That the early feeding of egg white favors the development of sensitization is widely accepted. Some pediatricians—myself included—feel that the too early introduction of other solid foods also favors the development of allergy.

The matter of adenoid-tonsillectomy in the allergic child is one of frequent concern. Some physicians feel that this operation should not be done in allergic children, or in children of allergic parents, during the height of the pollen season, as pollen sensitization is then more likely to occur. This may be a valid precaution, especially in areas where the pollen count rises to great heights. Not valid, in my opinion, is the avoidance of needed adenoid-tonsillectomy simply because the child is allergic—on the theory the allergy may be flared up—or the performance of the operation routinely in allergic children. I believe the indications for operation are the same in allergic and non-allergic children; the retention of obstructing adenoid tissue is no more logical in an allergic child than in one who is nonallergic.

Finally, I would like to venture the view that just as the retention of obstructive adenoid tissue is not logical, retention of a pet to which a patient is sensitive is equally illogical. There is no question, in my mind, that by condoning such an arrangement we physicians have permitted a great deal of asthma to persist in our patients. I have seen much more harm done in this way than is done psychologically by the removal of the dog or cat from the homes of asthmatic children. Our patients and their parents are like ourselves in wanting to have their cake and eat it, too. They would like to get rid of asthma, while keeping the cause of it. The attempt to do so is no more successful in this situation than it is in others like it. As physicians, it behooves us not to become party to this type of self-deception.

A discussion of this type would not be complete without mentioning the potential danger of giving horse serum or other serum to sensitized patients. Such sensitization may have been induced by previous administration of serum or may have occurred naturally, as in the case of a horse-sensitive asthmatic. It is, therefore, necessary to question the recipient about known sensitivity to horses, as well as previous administration of serum. Intradermal testing of such patients will reveal those in whom serum administration may be dangerous. Foremost among these is the horse-sensitive asthmatic whose skin test is markedly positive. Ordinary delayed serum sickness in a previously untreated patient following therapeutic doses of diphtheria or tetanus antitoxin is an example of justifiably induced iatrogenic disease.

ANTIBIOTICS AND IATROGENIC DISEASE

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The association of the term “iatrogenic disease” with the clinical use of antibiotics poses many problems.

Physicians generally are familiar with most of the untoward reactions that may follow the use of antibiotics, and many excellent reviews of the subject are to be found in the literature. One cannot divorce the undesirable effects of antibiotics from the beneficial ones and, in this light, therapy becomes a calculated risk. If the probable discomforts or
dangers outweigh the probable advantages, the cure may be worse than the disease, and one is then dealing with true iatrogenic disease.

Probabilities of this kind cannot be assessed easily with antibiotics because reactions vary so much with type of drug, dose, course, method of giving and in different patients. Certain reports may be biased one way or the other because of personal prejudices or unusual series. Some ill effects are undoubtedly related to unwise, improper or careless use of the drug; others are not. So true incidences are not accurately known. Reactions where antibiotics are being used needlessly for trivial infections or for unnecessary prophylaxis are particularly deplorable while risks are justified when dealing with severe infections known to respond. Evaluation is difficult with infections of borderline severity and those prone to exceptionally severe secondary bacterial complications.

Reactions may be mild or severe; none is negligible. Oxytetracycline, for example, is considered to be relatively harmless. Still, Jackson and his colleagues reported that 58% of patients with pneumonia showed untoward effects attributable to this antibiotic. Most reactions were mild, but the antibiotic was believed to have contributed in large measure to the fatal outcome in five of the seven patients who died in the 91 cases.

Tissue irritation and pain from injected drug is often regarded as warranted temporary inconvenience to the patient. The intensity of these reactions is usually less with the soluble preparations such as potassium penicillin and streptomycin than with repository forms such as procaine penicillin, benzathine penicillin G and suspension of chloramphenicol. The pain from some, notably bacitracin and polymyxin B, is disguised by mixing with procaine. There is often neglect of the deleterious mental and physical effects that pain might have on sick individuals particularly if long courses of therapy are given.

