Ivermectin: A Potent New Antiparasitic Agent

W. C. Campbell, M. H. Fisher, E. O. Stapley
G. Albers-Schönberg, T. A. Jacob

Summary. Ivermectin is the 22,23-dihydro derivative of avermectin B_1, a macrocyclic lactone produced by an actinomycete, *Streptomyces avermitilis*. It is active at extremely low dosage against a wide variety of nematode and arthropod parasites, apparently by virtue of its action on the mediation of neurotransmission by γ-aminobutyric acid. It is now in commercial use in various countries for the treatment and control of parasites in cattle, horses, and sheep, and is expected to become available for use in swine and dogs. Since studies with the drug in man are in a preliminary stage, it is not yet known whether ivermectin will be useful in human medicine.

Economic losses due to parasitic infection of livestock have been estimated at more than $3 billion annually in the United States alone (*1*). Parasitism is universal, and proportionately large losses are sustained wherever livestock are raised. While protozoal infections are of importance in some segments of the livestock industry, most of the economic losses are due to parasitic worms (especially nematodes) and arthropods, with the arthropods alone accounting for more than half of the total. Losses occur despite the development of many effective antiparasitic drugs in the last few decades. The limitations of chemotherapeutic control of parasites include the need to integrate treatment with epidemiological factors and management practices, the need to use different drugs for different kinds of parasite, and the emergence of drug-resistance in parasites.

Ivermectin is one of a family of recently discovered drugs, the avermectins, which constitute a new chemical class and which have a novel mode of action against a broad spectrum of nematode and arthropod parasites of animals. The avermectins are also active against plant-parasitic and free-living nematodes and arthropods (*2*). In this article we review the information on ivermectin as an agent for the control of endoparasites and ectoparasites of animals.

Microbiology

The discovery of the avermectins resulted from an intensive search for natural products with anthelmintic activity. Examination of microbial cultures by means of several different assays in vitro led to the detection of few active cultures and nothing of practical interest. However, introduction of a test in vivo (administration of test substances to mice infected with the nematode *Nematospiroides dubius*) resulted in the discovery of the avermectins (*3, 4*). This family of substances was found in the fermentation broth of one of the many actinomycete cultures received from the Kitasato Institute in Japan. The actinomycete, which has been named *Streptomyces avermitilis*, is morphologically distinct from other *Streptomyces* species (Fig. 1). Over 40,000 actinomycete cultures were tested in the same type of assay in vivo but no other culture was found capable of producing avermectins.

The medium used in the early fermentation studies gave a yield of approximately 9 micrograms of avermectins per milliliter of broth. Improvements in the medium resulted in five- to ninefold increases in yield (*5*). In an attempt to obtain superior mutants, the original culture of *Streptomyces avermitilis* was treated with ultraviolet light. One of the resultant mutants grew more rapidly, utilized sugar more rapidly, and produced avermectins at a higher rate for a much longer period. The combination of medium improvement and mutant selection resulted in more than a 50-fold increase in the yield of avermectins from broth.

Isolation and Structure Determination

The isolation of the natural products from broth was greatly aided by the observation that silica gel chromatograms of inactive fermentation batches lacked a number of characteristic, ultraviolet light–absorbing components (*3*). Examination of mass spectra indicated the existence of two series of compounds, designated A and B, within which are two structural subsets, designated 1 and 2 (each containing 5 to 10 percent of a lower homolog, A_1a, A_1b, and so on). The components could be separated by reverse-phase high-pressure liquid chromatography.

The structures of the avermectins were largely determined by high-resolution mass spectrometry and ^{13}C nuclear magnetic resonance spectroscopy (*6*). This powerful combination of physical methods provided, besides the most fundamental information about elemental compositions and double bonds and rings, a great number of narrowly circumscribed partial structures, such as a lactone or ester carbonyl group, one ketal, two acetal, and a tertiary oxygen function; particularly characteristic was one methylene group wedged between two electron-rich substituents (C-8a). This information allowed one to write a schematic structure, which, although it showed very little of the connectivities of the final structures, nevertheless contained all the characteristic features including two possibly identical dideoxy-*O*-methyl-aldohexose substituents. A comparison of this representation with the structures of known microbial metabolites suggested that the avermectins are related to the milbemycins, the structures of which had been determined by single-crystal x-ray crystallography (*7*). It was possible to interpret the very detailed avermectin data convincingly in terms of the milbemycin structures by assuming three structural changes: (i) a disaccharide substituent attached to a new hydroxyl function at C-13; this could be proven by ozonization followed by reduction which resulted in the isolation of the disaccharide attached to a pentane-2,3,4-triol; (ii) C-22,23-double

W. C. Campbell, M. H. Fisher, E. O. Stapley, and T. A. Jacob are Senior Directors of Basic Parasitology, New Lead Discovery, Basic Microbiology, and Animal Drug Metabolism, respectively, and G. Albers-Schönberg is Senior Scientist, New Lead Discovery, at Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065.

bonds or 23-hydroxy-22,23-ethylene substructures; and (iii) *sec*-butyl or *iso*-propyl substituents at C-25 instead of methyl or ethyl substituents. Eventually, avermectin B_1a and the aglycone of B_2a crystallized, permitting confirmation of the structures and determination of the relative configurations at all asymmetric centers by x-ray crystallography (*8*).

