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ZOONOSES AS A STUDY IN ECOLOGY

WITH SPECIAL REFERENCE TO PLAGUE, RELAPSING FEVER, AND LEISHMANIASIS

BY

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According to Karl Meyer (1942) the term "zoonosis" was first introduced by Virchow. In a recent publication of the World Health Organization the zoonoses have been defined as "those diseases which are naturally transmitted between vertebrate animals and man." Other definitions have been given from time to time, most of which are not very satisfactory. That given by the World Health Organization is probably the best, but it includes the word disease, which perhaps ought to be avoided, as in certain zoonoses one or more of the vertebrate hosts may show no symptoms of disease. In a recent textbook of protozoology it is even suggested that infections common to man and animals cannot be regarded as zoonoses when the animal host shows no symptoms. Chagas's disease, in which symptomless armadillos act as reservoir hosts, is given as an example. I shall try to refute this idea, and to emphasize that usually resistant or relatively insusceptible animals are the most efficient reservoirs of the zoonoses. It is of course not always easy to know when an animal is feeling ill, and a friend pertinently remarked, "How do you know the armadillo doesn't get a headache"; this was difficult to answer.

A simple definition which avoids some of the more obvious pitfalls is *infections of man naturally acquired from other vertebrates.* According to Metchnikoff, "Infection must be considered as a struggle between two organisms, the parasite and its host. . . . This struggle brings about adaptations on both sides."

A zoonosis can be considered in reverse, the infecting organism passing from man to animals and not vice versa. Monkeys are sometimes infected with quartan malaria and certain filariae in this way. Such infections might be called "anthroponoses," but the term is really superfluous, as most of the zoonoses show this quality of reversal. The zoonoses can be divided into two main groups: those transmitted by arthropods, and those which are not. Only the first group is considered in this paper.

Evolution and the Zoonoses

Garnham (1952) has commented on the evolution of the zoonoses, and according to him the story is something like this. First, the parasite lives happily, passing between its animal host and arthropod vector; next, man breaks into the circle and accidentally becomes infected; the parasite flourishes in this abnormal host and may be transmitted by a more domestic vector—for example, flea or louse. The disease then often assumes an epidemic form, and may pass from man to man. Relapsing fever illustrates some of these points. The causative spirochaete seems originally to have been a parasite of merions, gerbils, shrews, and other small mammals, the vectors being ticks of the genus *Ornithodorus.* Man became involved in this cycle, and, after being bitten, developed relapsing fever; this still happens in North Africa and around Dakar.

It is worth trying to trace the evolution of *Spirochaeta duttoni,* which causes tick-borne relapsing fever in Kenya and other parts of tropical Africa, the vector being *Ornithodorus moubata.* Some years ago a spirochaete, named *S. dipodilli* and closely related to *S. duttoni,* was isolated from pygmy gerbils (*Dipodillus* sp.) and *O. erraticus* from small burrows on Crescent Island in Lake Naivasha (Heisch, 1950). Near the small gerbil burrows are large burrows, which are excavated by ant-bears, occupied by warthogs or porcupines, and often contain large numbers of *O. moubata* (Heisch *et al.,* 1953). The presence of *O. moubata* came as a surprise, for the ticks usually have domestic habits, frequenting native huts, rest-houses, and the camp sites of travellers; ant-bear burrows may be their original or natural habitat. It was thought possible that in the remote past the gerbil spirochaete might have become established in the "burrow-haunting" *O. moubata,* and then have evolved into *S. duttoni.* Unfortunately there is no evidence to support this possibility: specimens of *O. moubata* from burrows have always been negative for spirochaetes, and so have the few porcupines and warthogs examined. In Kenya and other parts of tropical Africa, even if there was once a reservoir host of *S. duttoni,* it appears to have faded into the background, tick-borne relapsing fever no longer being a true zoonosis; it thus differs from the disease in America, where man is infected in caves, various small mammals acting as reservoir hosts.

