# Al-Rasheed University/ Collage of Pharmacy

Cardio-toxicity by: M.Sc. Nibras Jamal

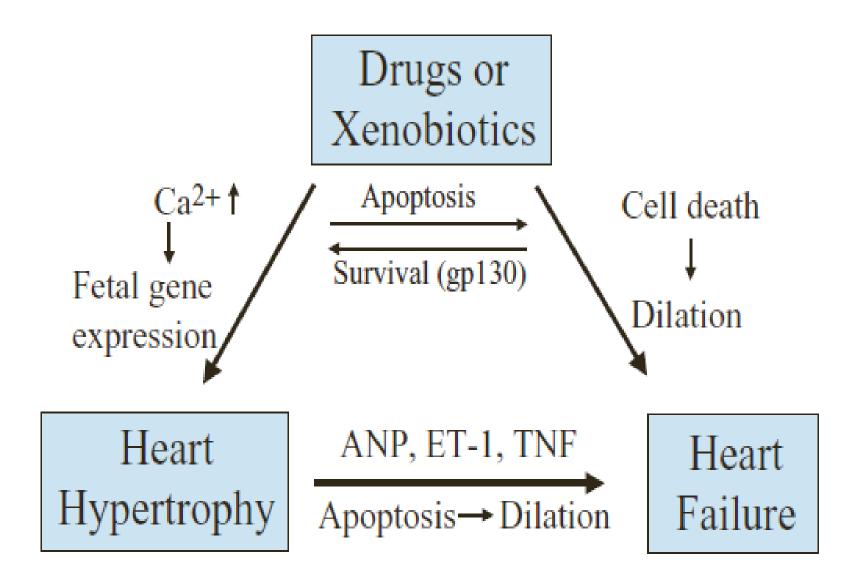
# **CARDIAC TOXIC RESPONSES**

- The ultimate functional effect of cardiac toxic manifestations is
- ✓ decreased cardiac output
- $\checkmark$  and peripheral tissue hypoperfusion,

These effects is caused by alterations in

- 1. biochemical pathways
- 2. energy metabolism
- 3. cellular structural and function of the heart
- 4. electrophysiology
- 5. and contractility of the heart.
- These morphological and functional alterations induced by toxic exposure are referred to as toxicologic cardiomyopathy.
- The critical cellular event leading to toxicologic cardiomyopathy is:
- ✓ myocardial cell death
- $\checkmark$  and extracellular matrix remodeling.

- Manipulation of genes responsible for cardiac function can lead to a significant phenotype, often in the form of cardiac hypertrophy and heart failure.
- It is difficult to apply this knowledge to patients:
- ✓ Acquired cardiac disease such as heart failure is the result of interaction between environmental factors and genetic susceptibility.
- ✓ Extrinsic and intrinsic stresses produce lesions that cannot be explained by a single gene or a single pathway.



# **Cardiac Arrhythmia**

- Cardiac rhythms under physiological conditions are set by pacemaker cells that are normally capable of developing spontaneous depolarization and responsible for generating the cardiac rhythm, called automatic rhythm.
- A cardiac rhythm that deviates from the normal automatic rhythm is called cardiac arrhythmia, often manifested in the form of tachycardia.
- There are several classes of tachycardia, including sinus tachycardia, atrial tachycardia, ventricular tachycardia, and torsade de pointes (TdP).
- Subclasses such as atrial fibrillation, atrial flutter and accelerated idioventricular rhythm.

# **Cardiac Hypertrophy**

- There are two basic forms of cardiac hypertrophy:
  - Concentric hypertrophy, which is often observed during pressure overload, and is characterized by new contractile-protein units assembled in parallel resulting in a relative increase in the width of individual cardiac myocytes.
  - Eccentric hypertrophy is characterized by the assembly of new contractile-protein units in series resulting in a relatively increase in the length of individual myocytes.
- Developing hypertrophy, during which period the cardiac workload exceeds cardiac output:
- □ compensatory hypertrophy, in which the workload/mass ratio is normalized and normal cardiac output is maintained;
- decompensatory hypertrophy, in which ventricular dilation develops and cardiac output progressively declines, and heart failure occurs.

## **Heart Failure**

- A traditional definition of heart failure is the inability of the heart to maintain cardiac output sufficient to meet the metabolic and oxygen demands of peripheral tissues.
- Definition has been modified recently to include changes in systolic and diastolic function that reflect specific alterations in ventricular function and abnormalities in a variety of subcellular processes.
- A detailed analysis to distinguish right ventricular from left ventricular failure can provide a better understanding of the nature of the heart failure and predicting the prognosis.

## **Acute and Chronic Cardiac Toxicity**

- Acute cardiac toxicity:
- ✓ cardiac response to a single exposure to a high dose of cardiac toxic chemicals.
- $\checkmark$  Is often manifested by cardiac arrhythmia.
- ✓ Myocardial apoptosis is also involved.

Examples:

- ✤A single high dose of arsenic can lead to cardiac arrhythmia and sudden cardiac death, which is easy to measure.
- A single dose of monensin leads to a diminished cardiac function progressing to heart failure requires a long-term observation (a few months) which is difficult to measure.

#### • Chronic cardiac toxicity:

✓ Response to long-term exposure to chemicals, manifested by cardiac hypertrophy and the transition to heart failure.