The absolute configurations as shown in Fig. 2 are based on the identification of the monosaccharide substructures with L-oleandrose, a constituent of the known macrolide antibiotic oleandomycin. A stereoscopic view of ivermectin (Fig. 3) has been adapted from the crystal structures of avermectin B_1a and B_2a aglycone by molecular modeling (*9*). Careful interpretation of 300-megahertz ^1H nuclear magnetic resonance spectra of the avermectins finally indicated that the solution conformations are well represented by the crystal structures (*8*).

One could postulate that the avermectin aglycones are derived by way of novel cyclizations of straight chains of irregularly alternating acetyl and propionyl residues. However, experiments to incorporate [1-^{13}C]propionic acid resulted in increased ^{13}C abundance at C-3, C-7, C-11, C-13, and C-23 but not at C-25. This suggested that the *sec*-butyl group at C-25 originates from L-methylbutyric acid derived from L-isoleucine, consistent with the absolute configuration at C-26. The 25-*iso*-propyl group similarly could be derived from L-valine. This hypothesis could be confirmed by the incorporation of large amounts of uniformly labeled L[^{14}C]isoleucine and L[^{14}C]valine into the corresponding avermectins (*10*). The overall biosynthetic scheme was also confirmed by the incorporation of [1-^{13}C]acetic acid and [2-^{13}C]acetic acid. Furthermore, the incorporation of 1-^{13}C,$^{18}O_2$-labeled propionic and acetic acid showed that all oxygen atoms of the aglycones, except for the C-6,8a and C-21,25 ether oxygens, are derived directly from the precursor acids (*11*).

Chemistry

Examination of the structures of the avermectins revealed that compounds of the 1-subset possess an olefinic bond between carbons 22 and 23 whereas in the 2-subset this bond is hydrated with the hydroxyl group at the 23 position. This difference has a profound effect on the conformation of the ring bearing these functionalities and causes subtle changes in bioactivity. For example, while avermectin B_1 was more active than avermectin B_2 upon oral administration, the converse was true when each was administered parenterally. It is particularly noteworthy that avermectin B_1 was considerably less effective against *Cooperia* species when treatment was given parenterally than when treatment was oral, while avermectin B_2 was much less active than B_1 against *Haemonchus* species. It therefore became an important objective to prepare compounds with the conformation of the 2-series but lacking the 22-hydroxyl substituent, with the hope that such compounds would retain the desirable features of both series.

Compounds of the a-series, possessing a methoxy group at the 5-position, were generally less effective than those of the b-series and were never seriously considered for development. Whether the 25-substituent was *iso*propyl or *sec*-butyl made so little difference to biological activity that their separation was unnecessary. Mixtures, based largely on the ratio formed in the fermentation, were used for chemistry and for biological evaluation. The most desirable compound, 22,23-dihydroavermectin B_1, required for its synthesis the selective reduction of one of the five olefins. Only the target olefin is *cis*-substituted, however, suggesting that synthesis might be achieved with the use of Wilkinson's homogenous hydrogenation catalyst $(PH_3P)_3RhCl$, which is known to be highly sensitive to the steric environment of an olefin. Hydrogenation of avermectin B_1 for 20 hours with Wilkinson's catalyst in benzene or toluene at 25°C under 1 atmosphere of hydrogen provided 85 percent of 22,23-dihydroavermectin B_1 together with 3 percent of 3,4,22,23-tetrahydroavermectin B_1 (*12*). 22,23-Dihydroavermectin B_1, containing at least 80 percent of 22,23-dihydroavermectin B_1a and not more than 20 percent of 22,23-dihydroavermectin B_1b, has been assigned the nonproprietary name ivermectin.

Antiparasitic Efficacy

Ivermectin is active against two major phyla of animal parasites—the Nemathelminthes or nematodes (roundworms) and the Arthropoda (insects, ticks, and mites). Studies on its mode of action suggest that ivermectin is unlikely to be active against species of the phylum Platyhelminthes (flukes and tapeworms); indeed those platyhelminths that have been exposed to ivermectin have proved insusceptible.

Nematodes. Natural nematode infections of livestock usually involve several species and various developmental stages. It is important, therefore, for an anthelmintic for livestock to have a broad spectrum of action and to be active against both immature and mature worms. Ivermectin has an extremely broad spectrum of antinematodal activity in a variety of domestic animals, being active against genera of the superfamilies Trichostrongyloidea, Strongyloidea, Metastrongyloidea, Rhabditoidea, Ascaridoidea, Oxyuroidea, Spiruroidea, Filaroidea, and Trichuroidea (*13–16*). Indeed,