In recent years it has been found that certain tick-borne spirochaetes can infect lice (Baltazard *et al.,* 1947; Heisch and Garnham, 1948; Boiron *et al.,* 1948). Thus in Kenya strains of *S. duttoni* develop readily in lice, and infected lice have even been found in nature (Heisch, 1949). These results support the hypothesis, first suggested by Nicolle and Anderson (1927), that louse-borne spirochaetes evolved from tick-borne ones.

Other zoonoses, in which man breaks into a cycle in animals, are plague and leishmaniasis. Plague is primarily an infection of wild rodents, and man gets infected only by accident. In parts of Siberia gerbils are the

reservoir host of cutaneous leishmaniasis, which is transmitted by "burrow haunting" sandflies. Man sometimes gets bitten and epidemics have occurred among Soviet troops camped near infected burrows.

In Kenya kala-azar was almost unknown before the second world war. Early cases were sporadic, but in recent years there has been a severe epidemic in the Kitui District, and a smaller outbreak near Marigat in the Rift Valley. No animal reservoir has yet been discovered, and, though one may exist, it is believed that man is the usual host, and that interhuman transmission can occur on a large scale. In Kenya the epidemiology of kala-azar is highly complex, and at least three species of sandflies are suspected as vectors; these emerge from termite hills. Apparently evolution is still taking place, and it is difficult to know what the final epidemiological pattern will be.

Holistic Tendency in Nature

It is evident from Professor Garnham's observations that in nature organisms may be parasites of man, of animals, or of both, and it is the last or zoonotic phase which concerns us here. The conception of a zoonosis is complex and includes an environment, as well as man, animals, sometimes arthropods, and a causative organism, the various parts forming a biological whole.

The importance of "wholes" has been stressed by General Smuts (1936). According to him there is a holistic (from ὅλος = whole) tendency in nature, parts combining into wholes, which in turn again combine, forming even more complex and significant wholes. A whole is not just the sum of its parts, but something more, something new; it is not just a mechanical system but "dynamic, organic, evolutionary, creative." The concept has little in common with the static absolutism of Hegel and other philosophers, and should not be confused with it. In nature, every organism, whether plant or animal, is a whole, and the modern science of ecology attempts to show how these various wholes react on each other, becoming linked, or rather combined, into new wholes, which are continually modified by changes in the environment.

A zoonotic whole is best considered in relation to the infecting organism or parasite, which makes use of some of the existing ecological links between man and animals in an environment, forming cycles or wholes of varying complexity. In fact, a zoonosis is really a small natural whole or holoid built, as it were, round an infecting organism. As already shown such systems, cycles, wholes, or whatever one prefers to call them, are seldom static, and at any time a zoonosis may cease to exist, the parasite becoming adapted to man and the animal reservoir fading into the background. Or the parasite, after passing through a zoonotic phase, may again become confined to animals, man fading into the background. Treating zoonoses as wholes in this way is useful, but perhaps rather artificial, as it depends on distinguishing between man and animals.

The Zoonoses and Ecology

The foregoing remarks make it clear that a study of the zoonoses is essentially a problem in ecology. Ecology has been defined as the "study of interrelation between organisms and the environment." There are two approaches—the *synecological* and the *autecological*. Synecology, as the name implies, is synthetic or holistic in character, the various plants and animals in a community being treated as a whole, the parts of which are in dynamic relationship, and influenced continually by the environment. Autecology deals with single organisms or species in relation to the environment; it has more in common with physiology and is not really ecology at all. Clumsy words like synecology and autecology should be replaced by ecology properly defined in the true holistic sense.

Audy (1954) names the whole assemblage or array of parasites associated with a host population the "parasite-pattern," and includes under parasites "all those viruses, bacteria, protozoa, fungi, worms, and arthropods which live on or in or at the expense of higher organisms such as the vertebrates, whether harmlessly or harmfully." The vectors and causative organism of a zoonosis form part of a general parasite pattern, though, actually, while unravelling a zoonosis much of the general parasite pattern gets worked out as well. Many of the ideas tentatively outlined in this paper have been influenced by the opinions of Audy, who for a number of years has been working on the ecology of scrub typhus in Malaya. Audy has long appreciated the importance and holistic nature of synecology, and has discussed various aspects in an interesting note on medical geography (Audy, 1954).

