The Clinical Use of Digitalis Preparations

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NOTE: In view of the length of this article, it will be published in two issues. This issue will contain parts I through IV. The second part, V through IX including the references, will be published in August, 1955.—ED.

Foxglove, like squill and many other plants now known to possess cardioactive principles, has been used medicinally for centuries. It was in the 18th century, however, when Withering immortalized the old woman of Shropshire in medical history, that the present vast use of digitalis had its beginning. Today, drugs of the digitalis family include those derived from Digitalis purpurea, Digitalis lanata and certain members of the strophanthus family. They are distributed for oral or parenteral administration under a bewildering number of names. The stock of a large pharmacy ordinarily includes 30 or more oral preparations alone, in tablets or capsules of many sizes, shapes, and colors. The physician who believes he can identify a digitalis preparation from a patient's description may find it disillusioning to inspect an array of these samples.

The cardioactivity of each of these preparations is based upon the content of one or more glycosides, each of which has a specific molecular structure. Some of the glycosides are present in the plant and are called natural glycosides. Others are derived from the natural glycosides by the removal of glucose and acetyl groups from the molecule, a procedure which alters relatively little the pharmacologic properties of the glycoside. The further removal of sugar groups (digitoxoses from the digitalis glycosides, rhamnose or cymarose from the strophanthin glycosides) leaves an aglucone, which is less potent than its parent glycoside. Each aglucone is a phenantherine structure to which is attached a lactone ring. The phenantherine...
structure itself is shared by many biologically important substances: cholesterol, ergosterol, sex and adrenal hormones, and bile acids, for example. The biological characteristics of the phenanthrene derivatives are largely determined by the nature and position of the substituent groups. The lactone ring at position 17 is characteristic of the selective cardiac action of the aglucones from which they are derived.

While the digitalis preparations constitute such a large family that to know the commercial name for every member of it would be a burden on the memory, the physician should be able to distinguish child from grandparent and cousin from brother. The adult working parents of the family are the glycosides. Their parents are the galenic vegetable preparations, of which whole leaf digitalis is an example, and their offspring are the aglucones, degradation products that with one exception are not present among the standard pharmacological preparations.

I. THE VARIOUS DIGITALIS PREPARATIONS

I. Digitalis purpurea in its whole leaf form is the only grandparent in general use. It consists of inert material and biologically active mixed natural glycosides. The biologic assay of digitalis is based upon measurement of the lethal dose in pigeons. So determined, the potency must be not less than 85 per cent nor more than 120 per cent of the potency of U.S.P. Digitalis Reference Standard. One U.S.P. unit is defined as 0.1 Gm. of reference standard. In 1936 the potency of the U.S.P. unit was increased by approximately 30 per cent in order to correspond with the International Standard. The term “cat unit” was formerly used to define the potency of digitalis biologically assayed in cats against a U.S.P. unit. A large number of whole leaf preparations or extracts, standardized in terms of U.S.P. digitalis units, are available under many trade names.

The natural glycosides of Digitalis purpurea are not prepared commercially in purified form, but two derivatives are in use:

a. Digitoxin is derived from a natural glycoside of Digitalis purpurea by the removal of glucose. The aglucone of the pure crystalline substance is digitoxigenin. As commercially distributed, digitoxin U.S.P. is not necessarily pure digitoxin. It is assayed chemically by a procedure that accurately measures its content of cardioactive glycosides. It must have a purity of not less than 95 per cent in comparison with U.S.P. Digitoxin Reference Standard. However, gitoxin is also measured in the chemical assay as though it were digitoxin. Commercial samples of digitoxin U.S.P. have been found to contain varying but appreciable amounts of gitoxin which has relatively little biologic cardioactivity. Thirty-one commercial preparations were recently tested by the pigeon bioassay technique for digitoxin formerly used (U.S.P. XIII and preceding). Three of these did not meet the potency standards then employed. However, two of the three were also inadequate chemically, to a lesser degree. Digitoxin U.S.P. is distributed under several trade names.

b. Gitalin (amorphous) is a mixture of natural glycosides prepared from Digitalis purpurea by a special extraction and purification process. It was formerly known as verodigin, N.F. No legal requirements for standardization have been established, but bioassay by the manufacturer is presumed to give uniformity approximating that of digitalis U.S.P.