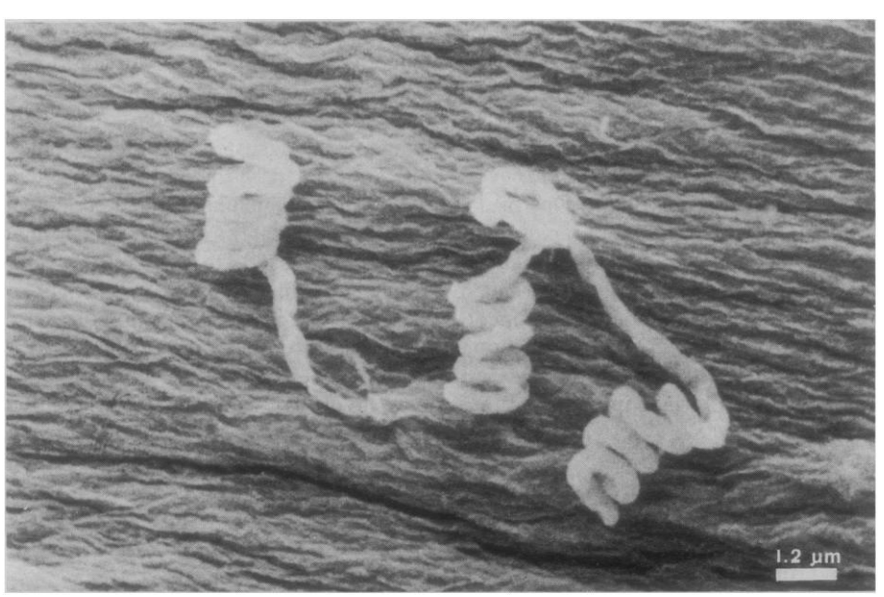

Fig. 1. Scanning electron micrograph showing sporophores of *Streptomyces avermitilis*, the microorganism that produces the family of substances named avermectins. The compact, slightly open form of the sporophores is among the morphological characteristics that distinguish *Streptomyces avermitilis* from other members of this genus.

among the many nematode genera against which it has been tested, none has been found that is not affected by ivermectin during at least one stage of the life cycle. In all but a few instances the drug is highly active against both immature and mature worms. Some nematode species may undergo a period of lethargus or hypobiosis, in which they remain as tissue-dwelling larvae for extended periods. These "hypobiotic L_4" larvae are important pathogens and are essentially refractory to all but a few of the most modern anthelmintics. Ivermectin is highly active against such larvae (*14–16*).

Perhaps the most striking aspect of the antinematodal action of ivermectin is its potency. This varies widely from species to species and stage to stage, but in all cases the minimum effective dosage is very much less than that of other anthelmintics. Among the most sensitive parasites are immature *Dirofilaria immitis* in dogs (ivermectin is effective at 0.001 milligram per kilogram of body weight when administered orally) and *Oesophagostomum radiatum* and *Dictyocaulus viviparus* in cattle (0.05 mg/kg, administered orally). In contrast, the anthelmintic thiabendazole is used at doses of 44 mg/kg in sheep and 88 mg/kg in cattle, while levamisole and fenbendazole are commonly used at 7.5 and 5 mg/kg, respectively. Among the least sensitive nematodes are *Nematodirus helvetianus* in cattle (82 percent efficacy at 0.2 mg/kg in one trial), *Toxascaris leonina* in dogs (69 percent efficacy at 0.2 mg/kg in one trial), and perhaps immature *Trichuris vulpis* in dogs (pending resolution of contradictory data). Two parasites against which activity has not been demonstrated even at high dosage (more than 1.0 mg/kg) are adult *Dirofilaria immitis* (heartworm) in dogs and immature *Trichinella spiralis* in the muscle of mice and pigs; it is, however, active against immature stages of the former and mature stages of the latter. The vast majority of nematodes, regardless of host species or stage of worm development, are highly susceptible to ivermectin when the drug is given as a single oral or parenteral dose at 0.1 to 0.2 mg/kg (*13–16*). A dosage of 0.2 mg/kg has been selected for field use in cattle, sheep, horses, and perhaps dogs, while the dosage for swine is expected to be 0.3 mg/kg.

Ivermectin-susceptible nematodes include forms that live in the extraintestinal tissues of the host as well as those with an intestinal habitat. Among the extraintestinal worms are Filaroidea, some of which are important pathogens both in domestic animals and in man. With one or two exceptions, ivermectin has failed to show activity against adult filariae, but it has proved highly effective against other stages of several important filarial species. It prevents maturation of *Dirofilaria immitis* when given 1 day or 2 months after inoculation of larvae into dogs. These laboratory data suggest, and recent field trials confirm, that dogs can be fully protected against patent heartworm infection (and thus against heartworm disease) by monthly treatment with ivermectin.

Efficacy of the drug against the skin-dwelling microfilariae of *Onchocerca* species in horses and cattle suggested that the drug might have useful activity against *Onchocerca volvulus*, the causative agent of human onchocerciasis (including the condition known as river blindness). Preliminary studies in West Africa suggest that ivermectin does reduce the number of microfilariae in the skin of lightly infected patients (*17*). Much further work will be required to determine the potential utility of the drug in the treatment or control of human onchocerciasis. Even if the drug does not prove beneficial in the therapy of patients with advanced forms of the disease, periodic treatment with ivermectin may well prove useful in preventing serious clinical manifestations (both dermal and ocular) in patients in whom such signs and symptoms have not yet developed.

