

CARDIOVASCULAR DISEASE: IN-DEPTH LOOK

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1 INTRODUCTION

Cardiovascular disease has topped the list of killer diseases every year since 1900 (except during the influenza epidemic of 1918) [1]. According to the American Heart Association, one American dies from cardiovascular disease every 36 seconds and nearly 80 million Americans currently have some form of cardiovascular disease. These diseases are costing Americans more than \$430 billion a year. However, remarkable progress has been made in the field of cardiology. The development of new drug treatments has helped cut death rates from cardiovascular disease by almost half since 1950. Drug discovery is vital in maintaining this momentum. There are currently over 250 drugs in development for treating heart disease and stroke.

There are many interesting stories in the development of cardiovascular drugs. In 1785, William Withering made the chance observation of the improvement in a patient with severe heart failure after ingesting an herbal remedy [2]. He went on to identify the active ingredient in this remedy to be extracts from the foxglove plant. Over the ensuing 9 years he carefully tried out different preparations from various parts of the plant and documented 156 cases where he described the effects and the best way of using it. He believed that digitalis had a diuretic effect in patients with a weak and irregular pulse. Withering had no real insight into the pharmacologic and physiologic effects of digitalis, and it was actually the courting of his wife that enticed him to advance his expertise in botany that allowed him to

make such an observation that inspired the development of digoxin.

The discovery of warfarin is linked to an observation made in the early 1920s of cattle in the northern United States and Canada that would die of uncontrollable bleeding from very minor injuries [3]. It was determined that the cattle were ingesting moldy silage made from sweet clover that functioned as a potent anticoagulant by reducing the amount of functioning prothrombin. The anticoagulant substance in moldy sweet clover was determined to be the coumarin derivative, 4-hydroxycoumarin. Over the next few years, numerous similar chemicals were developed that had the same anticoagulant properties, which eventually resulted in the development of warfarin in 1948. Warfarin was first registered for use as a rodenticide in the United States in 1952 and in 1954 was approved for medical use in humans.

Today cardiovascular drug development depends less on chance observations and more on logical scientific approaches. Most cardiovascular drugs used today were developed using the process known as “forward pharmacology” [4]. This approach begins by taking a pathophysiological or physiological process and carefully examining the role of individual mediators in that process in a disease. This leads to the characterization of entities responsible for a biological activity and to the identification of specific drug targets such as a receptor or enzyme. This process can be inefficient. The concept of the rennin–angiotensin–aldosterone system (RAAS) was first hypothesized in the 1930s. It took almost