THE ARTS AND SCIENCES

Biochemistry

ASPIRIN CAN BE DEADLY

By Phil Drotning

Aspirin in large doses can be deadly. The drug which Americans swallow in great quantities as a cure for everything from the common cold to alcoholic "hangover" is known to produce chemical reactions which slow blood coagulation and cause hemorrhage. Some doctors have long known that the indiscriminate use of aspirin is unwise, but it took an agricultural chemist to show precisely how it could be dangerous.

Dr. Karl Paul Link, of the Wisconsin Agricultural Experiment Station, made the discovery after nearly ten years of research begun to explain a strange bleeding malady which was bringing death to cattle. In 1939 one of Link's assistants, H. A. Campbell, isolated a white, crystalline substance present in badly-cured sweet clover hay — now made artificially under the trade-mark Dicumarol — which proved to be the anti-coagulating agent that caused hemorrhage in cattle. Researchers at the Mayo Clinic, in Rochester, Minnesota, wondered whether the new drug might not be used to prevent the dangerous blood clots which sometimes form after human surgery. Experiments proved the drug effective for this vital purpose.

Working under Link's direction, Dr. Charles F. Huebner found that one of the principal components of Dicumarol was salicylic acid — the active ingredient in aspirin. Link suspected that the presence of salicylic acid in both aspirin and Dicumarol could mean that aspirin also slowed blood clotting. His first experiment was practical, although completely unscientific. A maid in his home was subject to frequent nosebleeds. He questioned her and found that she was troubled with recurring headaches, and took huge doses of aspirin to alleviate the pain. Link suggested that she eliminate the aspirin. The nosebleeds ceased.

This observation was no proof, of course, but it gave added stimulus to Link's speculation regarding the effects of aspirin. Four of his assistants, Ralph Overman, William Sullivan, Lester Scheel and John B. Field, began experimenting with rats, to de-

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termine if salicylic acid alone would prolong clotting time. When aspirin was given to rats daily in sufficiently large doses, it first prolonged the clotting time of the blood, and then the rats died of hemorrhage.

Link turned the results of his animal investigations over to other scientists, who undertook clinical research to determine whether aspirin has the same effect on human beings. His animal research already had been checked by Dr. K. K. Chen and Charles L. Rose of Lilly Research Laboratories, Indianapolis, Indiana.

Dr. Shepard Shapiro, of New York University Medical School, assisted by Milton H. Redish and H. A. Campbell, checked the blood clotting time of patients and personnel at New York Welfare Hospital, Division III, and found that when large quantities of aspirin were given, blood clotting time was lengthened. Dr. Ovid O. Meyer and Beryl Howard, of the University of Wisconsin Medical School, experimented on thirty-one people at the Wisconsin General Hospital, most of them staff members, and also reported that aspirin lengthens clotting time in humans, sometimes on administration of as little as twenty grains, or four ordinary tablets.

How much aspirin can be taken before it becomes harmful? According to Dr. Link and other researchers, taking six to eight tablets of aspirin during one day will lengthen the clotting time of a normal, healthy adult. In such cases clotting time may be delayed for only two seconds or so, which is not dangerous. But if a person who is not in perfect health repeats the dose daily over a period of even a week, clotting time could be dangerously prolonged.

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Aspirin, chemically acetyl-salicylic acid, is a sort of Dr. Jekyll-Mr. Hyde offspring of a long line of distinguished and beneficial drugs known as salicylates. They have been prescribed by doctors for over a hundred years, particularly in the treatment of painful diseases like rheumatic fever, for which they are regarded as the sovereign remedy. *The annual American consumption of aspirin averages around 7,000,000 pounds.*

The salicylates are mild antiseptics; they reduce temperature; and they are anti-rheumatics. While aspirin eases headaches and deadens pain, it also slows down one of the body's most essential processes — the action of the liver in producing prothrombin, the substance which helps make blood clot. Human beings cannot live without prothrombin. Without it they would bleed to death from a razor scratch or a finger prick. Production of this essential substance is stimulated by Vitamin K.

Green vegetables like spinach, cabbage, and lettuce, and bacterial action in the intestine, ordinarily provide enough Vitamin K to keep the clotting time of the blood normal. But when aspirin is taken it breaks down into salicylic acid, some of which re-

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tards intestinal bacteria, cutting Vitamin K production, and part of which goes to the liver. If too much is consumed, production of prothrombin by the liver may be halted.