Arthropods. The effect of ivermectin on arthropod parasites has not been explored very extensively, but activity has been demonstrated against a wide variety of insect and acarine parasites (*18–20*). Parasitic fly larvae appear to be particularly susceptible to ivermectin. In the absence of suitable experimental models for cattle-grub (ox warble) infection, efficacy has been evaluated by treating cattle under conditions of natural exposure. For this purpose the standard anthelmintic dosage of 0.2 mg/kg, injected subcutaneously, has been used. This is probably well in excess of the minimum effective dosage, and the combined data from several dozen trials, involving approximately 2000 cattle, indicated 100 percent efficacy against all parasitic stages of *Hypoderma bovis*. The susceptibility of lice to systemic treatment of the host with ivermectin is affected, not surprisingly, by the feeding habits of the parasite. Thus the sucking lice (*Anoplura*) are more susceptible than the biting lice (*Mallophaga*). In cattle, for example, the field dosage of 0.2 mg/kg, subcutaneously, has been highly effective against *Haematopinus eurysternus* and *Linognathus vituli*, but only moderately effective against *Damalinia bovis*. In swine, a high degree of efficacy against *Haematopinus suis* has been demonstrated at subcutaneous dosages as low as 0.02 mg/kg.

Treatment of a host animal with ivermectin generally does not cause prompt death or detachment of ticks, but usually

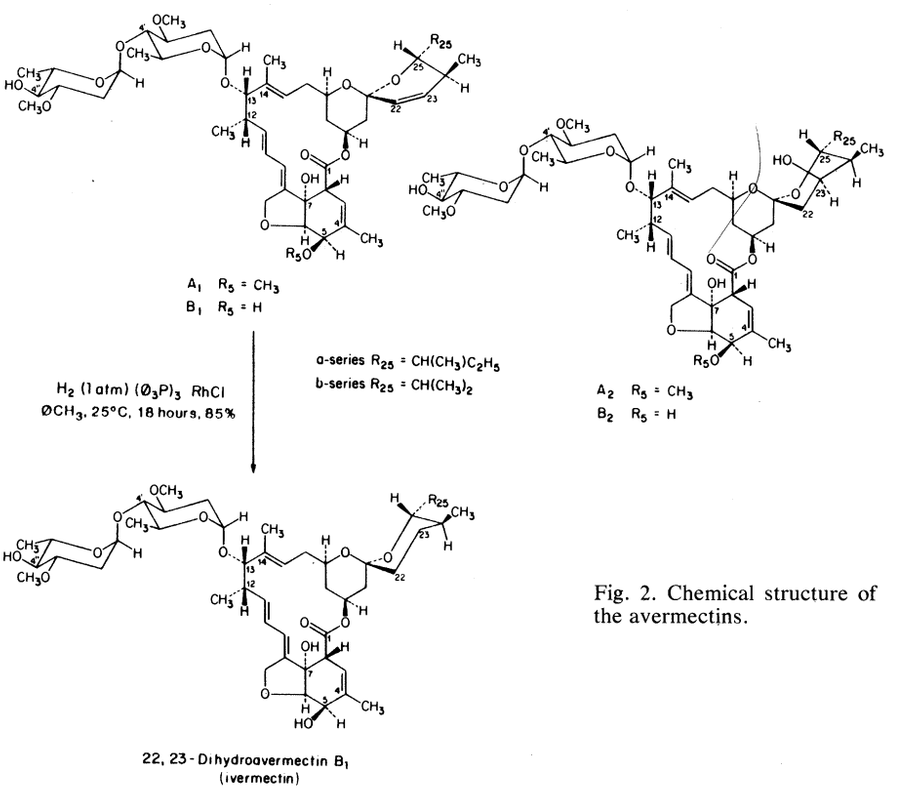

Fig. 2. Chemical structure of the avermectins.

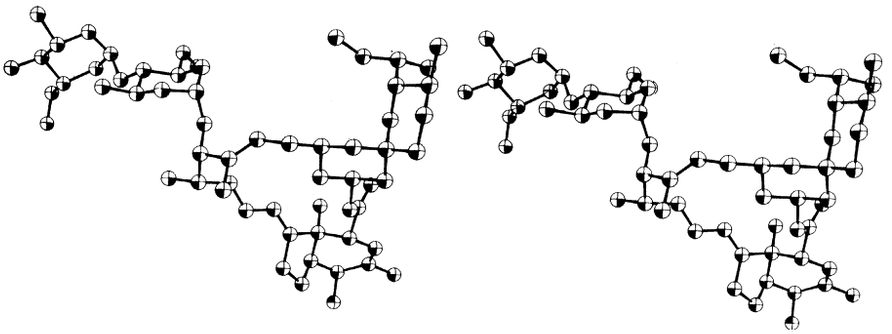

Fig. 3. Stereoscopic view of the structure of ivermectin [ORTEP (Oak Ridge Thermal Ellipsoid Program) presentation].

disrupts essential processes such as engorgement, molting, and reproduction. In the case of *Boophilus microplus* (an important pathogen and pathogen-vector) the effect of treatment was striking: when cattle received daily subcutaneous injections of ivermectin at 0.015 mg/kg and were subjected to repeated infestation with an organophosphate-resistant strain of *Boophilus microplus*, no engorged adult ticks could be recovered so long as the treatment was continued (and for 2 weeks thereafter). Some ticks, for example *Otobius* species, have been reported to have little or no susceptibility to ivermectin at ordinary dosages.

Some other acarine parasites are more susceptible than ticks to ivermectin treatment of their hosts. Mange mites (*Psoroptes* and *Sarcoptes* species) of cattle, for example, cease to be recoverable from skin scrapings about 2 weeks after treatment of the host with a single subcutaneous injection of ivermectin at 0.2 mg/kg, and a dramatic improvement in the clinical condition of the host ensues. Efficacy against mites in cattle was substantially less when the drug was given orally. *Sarcoptes scabiei*, however, an important pathogen both of swine and of man, has been shown to be susceptible to orally administered ivermectin; studies on experimental infestations in swine showed that a single oral dose at 0.18 mg/kg reduced the mite populations, and a dose of 0.3 mg/kg gave a 100 percent reduction in mite numbers and eliminated the clinical signs of infection.

