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Highlights of the HMA Council Meeting of March 3, 1992

The HMA Council met on 3 March 1992. The highlights of its action follow. Those present were: S Wallach, J Chang, A Don, J Spangler, J McDonnell, C Kam, R Stodd, F Holschuh, L Sakai, R Lee-Ching, M Cheng, L Magnussen, P DeMare, R Adaniya, P Blanchette, R Embry, R Kimura, HKW Chinn, M Shirasu, W Young, C Kadooka, R Goodale, J Betwee, H Percy, T Smith, G Goto, J Lumeng, WWY Chang and A Kunimoto. Also present were: Mrs S Magnussen-Aux; F Reppun-Editor, HMJ; V Woo-Legal Counsel; B Fong-Med Director, Aetna-Medicare; and G Starbuck-Chair, HMA Bodybuilding Committee. HMA staff present were: J Won, N Jones, B Kendro, J Asato, J Estioko, L Tong, P Kawamoto, K Hamada, and M Lindsey-recording secretary.

The Council approved assisting and developing a survey in conjunction with Straub Clinic to study Hawaii preventive services by primary care physicians in comparison to the *Guide To Clinical Preventive Services* prepared by the U.S. Preventive Services Task Force.

The Council opposes legislative Bill HB 2814, HD2 Relating to the Regulation of Nursing, for the following reasons:

1. The bill jeopardizes patient safety;
2. under the proposed definition of "collaboration", nurses agree the input of the physician is advisory only and they do not have to follow the physician's recommendations;
3. most states which allow prescriptive authority to nurses in advanced practice do so in a dependent relationship with the physician;
4. it proposes to limit practice to an institutional setting which will include hospitals, health centers, physician offices and group practices, all employee health clinics and only in "collaboration" with a physician;
5. in addition, both the Drug Enforcement Agency (DEA) and the Department of Health (DoH) have stated their opposition to this Bill.

Approval was given by Council for a promotional mailing to HMA members by Conomikes Medicare Hotline regarding the latest update on Medicare regulations as well as "how to deal" with breadbasket issues.

The Publications Committee recommendation to increase the *Journal* subscription rate to $18 for members and $25 for nonmembers was referred to the next Finance Committee 1993 budget session. A resolution will be submitted to the 1992 House of Delegates.

The HMA approved a brochure by the DoH regarding the risks of Anabolic Steroids to be distributed to the general public.

HMA will co-sponsor the "Friends, Fitness and Fun Fair" sponsored by the Friends of the Medical School and John A Burns School of Medicine by typesetting and providing camera-ready artwork for its flyers.

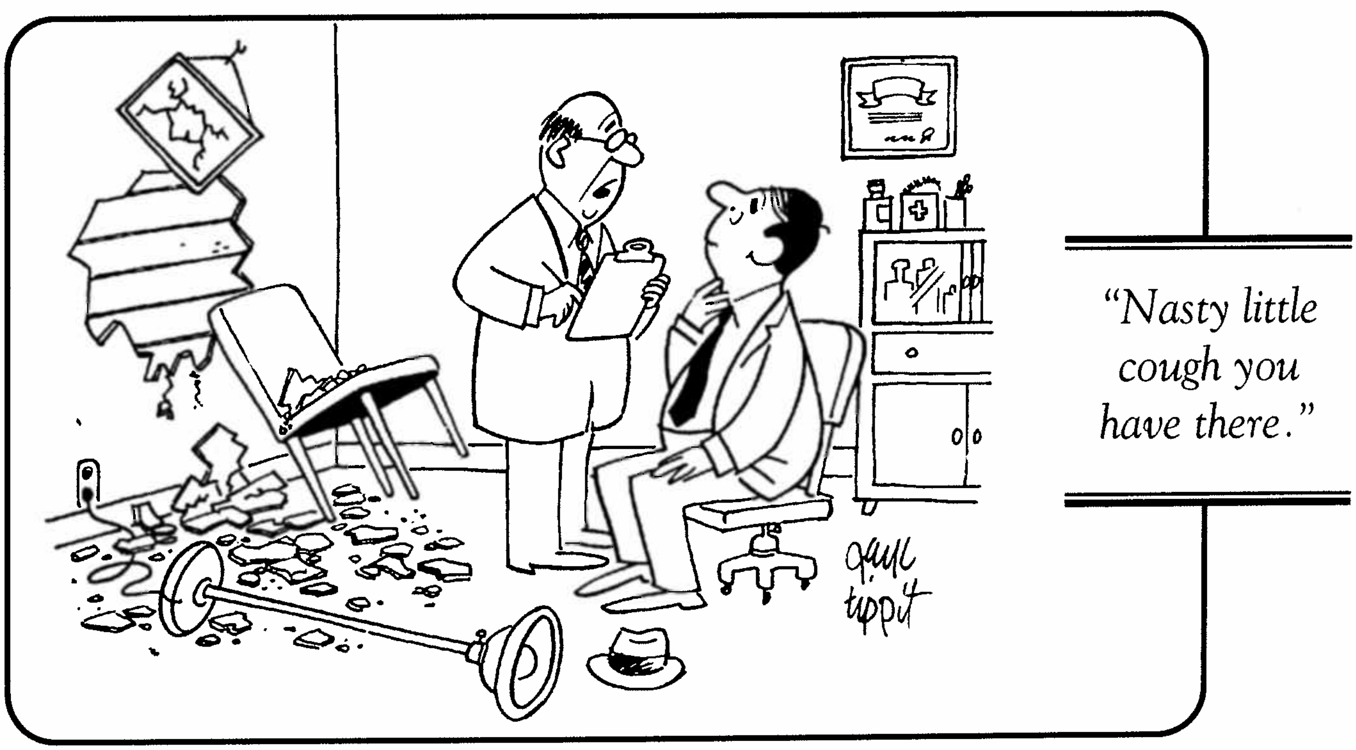
The recent malpractice workshops by MIEC, sponsored by HMA, received overwhelming turnouts in Oahu as well as on the Neighbor Islands.

HMA members will receive easy-to-read posters of Medicare Codes to assist office billings.

SMS Research recently conducted a smoking survey statewide which was supported by HMA. It showed there is increased support for restrictions on smoking and protection for nonsmokers.

HMA and Aloha Medical Mission are actively recruiting volunteer physicians to provide needed medical care to the Maililand Community for homeless families. To volunteer, please call Jan Estioko at HMA, 536-7702 or Aloha Medical Mission at 536-1588.

Andrew Don MD
Secretary



For the many faces of mild hypertension

THE MOST WIDELY USED CALCIUM ANTAGONIST AS MONOTHERAPY FOR MILD HYPERTENSION[1*]

- Effective 24-hour control[2]
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- Well tolerated[†]
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Calan® SR
(verapamil HCl) 180 mg
SUSTAINED-RELEASE CAPLETS

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*The recommended starting dose for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food.

†Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus.* New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol.* 1990;66:13I-15I. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol.* 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation.* 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology.* 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

4/11/91 • P91CA6277V

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Editorials

Ciguatera, once again

Ciguatera, a form of ichthyosarcotoxism, a term originating in the West Indies, is the name of a disease caused by the ingestion of Ciguatoxin; it is a poisoning of humans who eat certain fish. To call the disease Ciguatera fish poisoning is redundant.

Ciguatera has swum into the pages of the *Journal* on numerous occasions in the past: by Helfrich P in 1963, Bagnis R in 1968, Sorokin M in 1975, Anderson, Sims and Wiebenga in 1983 and in an editorial in 1988 that referred to the research by Dr Tilman Ruff of Australia on the marked rise in its incidence in the Pacific Ocean areas the result of the French nuclear weapons testing in Moruroa in the Tuamoto archipelago.

The entity has generated attention from the news media of late as a consequence of an increase in the number of cases occurring in the Islands. In particular, Paul Effler MD, Preventive Medicine Resident with the State Department of Health, writing in the *Communicable Disease Report* of February/ March 1991, reported 35 cases of Ciguatera within a 2-week period in February.

In this issue of the *Journal*, we publish a rather comprehensive review of Ciguatera that was submitted to us quite some time ago (we apologize for the long lead time) by James H Gollop MD MPH and by Eugene Pon MD MPH, Chief of the Epidemiology Branch.

In view of the DoH report that 14 of the 35 recent cases had to be hospitalized and 11 of those to intensive care units, it warrants publishing an article on the subject once again, to alert practicing physicians to the seriousness of this toxicity.

We endorse the publicity in the news media that alerts the eaters of Po'ou, Ulua, Papio, Palani and other littoral fishes, to be constantly aware and knowledgeable about the dangers of Ciguatera.

J I Frederick Reppun MD
Editor

Ciguatera: A review

James H Gollop MD MPH*
Eugene W Pon MD MPH**

Hawaii State Department of Health epidemiological records were reviewed for cases of ciguatera poisoning for the entire state, from January 1984 through December 1988. During the 5 year interval, the numbers of ciguatera poisoning incidents, number of cases, and date of onset were recorded, as well as age and sex of individuals involved. The place of catch of each fish was noted as well as whether or not the fish was obtained commercially. The parts of the fish consumed were also recorded.

A total of 150 ciguatera incidents occurred during this period, involving 462 individuals for an average annual incidence rate of 8.7/100,000 population. The 3 most frequently implicated species of fish were the Carangoides species (jack or papio or ulua), Ctenochaetus strigosus (surgeon fish or kole), and Aphareus furcatus (fork-tailed snapper or waha nui); however, more than 50 species of fish had caused one or more outbreaks. The most frequently implicated areas of the toxic fish were the Kona coast as well as the South Point of the island of Hawaii, and the Napali coast of the island of Kauai. Of the 150 outbreaks, 32 (21%) were related to commercial fish. The rest were related to sportfishing.