II. Digitalis lanata is not used in crude form, but it is the parent of several derivatives now in wide use:

a. Digilanid is a purified mixture of three natural glycosides, in the same proportions as in the plant, namely, about 47 per cent lanatoside A, 16 per cent lanatoside B, and 37 per cent lanatoside C.

b. Lanatoside A is not used in purified form, but two commercial preparations are derived from this natural glycoside: 1) Digitoxin, identical to that prepared from Digitalis purpurea, is derived by removal of glucose and acetyl. 2) Acetyl digitoxin, is derived by removal of glucose but not of acetyl. Its pharmacologic properties have been recently studied experimentally and clinically and it is now available commercially.

c. Lanatoside C, a purified natural glycoside, is in wide clinical use, especially intravenously for rapid effect. It is a U.S.P. preparation; its
potency, by pigeon bioassay, may legally vary from 85 per cent to 120 per cent of the Lanatoside C Reference Standard. 1) Digoxin is pharmacologically similar to lanatoside C and is derived from it by removal of glucose and acetyl groups. Digoxin U.S.P. contains not more than 110 per cent nor less than 90 per cent of the labelled amount, standardized by colorimetric assay comparison with U.S.P. digoxin Reference Standard.

III. Ouabain Injection U.S.P. is a natural glycoside obtained from the seeds of Strophanthus gratus or from the wood of the ouabao tree. It is assayed against a U.S.P. reference standard in pigeons, with the range 85 to 120 per cent permitted. It is for intravenous use only.

IV. Strophanthin K is a mixture of three or more natural glycosides derived from Strophanthus kombe. As prepared for intravenous use, it is standardized (N.F. IX) to half the potency, per milligram, of Ouabain U.S.P. K-Strophanthoside is a natural glycoside isolated from the mixture. The aglucose of each of the glycosides of strophanthin K and of ouabain is strophanthinidin.

a. Acetyl strophanthinidin is the only preparation now in use that is neither a glycoside nor a mixture of glycosides. It is a synthetic elaboration of the aglucose strophanthinidin. It is for intravenous use only. Its biologic effects are the most rapid in onset and the least persistent of any member of the digitalis family of drugs. It is biologically assayed in cat units against a reference standard. Five tenths mg. of the drug is approximately 3 cat-units.

II. THE DISTRIBUTION AND FATE OF DIGITALIS

An ingested digitalis preparation, if absorbed, must be distributed in the blood to various tissues, and finally destroyed or excreted. Until recently it has been impossible to study this problem adequately because there were no methods for the detection and measurement of the minute quantities of glycoside necessary to produce major biologic effects upon the heart. Two such technics have been developed. One, developed by Geiling and his associates, is based upon the radioactivity of a biosynthetic digitoxin incorporating C\textsuperscript{14} in the molecule. Minute amounts are detected by radioisotope technics. This method is extremely sensitive and accurate, but unfortunately, it is the C\textsuperscript{14} that is measured, not the digitoxin. Therefore, other methods must be used to differentiate the presence of the drug itself from its metabolic degradation products. Also, even in minute doses, C\textsuperscript{14}, with a half-life of 5,600 years, presents an uncertain hazard for experimentation in human subjects, although the amount remaining in the body after a few weeks is almost infinitesimal. The second method, developed by Friedman and Bine\textsuperscript{a} as a modification of the chick embryo heart technic of Paff,\textsuperscript{b} is based upon the development of arrhythmias in the embryonic duck heart when immersed in media containing cardioactive glycoside. With these two technics, much has been learned of the fate of digitoxin in man and animals. An excellent review of the critical experiments has been written by Friedman.\textsuperscript{11}

Investigators using many different technics have agreed that ingested digitoxin is completely absorbed. In varying degree, other glycosides are less potent orally than intravenously. Whether these other drugs are destroyed in, or poorly absorbed from, the gastrointestinal tract is not known. In the plasma, digitoxin is adsorbed on albumin.\textsuperscript{12,12} This probably accounts for the old observation that digitoxin in a plasma perfusate is less rapidly lethal to an experimental preparation than when it is delivered in saline. Digitoxin, bound to the albumin, is less free to traverse capillary and cell membranes. Adsorption does not occur between albumin and most other glycosides.