The early work on plague in Kenya illustrates the limitations of an autecological approach. Everyone was so convinced that the domestic rat (*Rattus* sp.) was the reservoir host that it was considered in isolation and not sufficiently in relation to the wild rodents which are the real source of *Pasteurella pestis* (Heisch *et al.*, 1953). The working out of the life-histories of arthropods in the artificial atmosphere of laboratories also verges on autecology, and, though such studies have a certain value, they can never replace work in the field. Elton (1927) has pointed out that the discoveries of Darwin "had the remarkable effect of sending the whole zoological world flocking indoors, where they remained hard at work for 50 years or more, and whence they are now beginning to put forth cautious heads again into the open air. But the open air feels very cold."

Host–Parasite Relationship

A most important aspect of the zoonoses and indeed of parasitic infections in general is what is known as the host–parasite relationship, by which is meant the nature of the interaction between the host and the parasite. It is suggested that the most important reservoirs of zoonoses and other parasitic infections are relatively insusceptible animals rather than highly susceptible ones. There is nothing new in this idea, and as long ago as 1926 that great protozoologist, the late Dr. Wenyon, wrote: "Whenever a parasite is discovered which brings about the death of its host in a short time, it may be safely assumed that the host is not a natural one, or that it is a natural one that is in some unnatural condition. After a time adaptation may occur and a host that was at first an unnatural one may gradually become a natural host."

Resistant animals are very important in plague. Thus in Kenya domestic rats (*Rattus* sp.) are highly susceptible and rapidly almost exterminated, while certain wild rodents (*Arvicanthis, Mastomys,* and *Otomys* sp.) are resistant and perpetuate the infection during enzootic periods. In South Africa two species of gerbil are involved (*Desmodillus* and *Tatera* sp.), one of which is resistant and the other susceptible. In California susceptible ground squirrels (*Citellus* sp.) die in large numbers, but the primary hosts are now believed to be various resistant field-mice (*Peromyscus* sp.) and wood rats (*Neatoma* sp.) which harbour *P. pestis* almost indefinitely. In Kurdistan the sole reservoirs of plague are highly resistant merions (*Meriones* sp.). For many years regions occupied by resistant namaqua gerbils (*Desmodillus* sp.) and merions were believed to act as barriers to the spread of plague, instead of being regarded as the real source of the infection.

Recently kala-azar has been extensively studied in Kenya, but, as already noted, no reservoir host has yet been discovered. If an animal host does exist, it may be so resistant that the infection can be detected only by special methods. When isolating *P. pestis* from wild rodents in Kenya (Heisch *et al.*, 1953), the pooled-tissue technique was employed, batches of spleens being emulsified and inoculated into guinea-pigs, for it was only by this indirect

method that the infection could be demonstrated at all. The same principle is being applied in kala-azar, the spleens of animals being inoculated into hamsters. Two hamsters actually became infected, one after being inoculated from gerbils (*Taterillus* and *Dipodillus* sp.) and the other from mongooses (*Helogale* sp.), but this may have been due to cross-infection in the laboratory. All known reservoir hosts of leishmaniasis, which include dogs, jackals, gerbils, and foxes as well as man, show a marked resistance to the infection.

Armadillos and antelopes, which harbour pathogenic trypanosomes, are excellent examples of resistant animals acting as reservoir hosts, the parasites causing no obvious symptoms. In the zoonoses mentioned in this paper the reservoir complex, or whole, includes arthropods as well as vertebrates, both helping to maintain the infection in nature. Sometimes, as in mite and tick-borne typhus, tick-borne relapsing fever, and perhaps certain virus diseases, the arthropod vector may be the principal host.