Not all local irritant reactions are so easily disregarded. Residual areas of degeneration and fibrosis in muscles have been seen, but are seldom looked for. Sterile abscesses have followed the injection of preparations in oil. One report suggests, maybe wrongly, that metastasizing fibrosarcomas arose in two patients at the sites of intramuscular injections of penicillin in sesame oil because of a carcinogenic effect from the oil. Four papers describe severe neuritis in 15 infants and adults where sensory losses and/or disabling motor paralyses followed intramuscular injections of penicillin, streptomycin or tetracycline. The disabilities persisted for months in some cases and in a few seemed permanent. The sciatic nerve was involved most frequently, following intragluteal injections, but the deltoid region was affected in five cases. In some patients the immediate onset of symptoms suggested a more or less mechanical type of injury; in others, notably after injection of penicillin, the symptoms appeared only after several days, leading to a belief that the effect was related to the known toxicity of penicillin for nerve tissue. We are aware of several unreported cases. This complication is admittedly of infrequent occurrence, but the consequences are disastrous.

Toxicity to the central nervous system evidenced by spasms, convulsions and coma and by persisting paralyses in survivors, has followed intrathecal injections of penicillin where the dose greatly exceeded 5,000 to 10,000 units. Somewhat similar reactions have resulted from excessive intrathecal doses of streptomycin. Febrile reactions with pleocytosis in the spinal fluid are often seen with usual intrathecal doses.

Most antibiotics can be given orally, thus avoiding painful and other tissue reactions, but with certain drugs this unfortunately results in a higher incidence of various gastrointestinal complications that are more troublesome and significant than those after parenteral use. The so-called "broad spectrum" drugs are the chief offenders, though others may be involved, and these side effects are not always controllable by adjustments of dosage. The mechanisms underly-
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ing these complications are poorly under-
stood. Some of the effects are related to a
change in the normal bacterial flora of the
tract; others are not. Some may be due to
a direct irritation of the gut or to an upset
in the absorption or utilization of certain of
the vitamin B components.

Nausea or nausea and vomiting may be
very upsetting, occurring in 15% of Jackson’s
series with oxytetracycline. Various forms of
glossitis and stomatitis are seen; these
occurred in 2% in Jackson’s series.

But far more troublesome, persistent and
sometimes serious are the disturbances of
the lower intestinal tract. The incidence of
anorectal-colonic side effects has been esti-
mated as about 20% in those taking broad
spectrum antibiotics, though much less with
other drugs. In Turell’s experience, about
57% of those showing upsets of the lower
gastrointestinal tract have perianal pruritis
alone, about 27% have diarrhea and 16%
have both pruritis and diarrhea.

Perianal pruritis is common, even early in
ambulatory patients, and though not fatal
some sufferers almost wish it were. It usu-
ally disappears within 1 or 2 weeks after
resuming the drug, but recovery may
be slow in as many as 30%. A few may re-
main problems for several months despite
active treatment with topical cortisone or
other therapies.

Diarrheal upsets vary from bothersome,
loose, frequent stools to severe, toxic, dys-
enteric-like diseases. The mild upsets, seen
often with trivial treatment for trivial in-
flections, may appear early and persist for
weeks after discontinuing the drug; the se-
vere types may be rapidly fatal. Dearing
and Heilman recorded 7 deaths in 29 such
severely affected patients; 4 in the 12 re-
ceiving antibiotics for preoperative prepa-
ration of the intestine and 3 in the 17 being
treated for various diseases. The fulmi-
inating, disastrous reactions are usually accom-
panied by partial or complete replacement
of the intestinal flora by staphylococci.