After oral ingestion, the quantity of digitoxin in the blood has thus far defied detection.\textsuperscript{11} Given intravenously, the disappearance of this glycoside from the blood has been measured by both of the technics described above. By bioassay, in normal human subjects, 50 per cent disappears within a few minutes. The subsequent drop is more gradual, with 40 per cent still present at one hour, and 15 per cent after two hours.\textsuperscript{13} With the C\textsuperscript{14} digitoxin technic, after one hour only 10 per cent remained in the
blood of patients with heart failure. Lanatoside C disappears much more rapidly than digitoxin, presumably because it is not adsorbed by albumin. Contrary to earlier observations, little glycoside is held in extracellular fluids. The digitoxin content of edema fluids is extremely low, never more than .02 mg. per liter. Mobilization of edema fluid does not mobilize digitalis. The digitalis toxicity that may follow mercurial diuresis is, rather, related to the associated potassium depletion.

In the past, it was believed that the myocardium had a unique affinity for digitalis. This belief is not supported by the results of assay by either technic. In experimental animals, equal or greater concentrations of digitoxin are found in the lungs, livers, and kidneys than in the heart. It may be washed out of the heart with little difficulty in excised preparations and it disappears from the heart and other organs of the intact animal within a few hours. Possibly the biologic effects of digitalis preparations are achieved at the cell membrane, without penetration of the cell by the glycoside or a biologically active degradation product. Whether or not this is true, digitoxin is detected in the soluble supernatant intracellular parts of emulsified cells, but not in the nuclear and mitochondrial portions.

Digitoxin excretion has been studied by the two technics in experimental animals and in man. Considerable species variation is found by both methods and the observations in animals are not applicable to man. In human studies, the results by the two methods are somewhat conflicting. Although 60 to 80 per cent of the C14 given in radioactive digitoxin ultimately appears in the urine, with a large excretion in the first few days, less than 10 per cent is thought to be in digitoxin; the rest is in degradation products. By the bioassay technic, the kidneys excrete, as biologically active digitoxin, 40 to 50 per cent of a single dose over a period of more than two weeks. No more than 5 per cent is excreted in a single day. Cardiac patients excrete the drug equally as well as normal persons, but with a slightly longer initial lag. On maintenance doses, whether 0.1 or 0.2 mg. per day is given, a little less than half the administered dose appears in the urine. In toxicity, urinary excretion may reach 0.1 mg. or more.

Little is known of the urinary excretion of glycosides other than digitoxin, or of the fecal excretion of any of the glycosides in man. There are reasons to believe that the latter is small. If the conclusions from bioassay techniques are correct, indicating a long-persistent urinary excretion of about half of the administered digitoxin, then in vivo destruction of the drug must be relatively small; 0.05 mg. per day has been considered a reasonable estimate. Conversely it has been concluded from radioisotope studies that almost all of the digitoxin is metabolically degraded before excretion. Within one hour after injection into a cat of radioactive digitoxin, 74 per cent of the C14 content of the heart is already in the molecules of degradation products. Further investigations will doubtless explain these discrepancies. Whether degradation is large or small, the metabolic steps in the process are obscure.

The results by either technic seem to diverge from clinical observation in some important respects. The peak biological effects of digitoxin in the intact human (about eight hours) are much later than the peak concentration of the drug in the hearts of experimental animals, and in man these biological effects persist long after either digitoxin or C14 metabolites of digitoxin have disappeared from the hearts of experimental animals. Resolution of these apparent discrepancies must await further development of our understanding of the exact way in which digitalis produces its effects.