Introduction and history

Ciguatera fish poisoning is a disease which results from the ingestion of reef fish. For many years it was primarily a concern of those residing in the tropics or subtropics. However, it is becoming increasingly significant for fish-eaters in temperate areas of the world as well, as fish has become more popular and quick air delivery of fresh fish is a reality[1-6]. Ciguatera fish poisoning is generally thought to be caused by a polyether toxin, usually ciguatoxin (CTX). It is likely however, that the symptom complex we describe as ciguatera, may actually be a result of the consumption of other polyether toxins, such as palytoxin, scaritoxin, maitotoxin and other as of yet unidentified toxins[7].

Ciguatera is not a new disease. The term was coined during the 18th century, when it was noted that a symptom complex would sometimes develop following the ingestion of a marine snail, *Turbo pica*, also commonly known as "cigua"[15]. There were reports of illness due to the consumption of fish noted by the Egyptians during ancient times[12]. There is also evidence to suggest that there were cases of ciguatera poisoning during the voyages of Captain Bligh and Captain James Cook[16,17].

The illness has been extending to new areas however, partly due to modern transportation, that allows fresh fish to be sold in inland areas, and also because of ecological changes that may be contributing to ciguatera endemicity in certain areas of the Pacific. The mechanism of these ecological changes is not well elucidated at this point, but it has been frequently noted that ciguatoxic fish will often increase, or suddenly appear in previously unaffected areas, following an upset in the benthic environment, as may occur during coastal construction projects or dredging, or underwater nuclear bomb testing[13,18].

The primary endemic areas, however, are still the tropical and subtropical coastal regions of the world, particularly in the South Pacific islands and the Caribbean[19,20]. In the United States, most cases occur in Hawaii and in Southeastern Florida, although cases have been reported from Texas, California and occasionally the inland states as the result of importing fish from endemic areas[1-6,12,13,21].

Pathogenesis

It has been determined that ciguatoxin is produced by a photosynthetic benthic dinoflagellate *Gambierdiscus toxicus*, which lives in the coral reef environment[8]. Herbivorous fish consume the organism in algae that contain the toxin and concentrate the CTX in their internal organs and flesh. These fish may then be consumed by larger carnivorous fish, which in turn concentrate the toxin to a greater extent. Thus, the toxin passes up the food chain to the human consumer. The presence of toxic fish tends to be sporadic and unpredictable, making it impossible without the use of scientific testing to determine whether or not a fish caught from a specific area, at a specific time, may be safe to eat.

Individual susceptibility to the toxin varies considerably. A given amount of fish, when consumed by one person may cause illness, whereas another person may remain well. It has been demonstrated that susceptibility to the toxin may increase after a previous exposure, and people who have suffered from ciguatera in the past may actually become more susceptible to the disease[9,10]. Even in the absence of symptoms

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For correspondence about the manuscript and request:
James H Gollop MD MPH
State of Hawaii Department of Health Tuberculosis Branch
1700 Lanakila Avenue, Honolulu, HI 96813
(808) 847-6542

* Preventive Medicine Resident
Hawaii State Department of Health,
Communicable Disease Division, Epidemiology Branch,
Honolulu, Hawaii.

** Branch Chief
Hawaii State Department of Health
Communicable Disease Division, Epidemiology Branch
Honolulu, Hawaii.

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at first exposure, those with frequent intake of ciguatoxic fish are more likely to become ill. This may be a matter of accumulation of CTX in the host, or possibly an immunologic reaction.

It is interesting to note that individuals suffering from ciguatera will often have symptoms after eating *any* seafood, and often nuts, nut oils and alcoholic beverages as well. The mechanism behind this phenomenon is as yet unknown, but it is recommended that individuals suffering from ciguatera follow a diet avoiding such products[11].

The toxin involved in ciguatera is odorless and tasteless. There is no ordinary means of detecting the presence of the toxin other than by scientific testing. The toxin is heat-stable, and is not destroyed by boiling, steaming, baking, smoking, salting, pickling or freezing[12,13,14].

The mechanism whereby the polyether toxins affect a human has not yet been elucidated. Originally it was thought to exert its effect by an anticholinesterase activity, but later it was found to have a more complex mechanism of action which has yet to be determined[22].

Clinical manifestations

The toxin primarily affects the gastrointestinal tract and the nervous system. Within about 4 to 10 hours after ingestion of a toxic fish, the individual typically develops gastrointestinal symptoms: Nausea, vomiting, diarrhea and abdominal cramps, often associated with a feeling of profound weakness and dysphoria. Muscle aches, joint pains, diaphoresis and chills may be present at this time as well. The gastrointestinal symptoms resolve after the first 12 hours of the illness[10,12,13,15,20,21].

Typically it is the neurologic symptoms that cause the prolonged discomfort in the disease. These neurologic symptoms generally begin at about the time the gastrointestinal complaints are resolving, and consist of dysesthesias and paresthesias particularly involving the perioral region and the distal extremities. Classically, one may experience the "temperature reversal phenomenon" whereas cold objects give a warm sensation and touching warm objects results in a cold sensation. Often on drinking cold beverages, the person will describe a feeling of tingling of the tongue; cold beverages may feel hot, and vice-versa. The feeling of paresthesias is usually quite distressing; it may be described by some as a painful burning sensation. Pruritus typically develops as well, about one day after the onset of the initial gastrointestinal complaints. Symptoms usually last about one week, although may persist for months and be exacerbated by the consumption of other food products, as described above.

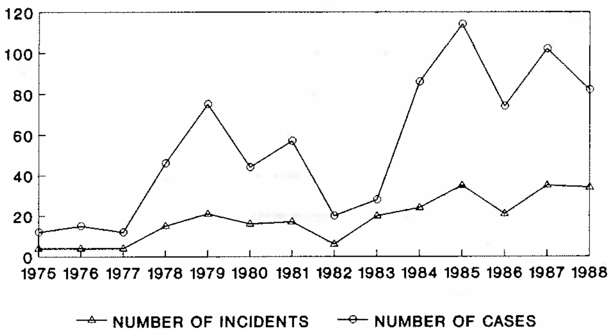
Ciguatera is generally a self-limiting disease, but death may occur as a result of cardiac dysrhythmias, hypotension, shock or cerebral edema. The case-fatality rate varies from 0.1% to 1%, depending on the geographic location[7,11,12,13].

Treatment

There is no specific treatment nor antidote for ciguatera. Treatment is generally symptomatic and consists of the administration of analgesics and specific drugs to treat the complications described above, should they develop.

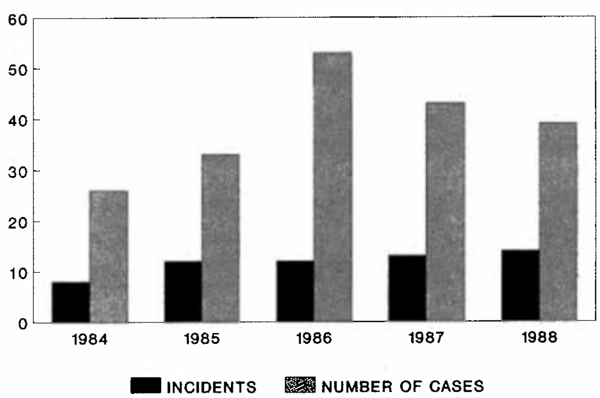
Mannitol, a commonly used diuretic, has been shown to

FIGURE 1:
ANNUAL INCIDENCE OF CIGUATERA
STATE OF HAWAII, 1975 - 1988



SOURCE: HAWAII STATE DEPARTMENT OF HEALTH

FIGURE 2:
CIGUATERA INCIDENTS
ISLAND OF HAWAII, 1984 - 1988



SOURCE: HAWAII STATE DEPARTMENT OF HEALTH

TABLE 1:
ANNUAL INCIDENCE OF CIGUATERA
PER 100,000 POPULATION
BY ISLAND AND YEAR: 1984 - 1988

YEAR	POPULATION	NO. CASES	ANNUAL INCIDENCE PER 100,000 POPULATION
OAHU			
1984	802,351	38	4.7
1985	812,784	29	3.6
1986	818,487	13	1.6
1987	830,597	40	4.8
1988	838,194 est.	27	3.2
KAUAI			
1984	44,167	17	38.5
1985	44,679	47	105.0
1986	46,440	8	17.2
1987	47,600	12	25.2
1988	47,700 est.	6	12.5
MAUI			
1984	74,750	5	6.7
1985	76,462	5	6.5
1986	78,790	0	0
1987	81,100	11	13.6
1988	90,300 est.	10	11.1
HAWAII			
1984	107,169	26	25.2
1985	108,910	33	30.3
1986	112,039	53	47.3
1987	114,434	43	37.6
1988	115,200 est.	39	33.9
STATE			
1984	1,037,206	86	8.3
1985	1,051,481	114	10.8
1986	1,064,732	74	7.0
1987	1,082,500	106	9.8
1988	1,091,394 est.	83	7.5
		TOTAL 462	AVERAGE 8.7

reduce remarkably the intensity and duration of symptoms of ciguatera in a number of patients[23]. As of yet, formal clinical trials using the drug have not been done; the mechanism of action of mannitol is unknown. It may be consequent to diuresis with subsequent rehydration that flushes out the ciguatoxin. It may be a matter of the effects of mannitol on the sodium and potassium channels in the cell membrane. Less likely is the possibility of some type of direct chemical detoxification by the action of mannitol.