Most such cases of enterocolitis will respond
promptly if a suitable antibiotic capable of
suppressing the staphylococcus is given
early, but minor disability may persist for
a long time. Quick tentative confirmation of
the diagnosis of staphylococcal enterocolitis
is best made by a direct microscopic exami-
nation of a stained film of the feces. Re-
placement of the intestinal flora by staphy-
lococci can occur without giving rise to the
disease.

Toxicities directed systematically at spe-
cific organs are seen. Infrequently occur-
ing, miscellaneous, sometimes fatal reac-
tions have been reported for most antibi-
otics, such as damage to the liver by exces-
sive administration of chlorotetracycline in-
travenously or by novobiocin. These
are often difficult to assess because factors
related to dose or to the abnormal physio-
logic state of the patient may contribute
greatly to the effects in each individual.

The ill effects of the streptomycins vary
with the dose, the duration of therapy and
the ability of the kidney to excrete the
drug. From 44 to 96% of patients receiving
a 4-week course of streptomycin may
show vestibular disturbances depending on
whether 1 gm or 2 gm are given daily. This
is largely reversible, but residual defects
may remain in 50% of affected subjects.

With dihydrostreptomycin, auditory dis-
turbances become more prominent than vestibular ones, and while these are slower to appear they tend to be more irreversible. The drug, neomycin, is particularly prone to give irreversible nerve deafness if given parenterally,\textsuperscript{26} and many patients may remain "stone" deaf. These dangers from streptomycin are disturbing when one considers how frequently fixed combinations of streptomycin and penicillin are given to infants and how hard it is to recognize early impairment of the eighth nerve in the very young.

Drug fever due to antibiotics is probably common, although seldom recognized as such. Its significance may be that it is often responsible for undue prolongation of a course of therapy.

Reactions to antibiotics attributable to allergic or hypersensitivity mechanisms are distinct hazards.\textsuperscript{1, 5, 35} They are, perhaps, related more closely to iatrogenic disease than most toxic manifestations of antibiotics because they may follow the first dose of the drug, even in individuals who are receiving such therapy for trivial reasons. These reactions may take many forms: various rapid or delayed skin manifestations running the gamut from simple erythemas through eczematoid and urticarial eruptions to exfoliative dermatitis; miscellaneous reactions; and anaphylactoid shock that is often fatal. The risks involved are estimated variously by different reporters, but the incidences are highest with penicillin, much lower with streptomycin and very low with the others. Novobiocin has produced a high incidence of skin rashes, possibly allergic in nature.\textsuperscript{36, 37}

After an injection of penicillin, it has been said\textsuperscript{38} that some reaction may be expected in 2.5% of children, in 5% of non-allergic adults and in 15% of individuals with an allergic diathesis. The risk from oral administration is less, estimated at about 0.2%. Reaction rates are said to be increasing by 1% each year, possibly because of prior sensitizing doses of penicillin. Reactions occur, however, in individuals not known to have received penicillin previously.

Anaphylactoid shock has been reported most frequently after the use of penicillin; all types of preparations have been involved including the crystalline potassium salt. Von Oettingen,\textsuperscript{1} from the literature published prior to 1953, lists 127 such penicillin reactions; 46 were fatal. Seventy-two of these reactions with 24 fatalities were related to procaine penicillin. There was little to implicate the procaine part of the molecule, but one might ask how often this relatively insoluble salt might have been injected inadvertently into a vein, a danger that has been shown by Kagan to exist experimentally.\textsuperscript{39} Almost all anaphylactoid reactions occur after injection of penicillin, but death has followed oral administration,\textsuperscript{40} and severe reactions have resulted from skin contact.\textsuperscript{41}

Estimates of the incidence of hypersensitivity reactions to streptomycin have varied from 0.4 to 5%. The commonest type is that reported by the British Ministry of Health\textsuperscript{42} where skin reactions occurred in 3.5% of nurses who were handling streptomycin. Von Oettingen lists seven anaphylactoid reactions to injected streptomycin with two fatalities. There was one nonfatal reaction to chlortetracycline.

