islets. *Diabetes* 1979; **28:** 1077–82.
14. Seigel E G, Janjic D, Wollheim C B. Phenytoin inhibition of insulin release: Studies on the involvement of Ca^{+} fluxes in rat pancreatic islets. *Diabetes* 1982; **31:** 265–9.
15 MacKinney A A and Vyas R. Diphenylhydantoin-induced inhibition of nucleic acid synthesis in cultured human lymphocytes. *Proc Soc Exp Biol Med* 1972; **141:** 89–92.
16. Thacker S B Meta-analysis: A quantitative approach to research integration *JAMA*, 1988, **259:** 1685–89
17. Chalmers T C. Selection and evaluation of empirical research in technology assessment. *Int J Technol Assess Health Care* 1989; **5(4):** 521–36.
18. Kimball O P and Horan T N The use of Dilantin in the treatment of epilepsy. *Ann Intern Med* 1939; **13:** 787–93.
19 Bakwin R M and Bakwin H. Psychologic aspects of pediatrics. Epilepsy. *J Pediatr* 1951; **39:** 766–84.
20. Turner W J. The usefulness of diphenylhydantoin in treatment of non-epileptic emotional disorders. *Int J Neuropsychiatry* 1967; **3:** Suppl. 2, S8–S20
21. Stephens J H and Shaffer J W. A controlled study of the effects of diphenylhydantoin on anxiety, irritability, and anger in neurotic outpatients. *Psychopharmacologia* 1970; **17:** 169–181.
22. Stephens J H and Shaffer J W. A controlled replication of the effectiveness of diphenylhydantoin in reducing irritability and anxiety in selected neurotic outpatients. *J Clin Pharmacol* 1973; **13:** 351–356
23. Maletzky B M and Klotter J Episodic dyscontrol: A controlled replication. *Dis Nerv Syst* 1974, **35:** 175–179.
24. Resnick O. The psychoactive properties of diphenylhydantoin: experiences with prisoners and juvenile delinquents *Int J Neuropsychiatry* 1967; **3:** S30–S48.
25. Fisher D and DiMino J M. Case presentation of an alternative therapeutic approach for the borderline psychotic heroin addict: diphenylhydantoin. *Br J Addict* 1975; **70:** 51–55.
26. De Sousa A and De Sousa D A. Diphenylhydantoin in heroin withdrawal. *J Comm Psychiatry* 1988; **11:** 3.
27. De Sousa A, De Sousa D A and Sinorawala A K. Diphenylhydantoin in alcohol withdrawal states *J Comm Psychiatry* 1988, **11:** 19–21.
28. Rao A *et al.* A controlled trial of phenytoin and chlordiazepoxide (librium) during the acute alcohol withdrawal period. Personal Communication, 1990.
29 Brown W T and Solomon C I. Delinquency and the electroencephalograph. *Am J Psychiatry* 1942, **98:** 499–503.
30. Baldwin R W. Behaviour disorders in children. *Md Med J* 1969, **18:** 68–71
31. Theophilo L. Effects of phenytoin on children's behaviour and attention disorders, submitted to the Health Foundation, manuscript in preparation, 1990.
32. Smith B H, Bogoch S and Dreyfus J. The Broad Range of Clinical Use of Phenytoin, Dreyfus Medical Foundation, New York, 1988
33 Barratt E S *et al.* The effects of phenytoin on aggression and mood among prisoners: a preliminary report. Submitted to *J Clin Psychopharmacol* 1990.
34. Barratt E S. Effects of Dilantin on impulse control (including aggression) among prisoners, presented at the Fourth Annual Gulf Coast Correctional Health Care Conference, TDC Hospital, University of Texas Medical Branch, Galveston, Texas, June 8–9, 1989.
35. Isaacs H. A syndrome of continuous muscle-fibre activity. *J Neurol Neurosurg Psychiatry* 1961; **24:** 319–25.
36. Zisfein J, Sivak M, Aron A M and Bender A N. Isaacs syndrome with muscle hypertrophy reversed by phenytoin therapy. *Arch Neurol* 1983, **40:** 241–2.
37. Brown T J. Isaacs syndrome. *Arch Phys Med Rehabil* 1984, **65(1):** 27–9
38. Bergouignon M Successful cures of essential facial neuralgias by sodium diphenylhydantoinate. *Rev. Laryngol. (Bordeaux)* 1941; **63:** 34–41.
39. Von Albert H H. Phenytoin infusion in the treatment of epilepsy, Advances in Epileptology, 14th Epilepsy International Symposium, Parsonage M (ed) Raven Press, New York, 1983, 307–12.
40. Hayward M. Headache and Pain in the Head and Neck in *Persistent Pain: Modern Methods of Treatment,* (edited Lipton S) Academic Press, London, 1977.