It is rather difficult to know what to call the various kinds of host. Perhaps resistant or relatively insusceptible animals might be termed "permanent hosts," and highly susceptible ones, "temporary hosts"; this would correspond to the natural and unnatural hosts of Wenyon (1926). Hosts can also be classified as "domestic" or "wild," and this may be important, as in many zoonoses the principal reservoirs are domestic animals, which bring the infection in close contact with man. The reservoir of a zoonosis is seldom just one animal, but usually includes several species, which are in close ecological association and act as a "zoological complex" or "biological whole." A good example is sylvatic plague in Kenya. At least three species of resistant rodents are involved, and these, acting in combination, probably perpetuate the infection far more efficiently than if one species acted alone. Highly susceptible hosts like *Rattus* are not included in the reservoir complex.

Hosts have also been classified as final or definitive and intermediate, depending on whether the development of the parasite in them is sexual or asexual. This results in certain ambiguities, and here the arthropod vector is regarded as the intermediate host, the final host being man or some other vertebrate.

Niches

Resistant and unduly susceptible animals fill different "niches" in nature. According to Elton (1927), the "niche of an animal means its place in the biotic environment, its relation to food and enemies." The word "enemies" is taken to include parasites.

Elton has also remarked that "when an ecologist says, 'There goes a badger,' he should include in his thoughts some definite idea of the animal's place in the community to which it belongs, just as if he had said, 'There goes the vicar.'" On seeing an arvicanthis round Rongai one might say, "There goes an animal that can have plague without noticing it."

Important niches are filled by vectors of zoonoses. Thus in plague the niche is filled by fleas, in leishmaniasis by sandflies, and in relapsing fever by ticks and lice. A particular niche is usually filled by different species in different parts of the world.

A study of niches enables us to see that in their organization different animal communities have much in common. It also helps in forming analogies. Thus it was hearing that Dr. Baltazard had discovered resistant hosts of plague in Kurdistan that made me look for similar animals in Kenya. The term "habitat niche" has a different meaning in ecology, which is explained below.

Focal Distribution of Zoonoses in Nature

A feature of certain zoonoses is their "focal distribution" in nature. This is well shown by plague, and, according to Karl Meyer (1942), "focal occurrence and discontinuous distribution is apparently one of the characteristics of sylvatic plague." While studying plague near Rongai in the Rift Valley of Kenya, a "focus" was found in a field, where *P. pestis* could be isolated from wild rodents long after the widespread epizootic had died down and the animals in adjacent fields had become negative. After the field was ploughed up no more infected rodents were found, conditions apparently being too unstable for the formation of a permanent focus. At Rongai "permanent foci" of sylvatic plague are believed to exist on the foothills of the escarpments where rodent burrows are relatively undisturbed, and not in the Rongai plain. The unstable plains in the valley are ideal for the dissemination of *P. pestis* when conditions are suitable, but the infection probably retreats to the foothills between epizootics. Dr. Baltazard (1955, personal communication) has found permanent foci of sylvatic plague on the foothills of the Himalayas; these never seem to form in the cultivated plains below.

Focal distribution is a marked feature of scrub typhus in Burma and Malaya. The vector mites are found in forest clearings, where they congregate, sometimes in enormous numbers, on patches of secondary vegetation known as "mite islands," often only a few yards across, in which the rodent hosts abound. When the mite islands are infected they are known as "typhus islands"; these are "erratically but not fortuitously distributed" (Audy and Harrison, 1951).

Relapsing-fever spirochaetes may also have a patchy or focal distribution in nature. Thus in Africa, where tick-borne relapsing fever is endemic, only some huts contain infected ticks. Other examples are *Spirochaeta latychevi* and *S. dipodilli*, which are parasites of rodents, and *Ornithodorus* ticks in burrows; the spirochaetes have a very patchy distribution, infected burrows being few and far between. Both the rodent spirochaetes are pathogenic for man, but only mildly so.

In parts of Kenya and the Karamoja District of Uganda, bush-babies (*Galago*) are believed to be reservoirs of yellow fever virus. Dr. Haddow, of the Virus Institute, Entebbe, informs me that infection in these animals is very localized, neutralizing antibodies being confined to groups or families of bush-babies living in widely scattered parts of the forest.

Focal distribution seems characteristic of most parasites in nature, but the ecological factors concerned are still largely unknown.