There are many other untoward effects of antibiotics that come about somewhat indirectly but which may nevertheless be classified properly as iatrogenic disease. These are the so-called replacement infections or superinfections. Most are related to disturbances in the normal flora of the body that follow antibiotic therapy.\textsuperscript{44} On occasions these added infections are of endogenous source, but more frequently their source is exogenous, and here another factor enters the picture of iatrogenic disease. This factor is our inability to protect hospitalized patients from the bacterial environment of the hospital, an environment which, because of the very nature of hospitals, abounds in microorganisms of selected virulence and of selected patterns of resistance to antibiotics. Cross infection, the widespread, often indiscriminate use of antibiotics, the emergence of antibiotic-resist-
Antibacteria are all interrelated phenomena that lead to the greater prevalence of superinfections in hospitalized patients than in those outside hospitals. The chief offenders in these infections are staphylococci, but many other microorganisms including Candida albicans may be involved.

The true incidence of new infections developing during antibiotic therapy and as a more or less direct result of that therapy is not known. Weinstein and colleagues, in a careful study of 3,095 patients, estimated the frequency as 2.19%. These occurred most commonly in children and usually after giving broad spectrum antibiotics. They often arose within a few days of starting therapy.

Antibiotics are often given for prophylaxis, the view being taken that this could benefit the patient without having harmful effects. This prophylaxis may be justified where one is dealing with specific infections such as those caused by hemolytic streptococci, or those due to meningococci, gonococci and a few others. There is little justification for antibiotic prophylaxis against the bacterial world at large. There is almost no evidence to support antibiotic prophylaxis during most of the common viral infections, including the common cold, atypical pneumonia, measles or poliomyelitis, nor during bacterial infections such as pertussis, or in clean elective surgery or where indwelling catheters or drainage tubes are used. Weinstein's studies indicate that such prophylaxis may in fact be harmful. Of 130 patients with measles receiving antibiotics prophylactically, 30.4% developed superimposed bacterial infections whereas this occurred in only 14.9% of 298 cases not receiving antibiotic. Complicating infections developed in only 16% of 165 cases of bulbar poliomyelitis not receiving drug, but in 53% of 63 similar cases who were given antibiotics. This unwise prophylaxis does little more than insure that the superimposed infections will be resistant to the antibiotics used.

The needless prescribing of antibiotics is wasteful; it is dangerous because reactions may occur or the patient may become specifically sensitized. At the army post in the village of Igloo, South Dakota, two enterprising doctors, Nolen and Dille, tried to determine if an abuse had been made of antibiotics among the residents of the village. There were 763 civilians who had lived in Igloo for a full 5 years, who had been employed at the army post. Of these, only 7.9% had never received antibiotics during the 5-year period. Among those who had taken antibiotics, the average number of occasions each individual had been so treated was 3.9 times. Fortunately the medical records of this group were available to decide if antibiotic use had been warranted. The two doctors were most gentlemanly, even allowing a 1°C rise above normal in temperature to be a valid reason for treatment. Despite their generosity, they concluded that antibiotic therapy had not been indicated on 52.5% of occasions.

We don't know how much good or how much harm was done in Igloo, South Dakota, but we suspect that there was dishonest thinking, albeit not conscious dishonesty. There may be a moral to be drawn from Igloo, but there is no need to spell it out here.

These then are some of the highlights of the topic, "Antibiotics and Iatrogenic Disease." The dangers and discomforts attending antibiotic use are many and varied—sensitization and hypersensitivity reactions, pain and other local effects, systemic toxic effects, the hazards of superinfections and replacement infections, and others. These are real hazards that should be stressed as well as the benefits. Because they are real, the giving of antibiotics is always a calculated risk and they should be used only when there are definite and valid indications.

REFERENCES

2. Kagan, B. M., and Faller, L.: Symposium on clinical advances in medicine; unto-


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T. E. Roy
Pediatrics 1958;22;164

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