III. The Nature of the Action of Digitalis

A list of all the subjective and objective changes possible when a cardioactive glycoside is given to a patient with congestive failure would fill several pages of small print. Some of these changes (e.g., gynecomastia) are incidental, and some are clinically undesirable in varying degree. Fortunately, the most impressive changes are those that reverse the abnormalities of the congestive failure. Among the most consistent of these are: The ventricular
rate slows, the cardiac output increases, the arteriovenous oxygen difference falls, the peripheral venous and right atrial pressures fall and the pulmonary arterial diastolic pressure falls. These cardiovascular hemodynamic changes are accompanied by variable renal vascular dynamic changes and a striking diuresis of water, sodium, and chloride. Since events in the heart, the peripheral vessels, and in the kidney are intimately interrelated, it has been difficult to differentiate primary from secondary effects of the drug.

The effectiveness of venesection in relief of congestive failure has been attributed to a reduction in venous filling-pressure load upon the heart to a point of greater contraction efficiency, i.e., “moving back” toward the peak of the Starling curve. McMichael and Sharpey-Schafer suggested that digitalis was effective in a similar manner, by a primary action in relaxing peripheral vascular tone. They found that a fall in right atrial pressure preceded an increase in cardiac output in patients with congestive failure given digoxin, and that similar effects were achieved by peripheral trapping of blood with thigh cuffs. Further observations from the same laboratories and by others have failed to support this view. Splanchnic trapping of blood in the normal dog after digitalis administration appears to have no counterpart in human congestive failure.

A primary renal action was long ago suggested by the diuresis that follows digitalis therapy. However, digitalis is not an effective diuretic in the absence of congestive failure or in noncardiac edema states except those associated with excessive adrenal steroids. Elevated renal venous pressure has been shown to decrease urine flow and sodium excretion. Although renal, hemodynamic changes are small and inconsistent, it is generally accepted that the diuresis produced by digitalis drugs is secondary to their primary action upon the heart.

Digitalis is effective in increasing the output of the heart in failure. It has no such effect upon the normal heart or upon the enlarged heart that is not in failure. The increased output is occasionally accomplished by slowing the rate or otherwise increasing the efficiency of the pumping mechanism as a whole. Mainly, the effects are the result of an increase in the contractile force of the heart muscle. How this is accomplished is not clear. Indeed, the fundamental reasons for impaired muscular function in clinical heart failure are obscure. There appears to be no deficit in utilization of oxygen by the failing heart. Neither does the synthesis of adenosine triphosphate (A.T.P.), the essential store of chemical energy, appear to be faulty. Rather, the heart in failure is inefficient in converting an adequate supply of chemical energy (A.T.P.) to the mechanical energy of contraction. Fascinating complexities of molecular construction and activity of the myocardium have been described by Szent-Gyorgyi. In the resting state, according to his views, the long, energy-collecting fibers of actin are held separate from the shorter, energy producing myosin by adenosinetriphosphate. The myosin molecules lie like stiff rows of sausages alongside the actin fibrils. With activation, the actin and the myosin join at every eighth link. With this contact, an enzyme is released from myosin that splits adenosine triphosphate from the actin. The adenosine triphosphate then provides the energy to fold the myosin by releasing the ionic structure that holds the link stiff. With the folding of the myosin, the actin fibrils are passively shortened. This act, multiplied by millions of actomyosin units, results in heart muscle contraction. Relaxation is accomplished in a sequence of comparable complexity. These events are exceedingly sensitive to changes in pH, temperature or ionic concentration. When conditions are not optimum, the effectiveness of myocardial contraction is diminished. Experimentally, digitalis tends to restore normal function under many of the unfavorable conditions. It may be that this is accomplished entirely by altering the membrane permeability for ions; the drug, however, has been shown to influence the behavior of actomyosin in vitro, after it has been divorced from cell membranes. Until the basic defects of the contraction mechanism in cardiac failure have been disclosed, the exact role of digitalis in restoring normality.
will remain obscure. It has been suggested that digitalis replaces the function of some unknown substance, normally present, that has become deficient or to which the muscle has become refractory.21