It is also recommended that the patient suffering from ciguatera be placed on a "ciguatera diet" which involves avoidance of *all* seafood (even including those which are not usually contaminated with ciguatoxin, such as shellfish), as well as nuts, nut oils, sesame oil and alcoholic beverages until symptoms have completely subsided, in order to prevent the worsening or prolonging of symptoms[11].

Epidemiology

Epidemiological studies have been carried out in the South Pacific and Caribbean ocean areas in order to determine the incidence in these endemic areas. Annual incidence rates varied during the interval 1979 to 1983 from one case per 100,000 people in the Solomon Islands to 1,338 per 100,000 people in Tokelau[19]. Other high incidence areas with rates calculated for the same interval were: French Polynesia with 585 cases per 100,000; Kiribati, with 462 cases per 100,000; and Tuvalu, 484 cases per 100,000[19]. During the years 1982 to 1987 the Marshall Islands had 234.9 cases per 1000 population[18]. A study from St. Thomas, U.S. Virgin Islands, revealed an incidence rate of 36.5 cases per 1,000 population in 5 years[9].

In the Virgin Islands, the most commonly implicated species of fish was the *Caranx ruber* (Carrang). In the South Pacific, in addition to the *Carangidae* (Jacks), *Lycodontis javanicus* (Moray eel) and *Lutjanidae* (snappers) were also highly suspect as the source of ciguatera[25]. In Fiji, the most commonly implicated species was *Sphyraena barracuda* (Barracuda)[24].

A previous epidemiologic investigation of ciguatera in the

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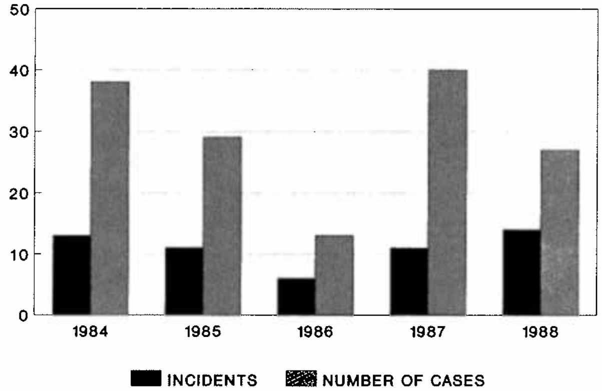
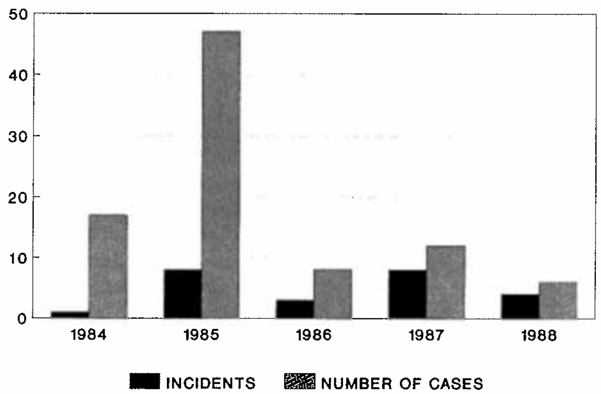
FIGURE 3:
CIGUATERA INCIDENTS
ISLAND OF OAHU, 1984 - 1988



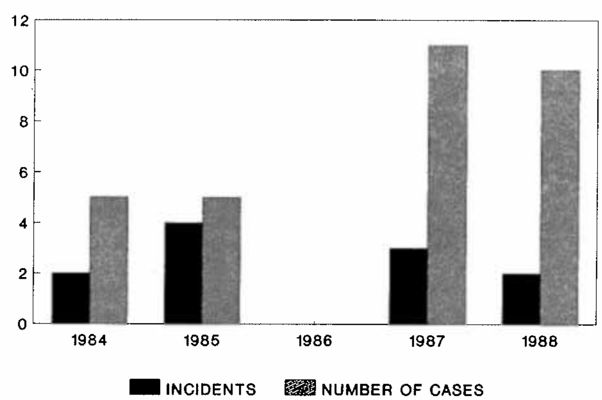
SOURCE: HAWAII STATE DEPARTMENT OF HEALTH

FIGURE 4:
CIGUATERA INCIDENTS
ISLAND OF KAUAI, 1984 - 1988



SOURCE: HAWAII STATE DEPARTMENT OF HEALTH

FIGURE 4:
CIGUATERA INCIDENTS
ISLAND OF MAUI, 1984 - 1988



SOURCE: HAWAII STATE DEPARTMENT OF HEALTH

Hawaiian Islands from 1975 to 1981 revealed an average incidence rate of 1.3/100,000 population. Again, the *Carangoides* species (Jacks or Ulua and Papio) was the most frequently implicated, followed by *Seriola dumerilii* (Amberjack or Kahala), and *Cheilinus rhodochrous* (Wrasse or Po'ou). Other implicated fish included the *Mulloidichtys samoensis* (Goatfish or Weke), *Scaridae* species (Parrotfish or Uhu), *Mugil cephalus* (Mullet or Amaama), *Epinephelus guernus* (Grouper or Hapuupuu) and *Acanthurus dussumieri* (Surgeonfish or Palani)[13].

The Hawaii State Department of Health (DoH) investigates each suspected case of ciguatera that is reported. Every ciguatera investigation involves an environmental, epidemiological and laboratory examination. The epidemiological investigation consists of determining the basic demographics of the cases: The timing and location of the outbreak; determining the parts of the fish eaten; the extent of symptoms; whether hospitalized; the number of work days missed and the duration of illness. This information is usually obtained by interviewing the patients and often their physicians as well.

The laboratory investigation includes the collection of any leftover fish samples and testing them with an ELISA test to determine semi-quantitatively the amount of polyether toxin present in the fish. This is done by a stick-test developed at the University of Hawaii[26].

The environmental investigation involves determining the place where the fish was caught or purchased; often means making a site-visit to the market or restaurant where the fish was obtained. Companion samples of fish from the same catch may also have to be tested. The merchant is advised not to sell any fish of the same species from the same catch, nor remaining parts of the same fish. The place of catch and the species of the fish is recorded (if available) and the involved merchants are given information about ciguatera and other types of fish poisoning.

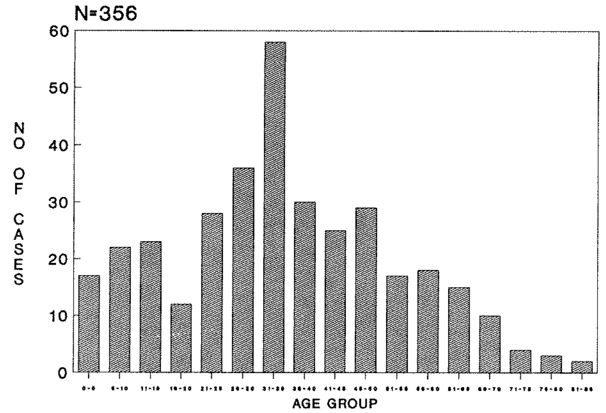
Materials and methods

DoH records of all reported ciguatera incidents were reviewed for the 5-year period 1984 to 1988. All probable or confirmed incidents were included in the investigation. Cases that occurred as the result of eating fish that were caught outside of the State were included.

A "probable" case was defined as "experiencing both gastrointestinal and paraesthetic symptoms within 30 hours following the consumption of a fish implicated in ciguatera". A confirmed case was defined as "a person with signs and symptoms compatible with ciguatera plus a positive poke-stick test of leftover fish eaten by that person." The term "incident" was used as opposed to "outbreak"; an outbreak generally refers to more than one person being ill, whereas an incident may refer to a single case. A person epidemiologically linked to an incident with a confirmed case and exhibiting at least some components of the gastrointestinal or neurological symptoms also was considered as a confirmed case. Information extracted from each chart included: The date of onset and location of the incident; the age and sex of the victims; the species of fish eaten; the place where the fish was obtained; and the parts of the fish consumed.

The species of fish involved was usually identified by a common or Hawaiian name by those who saw the fish before

**FIGURE 6:
CIGUATERA INCIDENTS
ISLAND OF HAWAII, 1984 - 1988**



SOURCE: HAWAII STATE DEPARTMENT OF HEALTH

it was consumed. Occasionally fish markets had to be consulted regarding the correct nomenclature, and in only one instance was the type of fish unknown.

Several incidents occurred after the consumption of more than one type of fish. In these cases, the names of all the fish that may have been involved were recorded. The stick-test results of the fish were recorded as positive, borderline or negative, and were designated as either from the fish eaten or a companion sample (fish of the same species, caught at the same time and same location as the original fish).

In order to help determine if there were unreported cases, emergency room records in 6 different hospitals throughout the State were reviewed in order to find cases with the diagnosis of ciguatera. None was found. The hospitals chosen were those whose record-keeping systems allowed such investigations to be performed. The information was stored and analyzed using the D-Base III plus program on a Wang PC-compatible computer at the DoH office. Graphs were produced by *Harvard Graphics.*

Results

A total of 150 incidents were reported during the years 1984 to 1988 in the State of Hawaii. These incidents occurred in all 4 counties of the State and were investigated by the DoH Epidemiology branch. The150 incidents (57 confirmed, 93 probable) involved 462 cases of ciguatera. There were 652 exposed individuals; the 462 cases, therefore, comprised an overall attack rate of 70.9%. However the attack rate varied greatly in each outbreak; some outbreaks had attack rates of 100%. The island of Hawaii reported the most incidents, followed by Oahu, Kauai and Maui respectively (Table 1).