Mode of Action

Most studies on the mode of action of ivermectin have been carried out with avermectin B_1, but it is presumed that all avermectins share a common mechanism. Early studies on the free-living nematode *Caenorhabditis elegans* and on *Ascaris suum* in vitro (*21*) indicated that avermectin B_1 acted neither as a nicotinic agonist nor as a blocking agent of cholinergic nerve transmission. The same investigators dissected the anterior end of *Ascaris suum* to expose one pair of intact commissures of the dorsal excitatory neuron and the ventral inhibitory neuron for electrophysiological studies (*21*). The dorsal excitatory motoneuron could be stimulated indirectly by way of the ventral nerve cord and a response recorded. Avermectin B_1, at a concentration of 5 micrograms per milliliter, abolished this response; washing the neurons with picrotoxin, an antagonist of γ-aminobutyric acid (GABA), restored it. These findings suggest that avermectin B_1 acts by blocking signal transmission from interneurons to excitatory motoneurons and that GABA is the neurotransmitter that is blocked.

The effect of avermectin B_1 on nerve transmission to muscle was studied further by using the stretcher muscle in the walking leg of lobster (*22*). The neuromuscular junction in this preparation is known to be innervated by one excitatory axon regulated by glutamate and one inhibitory axon regulated by GABA (*23, 24*). Avermectin B_1 inhibited both the excitatory and inhibitory postsynaptic potentials by reducing muscle membrane resistance. All responses were restored by picrotoxin. It is known that GABA receptors regulate the opening of chloride ion channels in crustacean muscle (*25*) and that those channels can be blocked with picrotoxin (*26*); hence, it is likely that avermectin B_1 stimulates GABA-mediated chloride ion conductance in this preparation. Thus, while avermectin B_1 appears to block interneuron–motoneuron transmission in nematodes and neuromuscular transmission in the lobster, the basic mechanisms are similar; both involve the GABA receptor.

If, as the data suggest, avermectin B_1 is antiparasitic because it stimulates GABA-mediated chloride ion conductance, the overall effect could be due (i) to avermectin B_1 acting as a GABA agonist, either at the GABA binding site or elsewhere on the protein, (ii) to stimulation of presynaptic GABA release, or (iii) to potentiation of GABA binding to its receptor. The low densities of GABA synapses in helminths and crustaceans hindered more precise elucidation of these possibilities; hence, mammalian brains, which have large numbers of GABA nerves, were selected for further studies. The data demonstrate that avermectin B_1 binds tightly to rat or dog brain synaptosomes with an apparent dissociation constant of 1 to 2 nanomolar, that at half-maximum concentration, that is, 2 to 3 micromolar, it stimulates presynaptic GABA but not glutamate release from rat brain synaptosomes, and that at 0.5 micromolar it stimulates GABA binding to rat brain synaptic membranes (*27*). The last result is significant in that it points out that avermectin B_1 does not compete with GABA for binding, hence it does not bind to the GABA binding site. Further studies are necessary to clarify which of these GABA-related effects are more important to overall antiparasitic activity of ivermectin and whether each effect enhances the other, resulting in immobilization.

Safety

One major difference between invertebrates and mammals is that in mammals GABA-mediated nerves occur only in the central nervous system, whereas in many invertebrates such nerves regulate peripheral muscles. Thus, a compound such as ivermectin, which acts on GABA-mediated nerves, should have a wide margin of safety in mammals if it does not readily cross the blood-brain barrier. In tests of brain concentrations of the drug, male rats were injected intravenously with tritium-labeled ivermectin at a dose of 0.3 mg/kg. The animals were killed from 1 through 24 hours later and their tissues were measured for radioactivity. The highest concentration attained in brain tissue was reached between 2 and 12 hours after injection and amounted to 20 parts per billion. In contrast, the maximum concentration in the muscle (the tissue with the lowest concentration after brain) was 300 ppb (*28*).

Ivermectin appears to have a very wide safety margin in target species, as illustrated by the following data (*29*). Cattle injected subcutaneously with a single dose of 6.0 mg/kg (30 times the recommended dose) showed no signs of toxicity. Toxicity and death were recorded with 40 times the recommended dose. Dogs given a single oral dose of ivermec-