Sites of Infection

Zoonoses are transferred to man and other vertebrates in a variety of places. Thus round Rongai man gets infected with plague in native huts, domestic rats (*Rattus* sp.) chiefly in village maize cribs, and wild rodents in burrows. In Kurdistan plague is almost entirely sylvatic, man being bitten by infected fleas near the burrows of merions. In East Africa tick-borne relapsing fever is contracted in huts; in America and the Middle East in caves. In Kenya kala-azar is probably caught away from houses near termite hills, while in India the disease is a domestic infection. In parts of Russia cutaneous leishmaniasis is transmitted to man near gerbil burrows by "burrow-haunting" sandflies. Yellow fever is often a house infection, but in Uganda man is infected in banana plantations on forest edges, and monkeys in forest canopies. In Malaya and Burma man contracts scrub typhus in forest clearings and forest edges.

These sites of infection show certain differences, some being unstable, others relatively stable. The plague-infected plain at Rongai and the forest clearings containing typhus islands are unstable areas, for man is continually ploughing up the one and cutting down the other. In fact, the balance of nature is always being upset. It is also doubtful whether the forest edges where man contracts yellow fever and scrub typhus are ecologically stable. In comparison huts, rodent burrows, caves, termite hills, and forest canopies are all relatively stable. Sometimes relatively stable habitats are present in an unstable area; they then partake of the general instability.

Ecologically unstable areas have certain characteristics. Plants and animals living in such zones are usually undergoing active succession, and are prevented from reaching that condition of relative stability known as climax. Species tend to appear that are absent from adjacent communities, and one or more species, whether present in adjacent communities or not, may appear in unusually large numbers. The occurrence of myriads of mites in the mite islands of Malaya, and the sudden appearance (when conditions are suitable) of innumerable wild rodents in the Rongai plain are examples of this. When such prolific species harbour parasites pathogenic for man his chances of becoming infected are much increased. Round Rongai it is only when the wild rodents are numerous that *P. pestis* reaches *Rattus* and finally man.

It is suggested here that it might be possible to call unstable areas "ecotones." The word is generally used, in a botanical sense, for transition or intermediate zones between adjacent plant communities. Might not this definition be too narrow? A striking feature of transition areas, marginal zones like edges, forest clearings, and cultivated plains is often their instability. The ecotone concept implies a state of tension in nature, a temporary or permanent loss of ecological balance. Ecotones may be man-made or occur naturally, as when places are periodically flooded, like certain river banks, mud-flats, and the sea-shore. A study of ecotones might throw light on the evolution of certain species. Audy and Harrison (1951) have pointed out that, in Malaya, rodents of the genus *Rattus* "have been greatly encouraged, and a number of commensal and subspecies have evolved in the artificial environments made by man."

A medical example of an ecotone might be the bowel of a patient suffering from dysentery. In a normal person the intestinal flora is in a state of equilibrium, but in dysentery and other infections of the bowel a single species may predominate and disturb the ecological balance. A similar effect may follow the administration of antibiotics. The elimination of susceptible organisms produces a bacteriological vacuum in which may develop a pathogenic staphylococcus, the life of the patient being endangered. Species of plant or animal which outstrip others and appear in abnormal numbers are comparable to cancerous cells, which defy the authority of the human organism as a whole and threaten to disrupt the co-ordinated complex of interlocking cell communities.

Forest edges are of particular interest, for they can be relatively stable or unstable and act as transition zones or end abruptly. Audy (personal communication) calls forest edges "fringe habitats" and the distinctive communities they contain "fringe communities"; such communities often contain species which are absent or very rare in adjacent regions. Important fringe species are *Aëdes simpsoni*, the vector of yellow fever in forest edges in Uganda, and a species of *Chrysops* which transmits loa loa on the west coast of Africa. Transition zones, whether stable or not, are important meeting-places for animals and arthropods, and an interchange of parasites is very likely to occur. Perhaps in East Africa the two cycles of yellow fever are or were linked in such a zone.