Although a significant increase in cases and incidents had been noted during the late 1970s and early 1980s, such increases have not been noted for the 1984 to 1988 period (see Figure 1). The island of Hawaii reported 8, 12, 12, 13, and 14 ciguatera incidents during each of the years from 1984 through 1988 (Figure 2). The other islands did not show significant increases during the same 5-year period (Figures 3, 4 and 5).

Kauai had 105 cases/100,000 population in 1985 primarily due to a problem with toxic *Ctenochaetus strigosus* (kole) fish

**TABLE 2:
INCIDENTS OF CIGUATERA BY SPECIES OF FISH IMPLICATED, STATE OF HAWAII: 1984 - 1988**

NAME OF FISH	NUMBER OF INCIDENTS
Ulua	19
Papio	16
Kole	15
Wahanui	12
Roi	7
Po'ou	6
Weke	4
Barracuda	4
Eel	3
Kahala	3
Palani	3
Uku	3
Ta'ape	3
Mullet	3
Opakapaka	2
Omilu	2
Moana	2

Fish may be implicated more than once.

**TABLE 3:
INCIDENCE OF CIGUATERA BY
AREA CAUGHT AND ISLAND: 1984 - 1988**

AREA CAUGHT	NO. OF INCIDENTS
OAHU	
Reef Runway	3
Kaena Point	3
Barbers Point	2
Haleiwa	2
Waianae Coast	2
Waianae	2
HAWAII	
South Kona	7
Milolii	7
South Point	6
Kawaihae	4
Keei	4
Puako	4
Kona	2
Punaluu	2
MOLOKAI	2
KAUAI	
Napali Coast	7
Nualolo	2

Fish may be implicated more than once.

(Continued on page 97) ➤


A+
NEW INDICATION

CIGUATERA *(Continued from page 95)*

FIGURE 7: CIGUATERA INCIDENTS 1984 - 1988

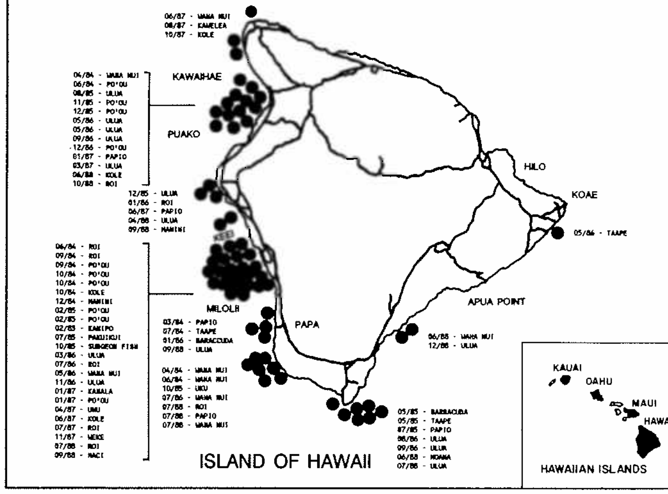
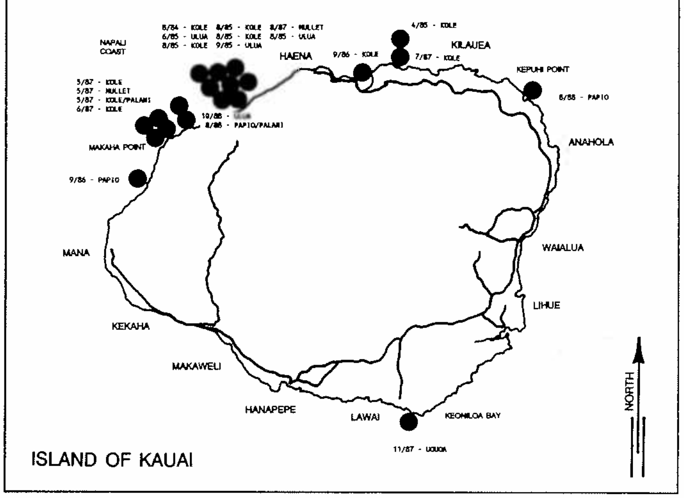


FIGURE 8: CIGUATERA INCIDENTS 1984 - 1988



on the Napali coast.

The sex differential was 182 male patients and 174 females. An age distribution curve shows a peak in the early fourth decade of life (Figure 6).

The most frequently impugned species of fish were the Papio and Ulua causing a total of 35 incidents (Table 2). Kole were implicated in 15 ciguatera incidents. The third most frequently involved fish was the Wahanui (*Aphareus furcatus* or fork-tailed snapper) in 12 incidents. Other fish involved in more than one ciguatera incident included: Roi (*Cephalophilus guttatus* blue-spotted grouper); Po'ou; Weke; Barracuda); eel; Kahala; Palani; Uku (*Aprion virescens* gray snapper); Ta'ape (*Lutjanus kasmira* blue-lined snapper); Mullet; Opakapaka (*Pristipomoides filamentosus* snapper); Moana (*Parupeneus multifasciatus* goatfish); and Omilu *(Caranx melampygus* blue crevally). There were additional individual incidents involving consumption of more than one of the above fish at a time, or other fish whose common names were: Sea bass, shark, rainbow runner, blue-lined surgeonfish,

(Continued) ➤

CIGUATERA *(Continued from page 97)*

FIGURE 9:
CIGUATERA INCIDENTS 1984 - 1988

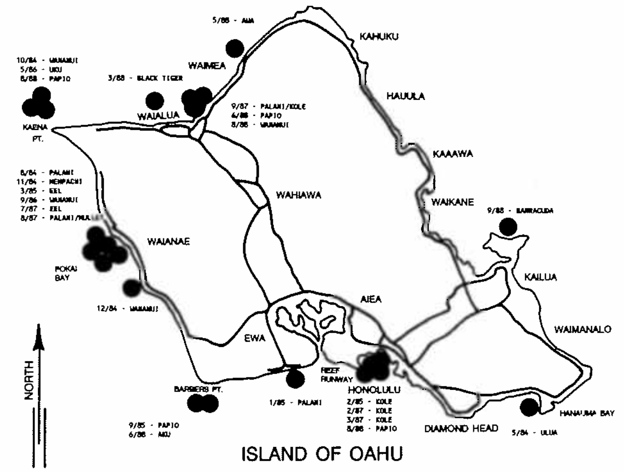


FIGURE 10:
CIGUATERA INCIDENTS 1984 - 1988

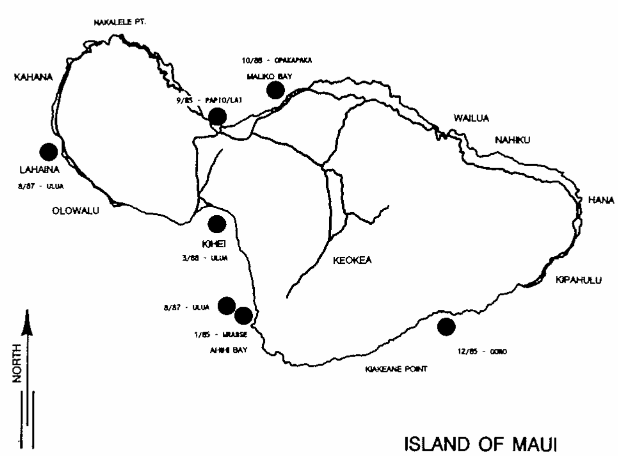
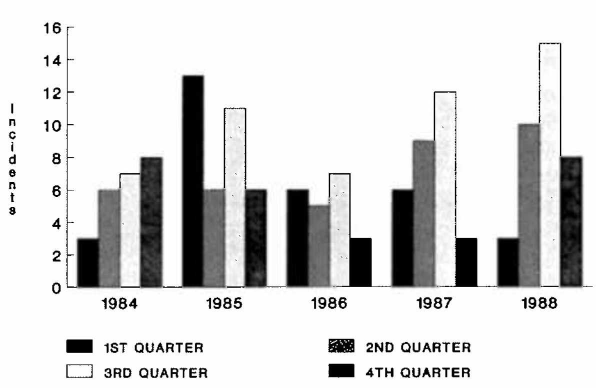


FIGURE 11:
INCIDENTS OF CIGUATERA BY QUARTER: 1984 - 1988



smoked mackerel from the Philippines (*Tinapa Galongong*), Wahoo, false mullet, Japanese barracuda, Achilles tang, black trigger, milkfish, convict tang, squirrel-fish, porgy and red snapper. Oddly, there was one outbreak attributable to the consumption of octopus and another to Aku.

The Kona coast of the island of Hawaii was responsible for the most incidents (Table 3). These fish were primarily caught by sportfishing off the Napali Coast of Kauai, South Point of Hawaii, Kaena Point, Barber's Point, Pokai Bay and the Waianae coast of Oahu (Figures 7, 8, 9 and 10). In addition to the sites represented on the maps, there were 2 episodes of ciguatera attributable to fish caught off Molokai, and one off the island of Lanai.

No marked seasonal variation was observed in ciguatera incidents, although there was a slight increase noted during the third quarter of the year (July through September), and a decrease during the fourth quarter (October through December) during the 5-year period studied (Figure 11).

Of the 150 known ciguatera incidents, in 130, records were kept indicating the parts of the fish that were consumed. In 59, parts of the fish other than the flesh, such as the head, viscera and roe, or a soup made from these parts, were consumed by at least one of the individuals who became ill.

Commercially sold fish accounted for 33 out of the 150 ciguatera incidents (22%). These fish were either consumed in a restaurant or were purchased from markets. The other 78% of incidents were attributable to fish caught recreationally.