W. G. Seymour, *Proc. Heartworm Symposium*, G. F. Otto, Ed. (Veterinary Medicine Publishing, Edwardsville, Kans., 1981), p. 131; J. W. McCall, B. A. Lindemann, C. A. Porter, in *ibid.*, p. 126; paper presented at the American Heartworm Society Symposium, Orlando, Fla., 1983; T. A. Yazwinski, W. Tilley, T. Greenway, *Vet. Med./Small Anim. Clin.* **77**, 225 (1982).
14. J. Armour, K. Bairden, J. M. Preston, *Vet. Rec.* **107**, 226 (1980).
15. J. R. Egerton, C. H. Eary, D. Suhayda, *Vet. Parasitol.* **8**, 59 (1981).
16. J. C. Williams, J. W. Knox, B. A. Baumann, T. G. Snider, M. G. Kimball, T. J. Hoerner, *Am. J. Vet. Res.* **42**, 2077 (1981).
17. M. A. Aziz, S. Diallo, I. M. Diopp, M. Lariviere, M. Porta, *Lancet* **1982-II**, 171 (1982).
18. D. Barth and I. H. Sutherland, *Zentralbl. Bakteriol. Parasitenkd. Infektionskr. Hyg.* **267**, 319 (1980); D. Barth and S. Brokken, *Vet. Res.* **106**, 388 (1980); C. Centurier and D. Barth, *Zentralbl. Bakteriol. Parasitenkd. Infektionskr. Hyg.* **267**, 319 (1980); T. M. Craig and J. M. Kunde, *Am. J. Vet. Med.* **42**, 1422 (1981); R. O. Drummond, T. M. Whetstone, J. A. Miller, *J. Econ. Entomol.* **74**, 432 (1981); J. R. Egerton *et al. (19)*; J. Euzeby, J. Bussieras, N. T. Hung, *Bull. Acad. Vet. Fr.* **54**, 273 (1981); P. Y. Ho and J. A. Conroy, unpublished data; J. L. Lancaster, J. S. Simco, R. L. Kilgore, *J. Econ. Entomol.* **75**, 242 (1982); R. P. Lee, D. J. D. Dooge, J. M. Preston, *Vet. Rec.* **107**, 503 (1980); W. P. Meleney, *Am. J. Vet. Res.* **43**, 329 (1982); J. Nolan *et al. (20)*; L. Pouplard and M. Detry, *Ann. Med. Vet.* **125**, 643 (1981); C. A. Wilkins *et al.*, in *Tick Biology and Control*, G. B. Whitehead and J. D. Gibson, Eds. (Rhodes University, Grahamstown, South Africa, 1981); T. A. Yazwinsky, L. Pote, W. Tilley, C. Rodriquez, T. Greenway, *Vet. Med. Small Anim. Clin.* **76**, 1749 (1981).
19. J. R. Egerton *et al. Br. Vet. J.* **136**, 88 (1980).
20. J. Nolan, H. J. Schnitzerling, P. Bird, *Aust. Vet. J.* **57**, 493 (1981).
21. S. Kass, C. C. Wang, J. P. Walrond, A. O. W. Stretton, *Proc. Natl. Acad. Sci. U.S.A.* **77**, 6211 (1980).
22. L. C. Fritz, C. C. Wang, A. Gorio, *ibid.* **76**, 2062 (1979).
23. H. Grundfest, J. P. Reuben, W. H. Rickles, *J. Gen. Physiol.* **42**, 1301 (1959).
24. H. M. Gershenfeld, *Physiol. Rev.* **53**, 1 (1973).
25. F. Motokizawa, J. P. Reuben, H. Grundfest, *J. Gen. Physiol.* **54**, 437 (1969).
26. A. Takeuchi and N. Takeuchi, *J. Physiol. (London)* **205**, 377 (1969).
27. C. C. Wang and S. S. Pong, in *Membranes and Genetic Disease*, J. R. Sheppard, V. E. Anderson, J. W. Eaton, Eds. (Liss, New York, 1982), vol. 97, p. 373.
28. T. A. Jacob, unpublished data.
29. R. T. Robertson, W. H. D. Leaning, I. H. Sutherland, unpublished data.

Recent Trends in Fertility in Less Developed Countries

Ansley J. Coale

Summary. The rate of increase of population in less developed countries accelerated rapidly from 1850 to 1960 because of a rapid decline in mortality while fertility remained high. In the 1960's, the birth rate as a whole began to decline more rapidly than the death rate—very rapidly in some populations, most notably that of China, more gradually in others, and not at all in some of the poorest populations. The momentum of growth implies continued increase in populations for several decades even in countries where fertility has fallen the most, and very large additional increases where there has been no decline in the rate of childbearing.

The significance of recent trends in the fertility of those countries that had not become highly industrialized before World War II—commonly designated as less developed countries (LDC's)—is best seen by looking at the sequence of their birth rates, death rates, and rates of increase during the past century or more and the projected rates for a similar period in the future. The approximate course of these rates in the less developed world as a whole from 1850 to 1980, and as projected to 2100, is shown in Fig. 1.

The rise in the annual rate of increase between 1850 and around 1960, to a peak of about 2.5 percent, is surely a unique episode in the history of these populations. Their mostly unrecorded demographic experience before 1850 doubtless included periods of substantial growth typically punctuated by setbacks associated with wars, epidemics, famines, or other catastrophes. But the sustained population increase since 1850 (quadrupling from 1850 to 1980) and the very rapid recent growth (tripling from 1920 to 1980) surely have no precedent.

The source of this notable acceleration is, as shown in Fig. 1, a decline in mortality, gradual until about 1930 and very rapid after World War II, while the birth rate remained high. The essentially constant high birth rate indicated in the figure until 1950 is verified in countries for which there is solid evidence, such as India and Egypt, with a long series of censuses from which the approximate birth rate may be inferred, and in Taiwan, with nearly complete registration of births since early in this century. A similar pattern of sustained high birth rates is generally accepted for other populations that lack extensive demographic records.