In addition to its influence upon the contractility of heart muscle, digitalis has important effects upon its other physiologic properties: excitability, automaticity, conductivity, and the refractory period. These effects are responsible for the therapeutic value of the drug in the control of ventricular rate in atrial fibrillation and flutter, and in the conversion of one arrhythmia to another or to sinus rhythm. They are also responsible for many undesirable disorders of cardiac mechanism. The problem has been investigated extensively in animals by Mendez and Mendez,44 Moe and Mendez,15 Farah and Loomis,16 Woske and his associates,17 and many others. From these studies it is apparent that the results are variable from species to species, that the properties of atrial muscle, conduction system, and ventricular muscle are diversely influenced by digitalis, that a given response may be reversed as dosage increases or if the nerve supply is disturbed, and that a change in cardiac mechanism is a net result of complex changes in several properties. In man, we can observe only the net result. The changes in individual physiologic properties can be reconstructed in terms of animal experimental results to only a limited degree.

Moe and Mendez15 discuss the factors involved in the ventricular arrhythmias induced by digitalis preparations. They are not a product of irritability, as the term is commonly used. In the dog, and presumably in man also, irritability (excitability), defined as the responsiveness to stimulation, declines as ventricular arrhythmias increase with higher drug levels. Rather, they are the result of increasing automaticity and decreased conduction velocity. Ectopic foci produce premature beats. Multiple ectopic foci, isolated from each other by conduction delay, result in progressive chaos terminating in ventricular fibrillation.

Digitalis may produce prolongation of the P-R interval. This is the result of delay in conduction velocity in the A-V conduction system. Atrioventricular block may be attributed either to a decline in intensity of the delayed stimulus to a level below the threshold required to stimulate the ventricle, or to a rise in that threshold as ventricular irritability declines. An increase in refractory period of the A-V node is the predominant factor in the control of ventricular rate with digitalis in atrial fibrillation. The effects of small doses of digitalis upon A-V conduction are caused by vagal stimulation and may be reduced or abolished by denervation, atropine, or exercise. At higher dosage levels, these effects are not reversed by interference with the vagal supply, and are the result of direct action of the drug upon the myocardium.48

Digitalis affects all of the physiologic properties of the sinus node and atrium directly, and indirectly, through vagal stimulation. The basis for the conversion of paroxysmal atrial tachycardia to sinus rhythm, or for the conversion of atrial flutter to fibrillation by the drug, is conjectural.

The Relation of Digitalis Action to Cations

The serum concentrations of various cations, especially sodium and potassium, may be altered very little in congestive failure.49 Conversely, the total body cations content and its intracellular and extracellular distribution are usually disturbed. These changes have an important indirect bearing upon heart function, especially as they relate to blood volume, venous pressure, and fluid accumulation. Unless the disturbances are unusually severe, they have little or no direct effect upon the contractile properties of the myocardium, nor do they directly induce disturbances in rhythm. They have a critical bearing upon the use of digitalis because the toxicity of the drug may be severely augmented without a parallel increase in its therapeutic properties.

The relationships of heart failure, potassium, and digitalis are discussed in some detail by Lown and Levine.16 Some potassium deficit, not necessarily associated with a low serum level, commonly occurs in congestive failure. Anoxia, acidosis, or inadequate nutrition may
be contributing factors. This potassium deficiency is made greater by many therapeutic procedures, for example, by dietary restrictions and the use of mercurial diuretics, ammonium chloride, resins or Diamox. Impaired renal function, diabetes, or the use of cortisone may further contribute. It has been shown that the dosage of a digitalis preparation sufficient to produce toxicity is appreciably reduced in the presence of potassium depletion, and that the duration of the toxicity is extended.\textsuperscript{16} Also, toxicity develops as potassium is withdrawn by hemodialysis.\textsuperscript{16, 56} Digitalis toxicity may be abolished in man\textsuperscript{61} and in animals\textsuperscript{16} by the administration of potassium even when the blood level is not depressed. High levels of serum potassium have profound effects upon the heart, but their influence upon the therapeutic action of digitalis in man has not been demonstrated. In animals, excessive doses of acetyl strophanthinid were required to produce toxicity when potassium levels had been elevated by hemodialysis.\textsuperscript{52}