In 89 incidents fish were available for testing using the stick-test, either leftovers of the fish actually eaten or fish from a companion catch. The putative fish itself was available for testing in only 61 incidents.

Discussion

The statewide incidence rate of 8.7/100,000 shows a significant increase over the previous epidemiologic study of 1975 to 1981 that demonstrated an incidence of 3/100,000[13]. The increase occurred largely during the early 1980s (Figures 1 and 2). (In referring to the figures, it is important for the reader to realize that the number of incidents correlates more closely with the actual endemicity of ciguatera at a given period of time rather than with the number of cases; the latter relates to the number of people who ate the toxic fish. Thus, a single outbreak affecting 100 people would be of less consequence epidemiologically than 100 different fish making 100 people ill.) This may be a result of increased awareness of the disease and better reporting, but it is also likely that there actually has been an increase in ciguatera in the Hawaiian Islands. This may be due to changes in the reef environment similar to what has occurred in the Marshall islands[18].

In the last 5 years, however, the ciguatera rates seem to have reached a plateau. The areas typically affected are the leeward coastal areas. Areas of dredging and construction will often show an increase in ciguatoxic fish, such as when the reef-runway at Honolulu International Airport was constructed. Construction lasted from May 1973 to December 1977. The first toxic fish began to be recorded in April, 1978, 4 months after the construction ceased, and toxic fish are still known to inhabit the region. The Pokai Bay area of the Waianae Coast underwent construction of a breakwater from April 1977 to

January 1979; it involved dredging, filling and blasting. After 15 months, reports of toxic fish began appearing, and to the present, the Pokai Bay area is known for its ciguatera problem[13]. The large increase in reported cases from the Kona coast of the Big Island may also be related to the multiple construction projects that occurred earlier this decade.

The age of onset of the disease correlates well with the ages of individuals more likely to be out fishing. If it is true that the susceptibility to ciguatoxin increases with repeated previous exposure, one would expect that older age groups with more years of exposure to ciguatoxin would have more cases of illness. Age distributions in other studies have been similar[9,27].

The slight increase in the number of ciguatera incidents during the third quarter of the year may be due to climatic changes of the reef environment, or an increase in fishing activity during that time of the year. The decrease during the fourth quarter may be due to cooler and increasingly rainy weather. A seasonal study from Puerto Rico showed definite seasonal trends with peak seasons for ciguatoxic barracuda occurring in January to May, and August to November[28].

In 59 of the 150 ciguatera incidents, at least one (and usually more) of the victims consumed a portion of the fish known to concentrate the ciguatoxin, notably the gut, liver, head and roe, as well as a soup or broth made of the latter. It is likely that many, if not most, of these outbreaks (a large proportion of the total) could have been avoided if the individuals involved had been educated regarding ciguatera and the concentration of the ciguatoxin in these parts of the fish.

Ciguatera is of great concern at local fish markets, which attempt to avoid the sale of toxic fish by avoiding buying fish caught near leeward reefs, as well as avoiding the sale of specific species known to be toxic. The Kahala is an example of a fish that is no longer sold in local markets due to its high prevalence for ciguatoxicity.

The use of the stick-test for commercial use does not appear to be cost-effective. It is reassuring to know that in the year 1987, among a total of 164,910 reef fish caught commercially, only 5 incidents of ciguatera poisoning were reported, only .003% of the total reef fish caught. The year 1987 is representative of other years as well, in which commercial ciguatoxic fish have only been implicated, ie in 3 to 10 incidents per year during the years 1984 to 1988.

The major source of ciguatera cases has been the fish caught by sportfishing, typically on weekends and holidays. If people could be educated to avoid consuming heads, viscera and roe of reef fish (especially a soup made of the above); and avoid fish caught in the areas known for being ciguatera-prone, the rates of ciguatera would decrease dramatically. The addition of the stick-test for use in sportfishing could reduce the rates of illness even more .

Since the future incidence of ciguatera is unpredictable, we cannot assume the problem will go away. We can, however, significantly reduce the probability of future outbreaks by educating the public, and by encouraging the use of the stick-test in sportfishing.

ACKNOWLEDGEMENTS

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■

Providing health care to Hawaii's elderly

Cullen T Hayashida PhD*
Warren Wong MD**

Hawaii's rapidly aging population is a challenge for Hawaii's health care providers. What with the high cost of care, limited health care resources, and a rapidly increasing population of frail elderly patients living in the community, will our medical practices be able to adapt to the care of patients who require more time and who will have not only multiple medical illnesses but complicated psychosocial conditions as well? Will our health care facilities be prepared for the typically longer stay and more expensive older patient? Will the cost of care in Hawaii keep on rising? Who will pay? Will this challenge turn into a crisis?

Demography of aging in Hawaii

Ours is one of the nation's most rapidly aging populations. In 1989, the ≥ 65 years population numbered 125,300 or 10.7% of the State's population. In comparison to the national average of 12.5%, Hawaii has a lower percentage of elderly. Within the next 2 decades, however, Hawaii's population ≥ 65 is projected to increase by over 50% while the total resident population is expected to increase by only 23.3%. This change represents a rate of growth more than 2.5 times the national growth rate of the elderly. Consequently we will witness before the turn of the century the convergence of the proportion of the elderly in Hawaii with the national average as depicted in Figure 1[1].

The dramatic rise in the proportion of elderly in Hawaii is partly attributable to the rapid rise in the life-expectancy of Hawaii's people. It is well established that Hawaii's life-expectancy at birth is the nation's highest. In 1985, Hawaii's life-expectancy at birth was 77.98 years; this was higher than every state in the Union. The corresponding figure for the entire U.S. for that same year was 74.7 years, or 3 years less. Based on available international evidence from other high life-expectancy countries in Europe and Japan, there is reason to believe that Hawaii's life-expectancy rate might be among the highest in the world as well[2].

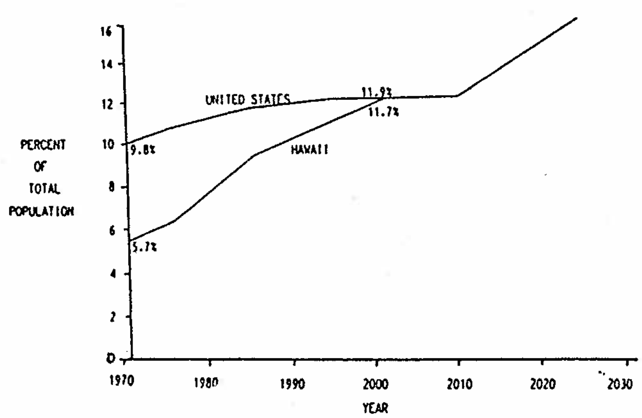
As portrayed in Figure 2, the elderly population (≥ 65 years) is aging in ways similar to patients for both the U.S. and Hawaii, ie moderate proportional increases occurring in the 75- to 84-year-old category, a large proportional increase occurring in the ≥ 85-year-old category and a proportional decrease occurring in the 65- to 74-year-old category. While this change is expected to occur over a 100-year period (1900 to 2000) for the entire U.S., it is occurring in Hawaii over only 50 years (1950 to 2000). The rapid increase particularly in the proportion of those over age 85 will place an enormous burden on available long-term care services since the need for long-term care rises sharply with age[3].

Present and projected health care delivery systems

The added challenge of providing health care to an aging population will further strain an already stretched health care system. In 1989, Hawaii's acute care bed supply of 193.4 beds per 100,000 remained far below the national average of 353.4 beds per 100,000[4]. Hawaii has maintained a significantly lower hospital admissions rate of 107.5 per 1,000 population versus 135.9 per 1,000 for the U.S. as a whole. As a consequence, Hawaii's hospital occupancy (82.8% versus 69.6% for the U.S.) and outpatient hospital services rates

FIGURE 1

Percent Elderly (65+) in Hawaii and U.S. 1970 to 2030



Source: Hayashida CT, Sherman S and Sasaki H. *Adult Day Care Centers in Hawaii: Comprehensive Assessment for Strategic Planning for the 1990s.* Kuakini Geriatric Care, Inc., Honolulu, Hawaii. December 1987. Page III-42.

(Continued on page 103) ➤

* Director
Maluhia Home Health Care
Maluhia Long-Term Health Center
Hawaii State Department of Health
** Medical Director
Skilled Nursing Facility
Kaiser Medical Center

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Before prescribing, please see full prescribing information. A brief summary follows.

INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m², respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, *triamterene, or amiloride*), potassium supplements, *or potassium-containing salt substitutes is indicated, they should be used* with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m², respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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PD-103-JA-7164-A2(022)

(2,074.5/1,000 versus 1057.5/1,000 for the U.S.), were appreciably higher.

Acute hospital bed availability is tight not only because of the low ratio of beds per 1,000 population, but also because of the shortage of long-term care beds. Approximately 200 acute care beds, representing 10% of Hawaii's total medical-surgical bed supply, are occupied by patients awaiting placement in long-term care[5]. The proportion of medical-surgical beds occupied by wait-listed patients on the Neighbor Islands is even greater. With only 3,416 long-term care beds available, Hawaii's ratio of 27.3 beds per 1,000 elderly is far below the national average of 65.5 beds per 1,000 elderly. Furthermore, since 1984, there has been an actual decline in the ratio of nursing home beds per 1,000 elderly.