The characteristic feature of the low rate of childbearing now found in the countries that were highly industrialized before World War II—countries commonly designated as more developed—is that most potential parents in these populations now limit their fertility by practicing contraception or abortion, and do so especially after a certain number of children, the desired number, have been born.

This kind of fertility limitation (attempting to stop after a certain point) may be called "parity specific" limitation, meaning that it is related to the number of children (parity) the mother has already had (*1*). That it is practiced is revealed in present-day sample surveys in which the relation of contraceptive practice to the number of children already born and to the desire to have no more is explicitly reported. Parity-specific limitation can also be inferred from various forms of historical data. Its introduction is indicated by a reduction in the mean age of mother at the birth of the last child, and its prevalence is indicated by the steepness of the decline in the fertility of married women with age.

Data of the appropriate sort drawn from national statistics in Scandinavia and from parish registers or genealogies in France, Germany, and England show that early European populations (from the mid-15th to the mid-19th century in England, in 17th- and 18th-century France, before the mid-19th century in Germany, and in the late 19th century in Norway and Sweden) did not employ parity-related restriction of fertility. Its absence is also evident in data from Korea before 1960, Taiwan before 1956, the rural population of China around 1930, and the rural populations of the Central Asian republics in the Soviet Union around 1960.

The author is with the Office of Population Research, Princeton University, Princeton, New Jersey 08544. This article was prepared at the Center for Advanced Study in the Behavioral Sciences, Stanford, California.

tin showed no toxic effects at 2.0 mg/kg. Mydriasis and tremors were seen at 5.0 mg/kg, and more pronounced toxic signs at 10 mg/kg; but death did not occur even at 20 mg/kg, which is 20,000 times higher than the dosage needed to suppress the development of heartworm in dogs. In horses, mydriasis was seen at 3.0 mg/kg and more pronounced toxic signs at 12 mg/kg, that is, 60 times the recommended dosage. Intramuscular injection of the drug in horses has, as with other such injections, been associated with clostridial myositis in a small percentage of cases. In some instances the clostrial infections were fatal, and strict aseptic precautions are necessary for intramuscular injection.

Treatment of pregnant laboratory rodents and rabbits with ivermectin resulted in abnormalities in fetal development only when the drug was given at or near maternotoxic dosages, and there was no evidence of teratogenicity in target animals treated repeatedly during pregnancy with dosages higher than those recommended (*29*). In cattle, for example, no fetal abnormalities were seen when the animals were treated subcutaneously at twice the recommended dosage on three occasions during pregnancy. Similarly, no teratogenic effects were seen when bitches were treated orally with ivermectin at 0.5 mg/kg on four occasions during pregnancy.

Metabolic Disposition

Studies on the metabolic disposition of ivermectin have been carried out in cattle, sheep, swine, and rats, with the drug labeled with tritium in the C-5 or C-22 and -23 positions. The animals were dosed once at levels of 0.3 to 0.4 mg per kilogram of body weight by the subcutaneous, oral, or intraruminal route. Regardless of the route only 0.5 to 2.0 percent of the administered radioactivity was excreted in the urine. The remainder appeared in the feces.

Animals were slaughtered over a period of 1 to 28 days after treatment, and about 25 tissues and body fluids were assayed for total radioactive residues. The liver and fat contained the highest radioactive residues in all species, with very little residue in the muscle and kidney. The radioactive residue in the edible tissues of cattle, sheep, and swine, as well as in plasma, was essentially all extractable in organic solvents such as toluene or methylene chloride. Thus, there were very little, if any, intractable, macromolecularly bound drug or metabolite residues. Solvent partition followed by reversed-phase high-performance liquid chromatography (HPLC) proved extremely effective in separating the components of the tissue residues. Analysis of these tissues showed that the major single component in the edible tissues of the cattle, sheep, and swine was the unaltered drug.

An unusual nonpolar fraction consisting of several HPLC peaks, and accounting for about 60 percent of the total residue in steer fat collected 28 days after treatment, was isolated by solvent fractionation and HPLC. Remarkably, when this isolate was hydrolyzed with either *p*-toluenesulfonic acid or by the enzyme cholesterol esterase, the major hydrolysis product was identified as the same 24-hydroxymethyl metabolite found in steer liver. These compounds were probably present in fat as the acyl esters of the metabolite. The metabolites found in the edible sheep tissues were very much like those found in the steer, and the metabolic disposition of the drug in the rat was very similar to that in the other species.

Discussion

Combination of activity against nematodes and activity against arthropods is of great practical importance because, in most species of domestic animal, separate treatments are routinely used for parasites of each group. Data obtained in many trials and many countries indicate that ivermectin possesses exceptional potency against an unprecedented array of nematode and arthropod parasites. It possesses a novel chemical structure and mode of action, which probably accounts for the fact that tests have failed to demonstrate any cross-resistance between ivermectin and several antiparasitic agents to which resistance has developed, namely organophosphates, chlorinated hydrocarbons, pyrethroids, amidines, benzimidazoles, and levamisole (*19–21*). Ivermectin is active when given orally or parenterally (although high efficacy against certain ectoparasites may require parenteral administration). It offers the practical advantages of being odorless and colorless, and it offers an unusually wide safety margin.