When aspirin is taken in recommended doses for one day only, the liver can make enough prothrombin so that the blood will clot normally the following day. But if too many aspirin tablets are taken for several successive days, enough prothrombin cannot be produced and clotting time lengthens.

Link and the other researchers found that the anti-clotting effects of aspirin can be controlled by including Vitamin K in the diet when heavy doses of the drug are administered. The vitamin brings prothrombin production back to normal. This same Vitamin K is prescribed by doctors for expectant mothers, to insure blood clotting in both mother and child at the time of delivery, and by the Army for soldiers who are about to go into battle, to hasten blood clotting if they should be wounded far from medical aid.

Although the idea that salicylates can cause death through hemorrhage is not a new one, Link's research may be the key to an unknown number of deaths from bleeding which medical science previously had been unable to explain. More than fifty years ago a German pharmacologist, Binz, pointed out that when salicylic acid was given to certain individuals suffering from rheumatic fever it caused dangerous hemorrhage from the mucous membrane. In 1926, two American scientists, M. C. Wetzel and J. D. Nourse, reviewed all the cases of oil of wintergreen (methyl salicylate) poisoning previously reported and found that in addition to changes in the blood vessels, the most common lesion was hemorrhage. Four years later a Hungarian clinician, Balazs, found hemorrhagic lesions in the stomach and intestinal tracts of "aspirin suicides."

The *Journal of the American Medical Association* in 1940 quoted the *Lancet*, leading British medical journal, regarding the surprising number of deaths reported in England due to the use of aspirin. The *Lancet* reported that aspirin was known to have caused forty-three suicides, eight accidental deaths, and fourteen doubtful deaths in England and Wales in 1938.

"The *Lancet* considers it 'curious' that a drug which caused sixty-five deaths in one year is not classified as a poison," the *Journal* said.

Dr. Link's findings later were reported in the *Lancet*, and the editors recommended use of his method of estimating prothrombin in the blood in cases of suspected salicylate hemorrhage. When massive doses of aspirin must be given, the *Lancet* suggests administration of Vitamin K, and in the treatment of salicylate hemorrhage, transfusion of fresh blood. Link has used this routine on rats, to restore prothrombin production, with complete success. He says he administers the Vitamin K by injection, rather than giving it orally, "to avoid in-

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sult to an already injured stomach."

Link himself never uses aspirin. "My money," he asserts, "is on an older and more firmly established remedy — good Bourbon." Yet for four months during the course of the experimentation, to satisfy his personal curiosity as to the effect of aspirin on human blood, he acted as his own guinea pig. He took aspirin tablets week after week, and tests of his blood made by a laboratory assistant revealed that only four to six five-grain tablets were necessary to make his blood clot more slowly.

He raised the dose to eight, to ten, and then to twelve tablets, dispersed in a glass of milk and taken within fifteen minutes of each other. "Ten hours after I had taken twelve tablets the assistant who tested my blood thought I was going to hemorrhage, clotting took so long," Dr. Link says.

Then came the day when he took a dozen tablets and no change in clotting time was detected. He had taken two milligrams of Vitamin K, an infinitesimal amount, along with the aspirin. This small amount of Vitamin K — one two-thousandth the amount of the aspirin — was enough to nullify the drug's action on clotting time.

In a recent editorial the *Journal of the American Medical Association* commented on Link's work and said that present evidence "indicates that aspirin and the salicylates are among the least toxic of active pharmacopeial preparations"; nevertheless, "this status . . . should not be interpreted as an excuse for failure to recognize hazards connected with their abuse."

It is obvious from Link's work that aspirin should be used with discretion.

Politics

THE BUS-BOY STATESMAN

By Fred Harms

When Nebraska Democrats woke up to their morning papers the day after their April primary elections, they were startled by a picture of a man in overalls standing before a geometric design chalked on a blackboard. He was George W. Olsen, an absolute political unknown, who had piled up 344 votes more than his party-sponsored opponent to become the Democratic nominee for Governor.

For George Olsen, who has never made a campaign speech nor buttonholed a voter, his victory in the primaries was the happy climax of thirty-four unsuccessful years of seeking public office. For the Democratic regulars of the state, Olsen's nomination meant a red face. They had underestimated the appeal of his Scandinavian name to Nebraska voters

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