Hawaii's health care system is clearly not meeting the needs of Hawaii's elderly population. And the back-up of long-term care patients in acute hospital beds is likely to worsen in coming years. Since March 1990, there has been no new construction of long-term care beds. In January 1992, were about 180 nursing home beds that have been approved by the Hawaii State Health Planning and Development Agency (SHPDA). These beds, however, are not expected to be available for at least another 2 years. Even then, this new supply will fall far short of Hawaii's growing demand for institutional long-term care services.

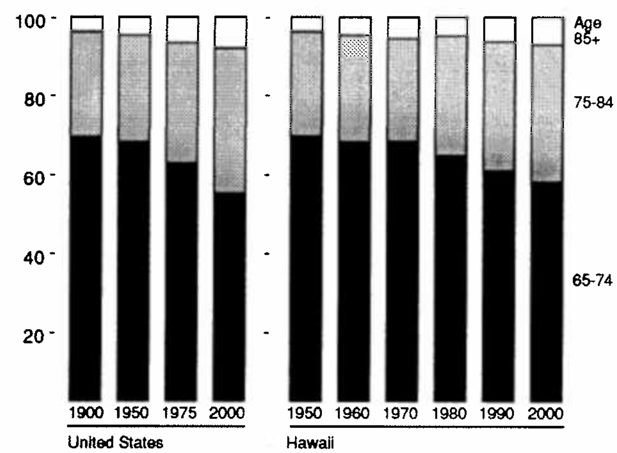
One reason for the historically low nursing home bed ratio is that Hawaii's families have long been the major source of long-term and informal support to the frail and dependent elderly population. In comparison to their Mainland counterparts, Hawaii's families may continue to be more supportive of their elderly parents.

More recently, other factors, such as the fiscal pressures for earlier discharge from acute care, as exemplified by the Medicare DRG hospital payment system, have been significant. The State's Medicaid program has faced increased budget tightening and, therefore, has been unable to increase its reimbursements for institutional long-term care services.

Increased competition posed by the visitor industry to entry-level workers represents a significant factor in curtailing the health industry's labor pool. Without adequate staffing, available beds cannot be used. This is compounded by the strict requirements for certification, licensing and training imposed by the state and federal governments.

The nursing home bed shortage is already beginning to have repercussions on the health care delivery system. Hospitals are competing for limited nursing home beds by structuring special arrangements for more favorable status with nursing homes. The paucity of vacancies in nursing homes is increasing as indicated by the subversion to sub-acute or super-SNF levels, and hospitals are forced to create their own nursing home units. Care homes of higher level that were able to transfer clients to nursing homes previously are now being denied that access. As a result, the Department of Human Services (DHS) has been forced to create a separate payment rate for care homes that have ICF-level clients in order to accommodate the backlog. Because of the premium on beds, nursing homes are in a position to admit patients selectively.

FIGURE 2



• The Aging of the Elderly Population
U.S. and Hawaii to Year 2000

Source: Hayashida CT, Sherman S and Sasaki H. *Adult Day Care Centers in Hawaii: Comprehensive Assessment for Strategic Planning for the 1990s.* Kuakini Geriatric Care, Inc., Honolulu, Hawaii. December 1987. Page III-44.

Patients who are difficult to care for or who have little or no financial support are unlikely to be chosen. As a result, their families are experiencing more stress and burden, which is conducive to an increase in elder abuse and neglect cases.

As for current and projected cost of health care services, according to the Hawaii State Executive Office on Aging, it is expected to grow almost exponentially from now into the 21st century. Consider these sobering statistics given in today's dollars. Within the next 30 years or by the year 2020[7]:

- The State's portion for the Medicaid program for elderly nursing home care will grow by more than 1,300% from $38.3 million in 1991 to over $544 million. This represents only 33% of the total cost, with families and the federal government also contributing a third each.
- The total long-term care bill, including the costs of nursing home and paid home care in Hawaii will grow by more than 1,000% to a staggering $2.05 billion.

The national deficit that has exceeded $4 trillion does not give Hawaii much hope that the federal government will be the expected panacea. Efforts to reduce Medicare's rate of expenditure have been made and will continue to be made. The U.S. government also considers its participation in the Medicaid program as a plausible target for federal budget cuts in the years ahead.

Conclusion

There is great pressure to control the cost of health care. At the same time, the aging population will have a higher prevalence of disease and will require more intensive acute and long-term care services. Hawaii, with its limited hospital bed capacity and high cost of care, is on the frontline of these challenges.

To keep challenge from turning into crisis, certain strate-

(Continued) ➤

HAWAII'S ELDERLY *(Continued from page 104)*

gies are necessary. Patients whose health is likely to deteriorate must be identified before it does. Once these patients are identified, there must be effective intervention. The special approach to geriatric syndromes and chronic diseases common to the elderly must be emphasized. There must be effective alternatives to hospitalization and institutional long-term care. (A forthcoming issue of this 2-part article will discuss such strategies.)

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■

These Glorious Golden Years!

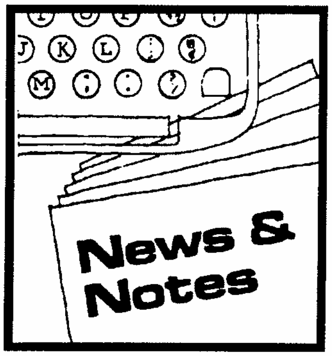
Remember, old folks are worth a fortune,
with silver in their hair, gold in their teeth,
stones in their kidneys, lead in their feet,
and gas in their stomachs.

I, myself, have become a little older since I saw you last,
and a few changes have come into my life since then.
Frankly, I have become quite a frivolous old gal.
I am seeing five gentlemen every day!

As soon as I wake up, Will Power helps me to get out of bed.
Then I go to see John. Soon, Charley Horse comes along, and,
when he is here, he takes a lot of time and attention.
When he leaves, Arthur Ritis shows up and stays the rest of the
day. He doesn't like to stay in one place very long, so he takes me
from joint to joint. After such a busy day, I'm really tired and
glad to go to bed with Ben Gay! What a life!

P.S. — The preacher came to call the other day.
He said at my age I should be thinking about the hereafter.
I told him, "Oh, I do, all the time. No matter where I am —
in the parlor, upstairs, in the basement — I ask myself,
'What am I here after?'"

Lillian Schwartz
Kukui O Pohai Nani



Henry N. Yokoyama MD

Life in These Parts ...

Of Dogs and Men

"How's your health these days," we inquired of Dennis Meyer who had missed several Friday morning medical conferences. "My dog and my son are out of bounds," Danny replied. It seems that Danny had returned from a 4 am emergency call on the day after New Year's. As he groped in the dark, he tripped over his dog, apparently a large animal that blended perfectly with the bedroom rug. (The Meyer family had burned their firecrackers late one day and their dog had taken refuge in the master bedroom.) "I could have landed on my face, so I instinctively rolled, a perfect Olympic 10." "A Judo fall, eh?" "No, it was on the wrong side ... I was in the air and the thought crossed my mind ... Shoot! Three days of ice and traction. And that's what happened ... I ripped my back muscles." We both grimaced. (Well, his son? It seems that after Denny recovered from his back injury, his son gave him the flu.)

* * *

QUOTABLES ... Infectious disease specialist Dick Frankel was the CPC discussant on February 14. He apologized: "This being Valentine's Day, you can shoot at the speaker's heart should he miss the diagnosis ..."

* * *

Second Opinion

Scene: Mid Pac CC 11th hole on a February Saturday afternoon. We overhead pathologist Art Salcedo remind urologist Masaru Koike: "Masa, I have an appointment with you next week." We teased, "Better do a 2-finger rectal — he may want a second opinion." Art good-naturedly enjoined, "Yeah, you can bill Medicare for the second opinion."

Oncology Dialogue

A 58-year-old, 60-pack-year oriental man saw his PMD for cough and was treated with antibiotics. A month later, he suddenly developed Lt-sided clumsiness and weakness and was admitted for workup. A family history revealed that both parents and 2 brothers had died of cancer. A resident picked up a left hemianopsia.

(Continued) ➤

NEWS AND NOTES

(Continued from page 105)

Radiologist Howard Arimoto described CT scans showing a 6$\frac{1}{2}$ cm^2 RLL mass and mets to skull, rib cage and spine confirmed by nuclear med specialist Michael Ling's nuclear imaging. Pathologist Larry McCarthy described biopsies of the RUQ and RLL tumors as "foci of subepithelial small cell Ca, poorly differentiated with mitotic figures."

Moderator Ken Sumida asked, "Dr Furuike, can you give us some hints on risk factors and presenting symptoms for small cell Ca?" Pulmonologist Al Furuike was concise: "The symptoms are those of a rapidly growing tumor with extensive mets. The main risk factors are smoking and radiation. Lesser factors include exposure to asbestos and industrial gases." Ken added, "In my residency, I was told that if there were no smoking history, the tumor was not small cell Ca." Pathologist Grant Stemmerman added epidemiologic data: "The Japanese as a group, given the same cigarette consumption, have half the incidence of lung Ca. It must be genetic and related to some tumor-suppressing factor absent in some families."

Ken turned to oncologist Carl Higuchi: "How about chemotherapy?" Carl painted a dismal picture for small cell Ca. "The survival is less than 2 months without treatment and 7 to 11 months with treatment." Ken: "How about prophylactic cranial radiation in patients with limited disease?" Carl: "Even prophylactic cranial radiation with chemotherapy in a patient with limited disease is controversial." Ken elucidated further: "In patients over 65, cranial radiation is contraindicated because of the high incidence of dementia. Limited disease is when the cancer is intrathoracic and extensive disease when the cancer is extrathoracic. So, should we try to pick up early disease with diagnostic surveys?" Al Furuike was not enthused: "Early diagnosis is a matter of luck."