Ivermectin is not effective against all parasites. It has not been shown to be active against protozoa, flukes, or tapeworms, presumably because neurotransmission in these groups is not GABA-dependent. It is not active against all lifecycle stages of all nematode species; but the insusceptible stages are few in number and usually minor in importance. It has a wide range of activites against parasitic arthropods. In the case of ticks it does not cause prompt death or detachment of the parasites at dosages used for the control of parasites in general. It does, however, suppress engorgement, molting, and reproduction of ticks, and studies are being conducted to determine whether these effects can be exploited by special treatment stratagems.

On the basis of its spectrum of efficacy, safety, and novelty of biochemical action (lack of cross-resistance with other drugs), invermectin seems to have the potential to contribute in important measure to the control of parasites in animals. Sufficient data have not yet been collected to assess its potential contribution to the control of parasites in man.

References and Notes

1. This estimate does not include losses due to viruses, bacteria, or nonparasitic pests such as biting flies and is derived from R. O. Drummond, G. Lambert, H. E. Smalley, Jr., C. E. Terrill, in *Handbook of Pest Management in Agriculture*, D. Pimentel, Ed. (CRC Press, Boca Raton, Fla., 1981), vol. 1, pp. 111–127.
2. I. Putter, J. G. MacConnell, F. A. Preiser, A. A. Haidri, S. S. Ristich, R. A. Dybas, *Experientia* **37**, 962 (1981).
3. R. W. Burg *et al.*, *Antimicrob. Agents Chemother.* **15**, 361 (1979); J. R. Egerton, D. A. Ostlind, L. S. Blair, C. H. Eary, D. Suhayda, S. Cifelli, R. F. Riek, W. C. Campbell, *ibid.*, p. 372.
4. T. W. Miller *et al.*, *ibid.*, p. 368.
5. E. O. Stapley and H. B. Woodruff, in *Trends in Antibiotic Research*, H. Umezaea, A. Demain, T. Hata, C. R. Hutchinson, Eds. (Japan Antibiotics Research Association, Tokyo, 1982) pp. 154–170.
6. G. Albers-Schönberg *et al.*, *J. Am. Chem. Soc.* **103**, 4216 (1981).
7. H. Mishima, M. Kurabayashi, C. Tamura, S. Sato, H. Kuwano, A. Saito, *Tetrahedron Lett.* (1975), p. 711.
8. J. P. Springer, B. H. Arison, J. M. Hirshfield, K. Hoogsteen, *J. Am. Chem. Soc.* **103**, 4221 (1981).
9. We thank G. Smith for his collaboration in producing the stereoscopic picture.
10. G. Albers-Schönberg, A. W. Douglas, R. T. Goegelman, L. Kaplan, A. J. Kempf, T. B. Tunac, in preparation.
11. D. E. Cane, T.-C. Liang, L. Kaplan, M. K. Nallin, M. D. Schulman, O. D. Hensens, A. W. Douglas, G. Albers-Schönberg, *J. Am. Chem. Soc.*, in press.
12. J. C. Chabala *et al.*, *J. Med. Chem.* **23**, 1134 (1980).
13. **For cattle**: J. Armour *et al.* (*14*); G. W. Benz and J. V. Ernst, *Am. J. Vet. Res.* **42**, 1409 (1981); *ibid.*, p. 2097; J. R. Egerton *et al.* (*15*); E. T. Lyons, S. C. Tolliner, J. H. Drudge, D. E. LaBore, *Am. J. Vet. Res.* **42**, 1225 (1981); J. C. Williams *et al.* (*16*); T. A. Yazwinski, M. Williams, T. Greenway, W. Tilley, *Am. J. Vet. Res.* **42**, 481 (1981). **For horses**: T. M. Craig and J. M. Kunde, *ibid.*, p. 1422; J. A. DiPietro, K. S. Todd, T. F. Lock, T. A. McPherson, *ibid.* **43**, 145 (1982); M. A. Hasslinger and D. Barth, *Dtsch. Tieraerztl. Wochenschr.* **89**, 62 (1982); R. P. Herd and J. C. Bonham, *Am. J. Vet. Res.* **42**, 1953 (1981); J. R. Egerton, E. S. Brokken, D. Suhayda, C. H. Eary, J. W. Wooden, R. L. Kilgore, *Vet. Parasitol.* **8**, 83 (1981); T. R. Klei and B. J. Torbert, *Am. J. Vet. Res.* **41**, 1747 (1980); *J. Parasitol.* **66**, 859 (1980); E. T. Lyons, J. H. Drudge, S. C. Tolliver, *Am. J. Vet. Res.* **41**, 2069 (1980); *ibid.* **42**, 1046 (1981); J. Schröder and G. E. Swan, *J. S. Afr. Vet. Assoc.* **53**, 127 (1981); J. O. D. Slocombe and B. M. McGraw, *Am. J. Vet. Res.* **42**, 1050 (1981). **For swine**: T. B. Stewart *et al.*, *ibid.*, p. 1425; *ibid.*, p. 1427; S. M. Taylor and G. R. Pearson, *Vet. Bull.* **51**, 6844 (1981). **For dogs**: D. L. Anderson and E. L. Roberson, *Am. J. Vet. Res.* **43**, 1681 (1982); L. S. Blair and W. C. Campbell, *ibid.* **41**, 2108 (1980); L. S. Blair *et al.*, *ibid.* **44**, 475 (1983); *Res. Vet. Sci.* **33**, 386 (1982); R. F. Jackson and