Relatively stable habitats like huts, caves, animal burrows, and termite hills, near or in which zoonoses can be transferred to man, are known to ecologists as "habitat niches"; they are sanctuaries protecting certain species from a potentially hostile environment. Forest edges, other transition zones, and forest canopies, though sometimes unstable, may be relatively stable; they then have more in common with habitat niches than ecotones. It is, of course, sometimes difficult to decide whether a particular area is unstable or not, and the foregoing remarks are tentative only.

The suggestion has been made that in Kenya and India the permanent foci of sylvatic plague are more likely to be found on relatively stable foothills than in plains rendered unstable by cultivation. The idea may have a wider application, and perhaps organisms causing zoonoses and other parasites can become firmly established in nature only if part of their life history is spent in an animal or animals living in a relatively stable environment. This view at present is somewhat speculative.

Food-chains and Cycles

A study of what ecologists call "food-chains" and "food-cycles" is an important aspect of the synecology of the zoonoses. Animals linked by food form food-chains, and all the food-chains in a community form the food-cycle. In an animal community herbivores are preyed on by carnivores, which in turn are preyed on by larger carnivores, until an animal is reached which virtually has no enemies. The animals at the base of the chain are smaller and more numerous than those at the top. Elton (1927) has called this the pyramid of numbers.

Elton has suggested that parasites are really small carnivores, though they often do not kill their prey. The large components of parasite food-chains get smaller instead of larger, and more numerous instead of fewer; in fact, the pyramid of numbers is inverted. A study of the food-cycle and plague at Rongai shows that various ectoparasitic fleas pick up *P. pestis* from several rodent hosts. Plague bacilli develop rapidly in these fleas and are transmitted to man. Eventually the plague bacilli in the fleas may be attacked and destroyed by even smaller and more numerous organisms known as bacteriophages.

The importance of food-cycle studies has been stressed by Elton, who wrote: "Since the food cycle is so important in determining many of the possible modes of transference of parasites from one host to another, it is plain that biological surveys carried out along food-cycle lines would be of great value in narrowing the field of inquiry when the life history of any particular parasite is being studied." The value of food-cycle studies, particularly in relation to the food preferences of various disease-transmitting arthropods, is now fully appreciated. Dr. Weitz, at the Lister Institute, under the inspiration of the late Professor Buxton, has formed a most valuable unit, which devotes much time to the identification of arthropod blood meals from all over the world.

Animal Communities

Most animals fluctuate greatly in numbers, and this must be taken into account when studying the zoonoses. At Rongai outbreaks of plague usually coincide with a remarkable increase in the wild rodents; when their numbers drop, which often happens quite suddenly, the link with the domestic rats (*Rattus* sp.) is temporarily broken and human infections cease for the time being. Plague and the regulation of numbers in wild animals has been discussed by Elton (1925), but the effect on resistant animals is not mentioned. In Kenya epizootic plague decimates the highly susceptible domestic rat, but several species of wild rodent are scarcely affected; they are, however, susceptible to other infections, and at times parts of the Rift Valley have been littered with wild rodent corpses. The periodic reduction of numbers in vertebrates is often caused by disease.

Other rodents as well as *Rattus* are highly susceptible to plague in other parts of the world, examples already given being ground squirrels in California and lobengula gerbils in South Africa. Periodically, these species are almost wiped out by plague in certain areas, and it may take as long as five years for their numbers to build up again; this affects the incidence of human infections. In South Africa the periodic fluctuation of rodent populations has been extensively studied by Davies.

Another important matter, which can only just be mentioned here, is the range or distribution of various species in nature. Animal hosts and arthropod vectors are dependent on their environment, and the occurrence of zoonoses in definite areas is essentially a zoogeographical problem.

Conclusion

Although the importance of a synecological or holistic approach is stressed, it would be a mistake to take this too literally. Ecological processes are so complicated that there is a danger of getting involved in a mass of irrelevant ecological detail, and of forgetting that when studying a zoonosis the natural history of the causative organism is our chief concern. The infecting organism is in fact the pivot round which the ecological investigation revolves.

If the views expressed here have any validity, they probably apply not only to the zoonoses but to parasitic infections in general.