Cancer surgeon Scott Hundahl contributed one of his gems: "I reviewed the literature recently. In the early days, all lung cancers were treated surgically ... Small cell Ca in the lung periphery behaves differently, as a limited disease, so in a limited subset, there still may be a role for surgery. In older series, it was surgery, then chemo. In recent studies, it is chemo, then surgery..."

Eugene Matsuyama asked if there were any correlation with high ethanol consumption and smoking. Ken turned to Stemmy: "Perhaps with squamous cell Ca?" Stemmy: "No." Scott added an aside: "I read a recent article that claimed drinking green tea and smoking had less lung Ca. Perhaps it was written by some tea growers association in Japan." Stemmy: "We've studied green tea and black tea and found no correlation with lung Ca."

(Continued on page 109) ➤

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Susan M. Rice

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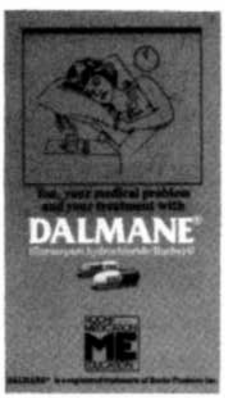

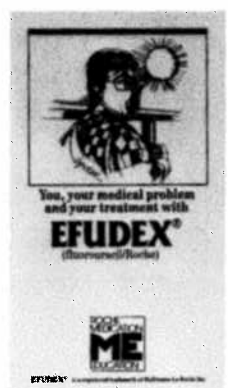

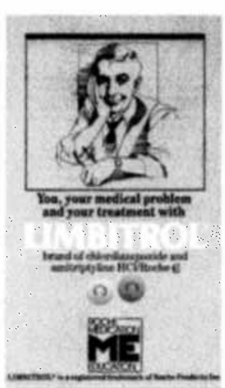

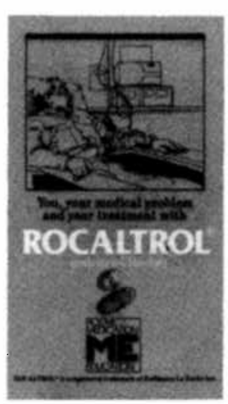

NEWS AND NOTES
(Continued from page 106)

Conference Notes

Visiting professor Peter Lipsky from University of Texas spoke about rheumatoid arthritis on January 24 at Mabel Smyth.

Rheumatoid arthritis: a. 80% have significant deformity, b. Treat early because most of the loss of function occurs the first year.

Diagnosis of RA:

Is it Arthritis?

+	—
Articular	Nonarticular (Fibrositis or fibromyalgia)
Inflammatory	Noninflammatory
Systemic	Asymptomatic: Seronegative Spondyloarthropathy
<2 months	>2 months (RA or other connective tissue damage

Fibrositis: a. Trigger points, b. Pain in soft tissue, c. Non-restful sleep
Articular: a. Inflammatory — High C-Reactive protein and high sed rate
RA: Almost always symmetrical

< 2 months	> 2 months
Viral Infection	Rheumatoid Arthritis
Drug Reaction	Other connective tissue disease

Treatment of RA:
a. Therapy is empiric; based on clinical experience and not on pathophysiologic or pharmacologic principles.
b. Relationship between drug action and disease process is unclear:
  1. Relevant drug action is often unclear
  2. Pathophysiology of the disease evolves
c. No major impact of therapy on progression to deformity.

Drugs and Agents

	NSAID	Slow-Acting Agents
Anti-inflammatory	Prominent	Minimal
Onset Action	Intermediate	Delayed
Effect on Acute Phase	Minimal	Neutralization
Effect on Bone Erosion	None	Minimal
Effect on Natural Hx of Dis	None	None

*In some individuals, NSAIDs have more profound effect.
Traditional approach: Start with NSAIDs and then use slow-acting agents.

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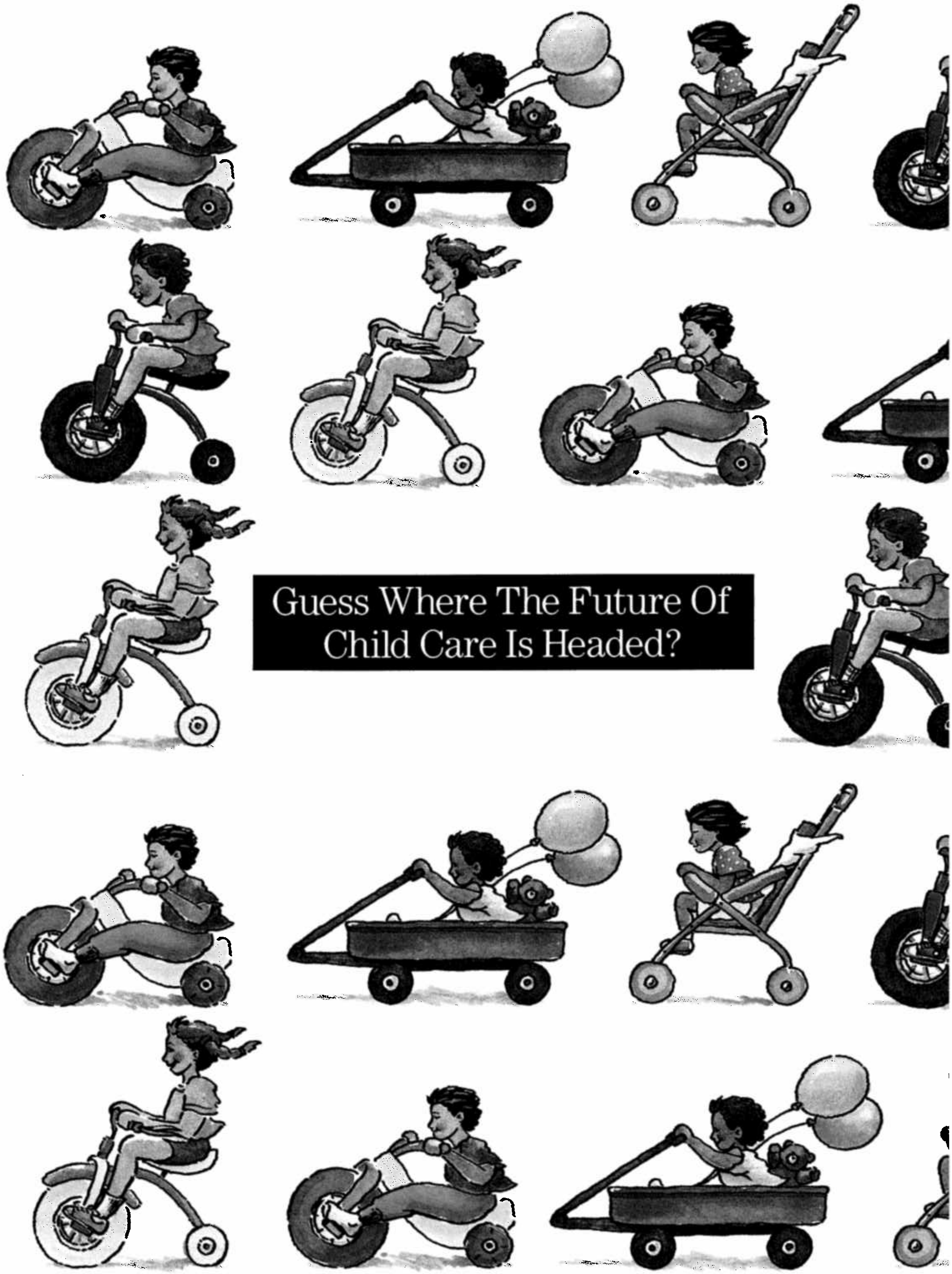
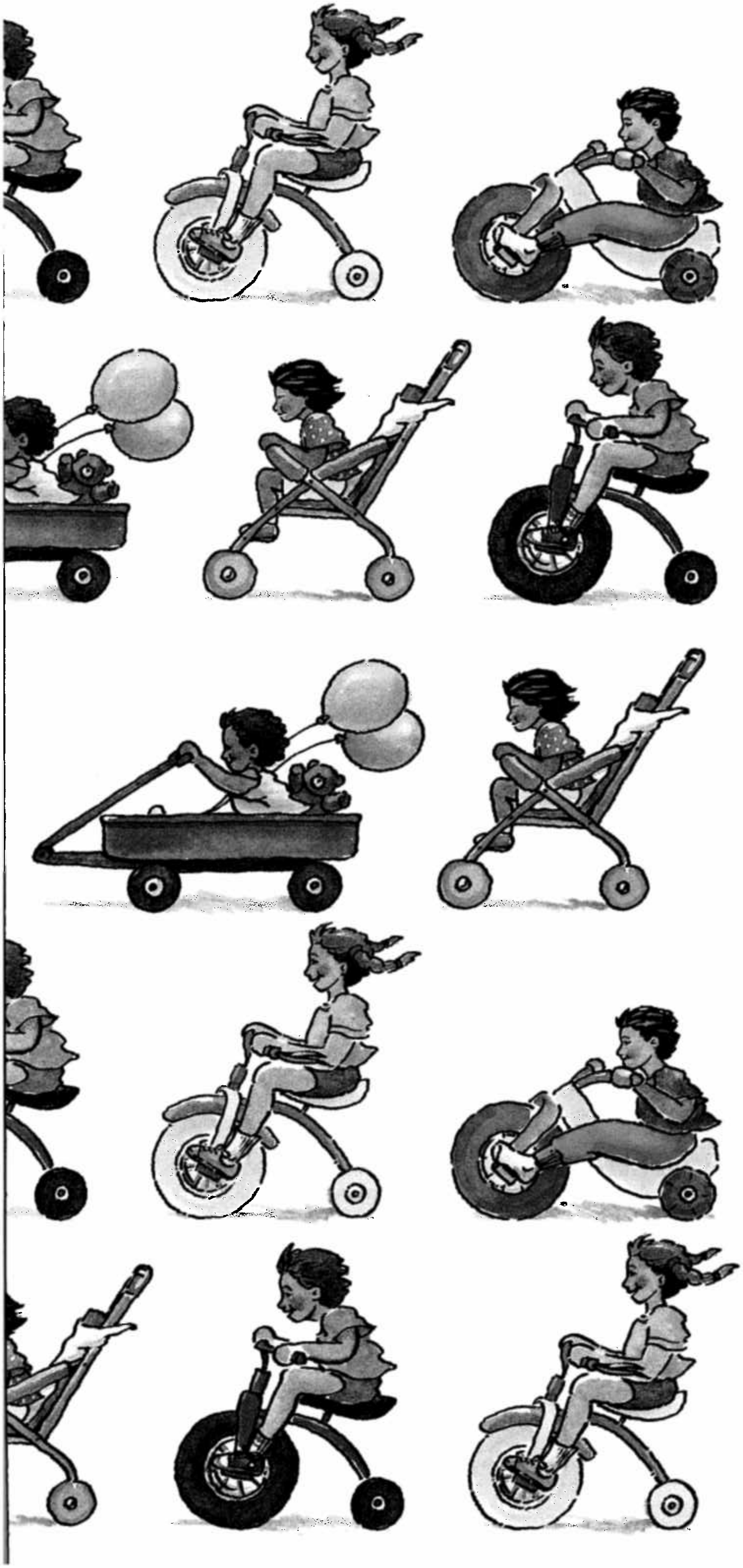