41. Budd K. Psychotropic drugs in the treatment of chronic pain. *Anesthesia* 1978; **33:** 531–34.
42. France, R D and Rama Krishnan K. R. Psychotropic Drugs in Chronic Pain. *American Psychiatric Press* 1988; Washington, pp. 323–74.
43. Ventafridda V, Caraceni A, Saita L and DeConno F. WHO method for cancer pain relief. *Indian J Pain* 1987; **2(2):** 78–81.
44. Fields H L. Anticonvulsants, psychotropics, and antihistaminergic drugs in pain. *Management in Pain* 1987; McGraw-Hill, New York, pp. 285–305.
45. Bhatia M T. Phenytoin in rural cancer patients, presented at the 6th World Congress on Pain, Adelaide, Australia, April 1990.
46. Shah S. Use of phenytoin in head and neck cancer pain, paper presented at the 6th World Congress on Pain, Adelaide, Australia, April 1990.
47. Yajnik S. Phenytoin as an analgesic in cancer pain, submitted to the *Journal of Clin Pain and Symptom Management,* 1990.
48. Shapiro M. Acceleration of gingival wound healing in non-epileptic patients receiving diphenylhydantoin sodium. *Exper Med Surg* 1958; **16:** 41–53.
49. Payen J. A study of changes in the gum during treatment with diphenylhydantoin sodium. *Rev Odonto-Stomatol* 1972; **19:** 47–53.
50. Savini E C, Poitevin R and Poitevin J. New treatment of periodontolysis. *Rev Odonto-Stomatol* 1972; **19:** 55–61.
51. Ludwig R and Otto G. Therapeutic effect of topical phenytoin application. *Russ Pharmacol Toxicol* 1982; **45(3):** 101–3.
52. Chikhani P. The use of 'diphenylhydantoin sodium' in the treatment of periodontal disease. *Actual Odonto-Stomatol* 1972; **98:** 1–8.
53. Rodriguez-Noriega E, Esparza-Ahumada S, Andrade-Perez J S, Espejo-Plascencia I and Chapa-Alvarez R. Treatment of ulcerations in soft tissues with topical diphenylhydantoin. *Invest Med Int* 1983; **10:** 184–6.
54. Mendiola-Gonzalez J F, Espejo-Plascencia I, Chapa-Alvarez J R and Rodriguez-Noriega E. Sodium diphenylhydantoin in burns: Effects of pain and healing. *Invest Med Int* 1983; **10:** 443–7.
55. Lodha S C *et al.* The role of phenytoin in the healing of large abscess cavities. *Br J Surg* in press, 1990.
56. Malhotra Y K and Amin S S. Role of topical phenytoin in trophic ulcers of leprosy in India. *Int J Lepr* in press, 1990.
57. El Zayat S G. Preliminary experience with topical phenytoin in wound healing in a war zone. *Milit Med* 1989; **154:** 178–180.
58. Muthukumarsamy M G *et al.* Topical phenytoin in diabetic foot ulcers, *Diabetes Care,* in press, 1990.
59. Bogaert H *et al.* Trophic leprosy ulcers: Treatment with topical and systemic phenytoin. *Int J Dermatol* 1988; **29(2):** 156–57.
60. Modaghegh S. Use of phenytoin in healing of war and non-war wounds. *Pharmacol Ther* 1989; **28(5):** 347–50.
61. Smith B H, Moore M and Jain K. Topical phenytoin and wound healing, proceedings of the First International Conference on the Uses of Phenytoin in Dermatology. *Int J Dermatol* 1988; **27:** 528–30.

★ ★ ★

Potassium and Magnesium in mild essential Hypertension

Hypertension or high arterial blood pressure is neither a disease nor a syndrome. It merely represents one end of the Gaussian curve of the Mean Arterial Pressure. Less than one-tenth of the hypertensive population have a specific-disease-related hypertension. In this minority of cases, treatment of the primary cause invariably cures the hypertension. No antihypertensive drug is absolutely safe. Almost all drugs make life difficult for the patient with an essentially asymptomatic condition like hypertension. It has to be recognised that for a physician who has to treat a patient, optimal therapy is elusive at this time.

The antihypertensive activity of potassium alone and in combination with magnesium was studied in patients with mild hypertension in a double-blind, randomized, placebo-controlled, crossover clinical trial. The duration of the trial was 32 weeks. The treatments were potassium 30mmol/15ml or potassium 30mmol/15ml plus magnesium 10mmol/15ml or matching placebo twice a day. The sources of potassium and magnesium were potassium chloride I P and magnesium chloride I P, respectively. All patients had a normal diet and normal sodium intake. Blood pressure and heart rate were measured weekly and blood biochemical tests were done monthly. The results showed that potassium significantly reduced both systolic and diastolic blood pressure ($P<0.001$) and serum cholesterol ($P<0.05$). Magnesium did not have an additional effect. These results suggest that potassium could be a valuable alternative to diuretics, beta blockers and other pharmacological agents in mild hypertension and is well tolerated. Further controlled studies, both short-term and long-term, may be required to delineate the place of potassium in the therapeutic armamentarium available to physicians to treat mild hypertension and to examine its possible role in reducing mortality due to stroke.

Excerpted from Patki P S, Singh J, Gokhale S V, *et al.* Efficacy of potassium and magnesium in essential hypertension: A double-blind placebo-controlled, crossover study. *British Medical Journal* 1990; **301:** 521–23.