Summary

The zoonoses, which are defined as *infections of man naturally acquired from other vertebrates*, are treated as a problem in ecology. This entails studying the interrelation between man, animals, a causative organism, the environment, and sometimes arthropods. Such an approach is holistic or synecological—wholes being regarded as more important than parts. Holism is a dynamic not a static conception.

The evolution of the zoonoses is discussed, particularly in relation to plague, relapsing fever, and leishmaniasis. The most important reservoirs of zoonoses and other parasitic infections are usually resistant or relatively insusceptible animals rather than highly susceptible ones. Plague and Chagas's disease illustrate this. Resistant and unduly susceptible animals occupy different "niches" in nature. By "niche" is meant the place of an animal in its biotic environment. Zoonoses often have a "focal distribution" in nature. Thus wild rodents infected with plague may occur in "pockets," and the vector mites of scrub typhus congregate in "typhus islands."

An unstable environment often favours the transference of zoonoses to man and animals. Examples are the plague-infected plain of Rongai, in Kenya, the typhus-infected forest clearings in Malaya, and the yellow-fever infected forest edges in Uganda. Ecologically unstable areas are termed "ecotones." Zoonoses can also be transmitted in or near relatively stable sites such as huts, rodent burrows, caves, and termite hills. These are known as "habitat niches." Animals and arthropods in a community are linked by food, and the importance of what are known as "food chains" and "food cycles" is discussed in relation to the transference of zoonotic infections from one host to another.

Reference is also made to the fluctuations in numbers of various animals in nature, and how this affects the incidence of zoonotic disease. Certain highly susceptible rodents are periodically decimated by plague; this breaks the link with man, and human infections cease for the time being.

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CHEMICAL AND CLINICAL PROBLEMS OF THE ADRENAL CORTEX*

BY

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Some Factors Governing the Response to Corticotrophin

Growth Hormone

In 1951 Stack-Dunne and Young stated that they were able to obtain preparations from the anterior pituitary having two distinct kinds of activity. These separate preparations produced either a fall in the adrenal ascorbic-acid content or an increase in adrenal weight. They used growth hormone as a source of the adrenal weight factor, but did not consider that this factor was necessarily growth hormone itself. There seemed to be clinical data supporting the view at the same time, for at the same meeting to which Stack-Dunne and Young gave their paper we presented our early data on discrepancies between human response and the assay potency as determined by the Sayers method. However, as we have seen, this seems to have been explained on grounds of destruction or inactivation of the corticotrophin in the patients receiving it. The substance promoting adrenal weight and associated with, but not necessarily identical with, growth hormone also causes increased mitotic activity in the adrenal cortex and differs from the ascorbic-acid-depleting substance which is probably responsible for release and synthesis of corticosteroids (Cater and Stack-Dunne, 1955).

Forsham *et al.* (1955) summarized some experiments using a substance prepared by Rinfret from pig pituitary which was not itself steroidogenic but which, when given to a patient subsequently given corticotrophin, augmented the urine steroid response measured by the Porter–Silber method. A commercial growth-hormone preparation did not have a similar effect. We were fortunate enough to have at our disposal a small quantity of one of Young's growth-hormone preparations which he thought would be active with respect to the adrenal weight factor, although it had not been specifically tested for this activity. This substance was administered to a patient with Simmonds's disease whose adrenal had already been and continued to be stimulated with corticotrophin. We judged that in these circumstances the patient would also be deficient in growth hormone or the adrenal weight factor, and would be quite sensitive to it. There was a rapid increase in blood-sugar level, presumably due to the growth hormone itself, given intramuscularly 25 mg. twice daily for five days, but no increase in the ketogenic steroid or ketosteroid excretion. This negative result cannot be construed to be entirely contradictory to the hypothesis presented. It may well be that too little material was given for too short a time, or, as we shall see, that the absence of some other factor was limiting the response.

There is a clinical example before us worthy of attention with regard to this matter—namely, acromegaly. It is a commonplace that the adrenal cortices of patients with acromegaly are large and often contain subcapsular nodules. There is no unanimity of opinion about their

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