Guess Where The Future Of
Child Care Is Headed?



We're building a whole new city here in Kapolei.

And soon Seagull Schools will be building an important part of it.

Seagull Schools plans to develop the state's largest child care center in the City of Kapolei. This 1.25 acre facility will provide care for up to 280 children.

Obviously, Seagull thinks Kapolei is a youngster with some real potential. Which isn't surprising when you consider that the population of West Oahu will increase by 200 percent in the next 20 years. Some of Hawaii's largest companies are building here. And Kapolei Shopping Center is scheduled for completion in 1993, with 28 tenants aboard and more on the way. While hundreds of new homes are under development throughout the area.

If you're looking for a place to grow, whether you're nurturing a business or a family, call us at 544-3224.

Because there are big reasons for moving to Kapolei. And lots of little ones, too.

The City of Kapolei
A New Direction

A development of The Estate of James Campbell.

Maka O Ka Kauka

Russell T. Stodd MD

Oh, how full of briers is this working-day world!

A mini-flap has developed in regard to the removal of pterygium at the time of cataract surgery. A petition was filed by an Oahu eye surgeon requesting payment, but after review by an HCMS physician panel (including an ophthalmologist), the procedure was deemed not reimbursable unless the pterygium had become obstructive to vision. Behind the public discussion, Medicare officials claim that this combined procedure occurs at a frequency of about 5% or less, but for a particular eye surgeon, the rate approaches 40 to 50%. Ah, the all-seeing, all-knowing, all-omniscient computer strikes again.

If it doesn't work, expand it.

Our State government only 2 years ago enjoyed a $500 million surplus. While it would seem appropriate to return a large measure of this to the taxpayers, our legislature chose not to do so. The product of their action was that the politicians found a way to spend the money by funding various programs, for example, a luxurious Capitol renovation. However, the rest is a fiscal nightmare because those programs funded during times of plenty become a terrible burden when revenues dry up. Thus, now the DOE cannot fund school repairs, cannot hire more teachers, and Oahu's sewage system is smelling up the north Pacific. The State hospitals have been put on a cash-only basis by suppliers due to unpaid bills. Additionally, public employee incomes have risen at 4 times the pace of pay in the private sector during the past decade. The "solution," — an additional tax called a LOTTERY!

There is no job so simple that it cannot be done wrong.

Today, thanks to men like Edison and Franklin, and frogs like Galvani's, we receive almost unlimited benefits from electricity. For example, in the past decade scientists developed the laser, an electronic appliance that emits a beam of light so powerful that it can vaporize a bulldozer 2,000 yards away; yet so precise that doctors can use it to perform delicate operations on the human eyeball, provided they remember to change the power setting from "VAPORIZE BULLDOZER" to "DELICATE." *(Dave Barry)*

If God created us in his own image, we have more than reciprocated.

To practice medicine in the last decade of the 20th century, hospitals, doctors, pharmacists, and other health care providers, have become inextricably tied to the computer. One major downside is that access to records is now all too easy. A company, Physician Computer Network, Inc., thinks its swelling data base of patient records will become a commercial treasure. An invisible new traffic in patients' private medical records, prescription records, and hospital data is alarming physicians and pharmacists. Patients with AIDS and other ailments are especially vulnerable to a breach of confidentiality. No doubt, ophthalmic prescriptions, number and type of IOL implants, plus age, sex and whatever of patients, these data are at the computer consoles of Alcon, Allergan, Zeiss, Storz, IntraOptics, Merck, etc, whenever desired, compliments of PCN and other hacker invaders. "Data is like a whore. It gets passed around from hand to hand, in spite of the rules."

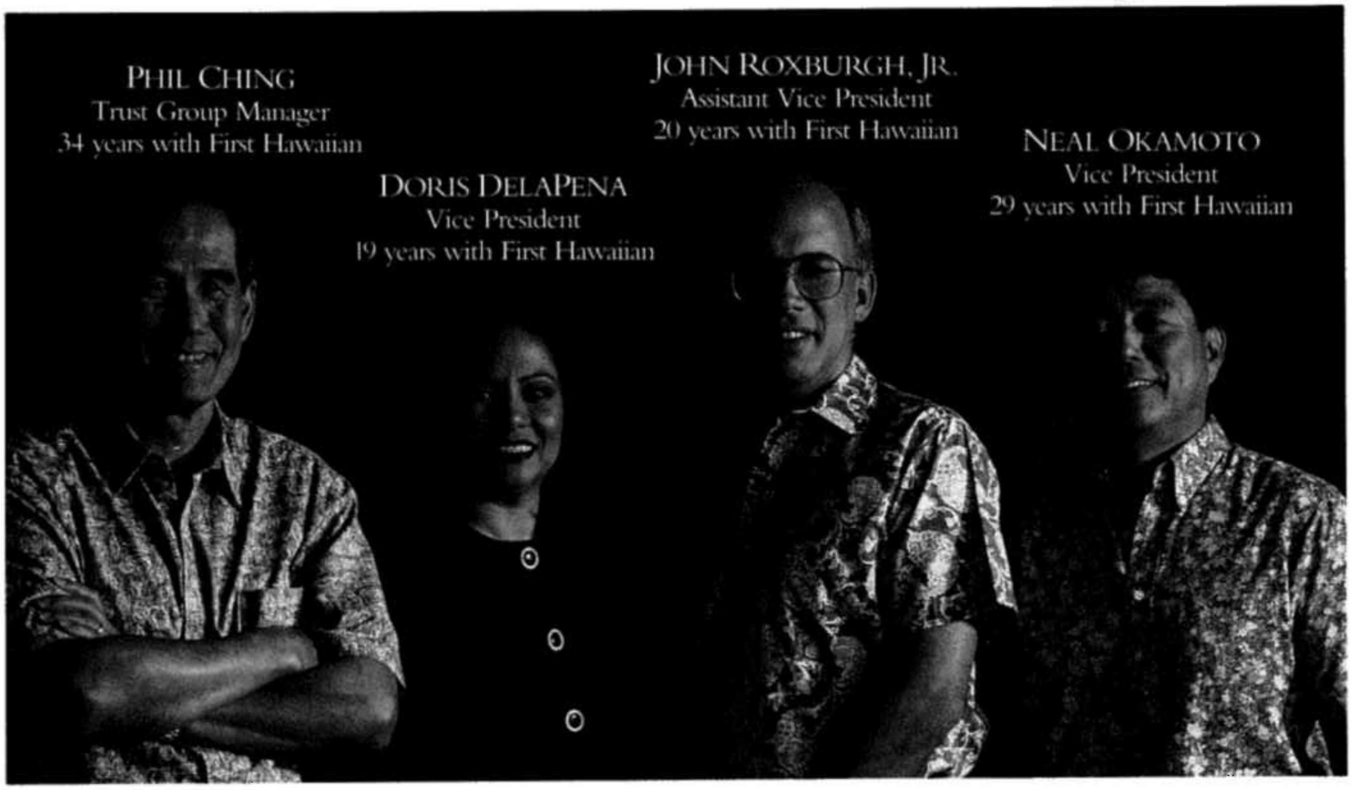
The function of the expert is not to be more right than other people, but to be wrong for more sophisticated reasons.

Leaving behind a trail of confusion and controversy for Medicare recipients and physicians alike, HCFA Administrator Gail Wilensky is leaving the agency. In his perennial search for "yes persons," President George Bush has appointed Dr Wilensky to deputy assistant to the President for policy development. One of her jobs will be to advise the President on health care reform issues. In her place, Associate Administrator Robert Streimer will likely be the acting chief until a permanent agency head can be installed after the November election. No changes are expected in policies.

Aloha, and keep the faith.

rts

Let us handle your pension plan and you could get 102 years.



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