Sodium deficiency or excess has no such clearly defined influence upon the behavior of digitalis. Calcium and digitalis are synergistic in their propensity to produce an excessive duration of muscle contraction (contracture). Several sudden fatalities have resulted from the intravenous administration of calcium to digitalized patients.\textsuperscript{53}

**Quantitative Differences in Cardiac Drugs**

The qualitative biologic effects of the cardiovascular glycosides are very similar. Indeed, many consider them to be essentially identical in all major characteristics. Some observers, especially in Europe, believe that strophanthus derivatives exert a relatively greater influence upon myocardial contractility and a lesser effect upon junctional tissue conductivity as compared with digitalis and its derivatives. Others assert that preparations vary in the “margin of safety” between the effective therapeutic dose and that which causes toxic manifestations. Although such qualitative differences remain controversial, quantitative differences are very obvious, especially in the percentage of drug absorbed from the gastrointestinal tract, in the rate of measurable onset and cumulation of biologic effects, and in the duration of the effects.

Strophanthus preparations are either destroyed or so poorly and irregularly absorbed from the gastrointestinal tract that enormous doses by mouth are required to produce any appreciable effect, and the therapeutic results are erratic. These drugs should never be used orally. Conversely, digitoxin given orally is completely absorbed within a few hours; hence the effects of a given dose after oral administration are somewhat delayed, but ultimately the same as those to be expected when the drug is given intravenously. Other preparations are incompletely absorbed, as determined by the relative oral and intravenous dosages required to produce an equivalent effect. So determined, about 10 per cent of lanatoside C, 20 per cent of the whole leaf digitalis preparations and 50 per cent of digitoxin are absorbed from the gastrointestinal tract,\textsuperscript{54} and about 67 per cent of acetyl digitoxin.\textsuperscript{5} Incomplete absorption is evidently responsible for the differences between oral and intravenous dosage requirements of all of these other preparations. If absorption were highly erratic between different individuals, the difficulty of reasonable prediction of dosage requirements would be increased. If the degree of absorption were highly variable in the same individual at different times, stable maintenance would be impossible. Fortunately, neither of these problems appears to be of major importance in clinical practice (except, perhaps, in the oral use of lanatoside C).\textsuperscript{54, 56} This is attested to by the long and successful treatment record of oral digitalis leaf preparations.

The various cardiovascular glycosides influence the heart at variable speeds. Whether the race for biologic effect is measured in an excised turtle heart, a dog heart-lung preparation, or in an intact human subject, the relative order of the drugs remain the same: digitoxin is the slowest, acetyl strophanthinid the most rapid, and the others are in between. The reasons for these differences are not clear. Digitoxin may well be delayed in transit to the heart muscle because it is bound to plasma
albumin. Variation must also exist in the rate at which an effect is produced, once the active principle is present at the cell. Acetyl strophanthidin, for example, is much more rapid in action than lanatoside C despite the fact that, as far as is known, neither is appreciably adsorbed by proteins. Perhaps a "selective cardiac affinity" does exist for some glycosides, although it has not been demonstrated for digitoxin, as noted above.

The development of progressive degrees of biologic effects resulting from the administration of a single dose of different cardioactive preparations is plotted against time in figure 1, with intact man the experimental subject. The curves are derived from a large number of investigations. They are, at best, rough approximations because the responses of different individuals are not uniform; indeed, the preparations themselves are not completely uniform in composition or potency. The terms slight, considerable, submaximal and maximal are deliberately vague. One does not get a "half-maximal" response with half of a "full therapeutic dose." A "half-dose" may reduce the rate in atrial fibrillation from 160 to 85, whereas the "full dose" may reduce it, in the same patient, from 100 to 75. Another patient may show little or no benefit from a "half dose," but a very striking response from a "full dose." It is this very ill-definition of the "level of digitalization" that has made clinical and experimental comparisons between the various digitalis preparations so difficult to evaluate.

The upward curves have several connotations bearing upon the clinical use of digitalis preparations. Among these, two are of special importance. One pertains to the selection of a suitable drug. On the rare occasions when the safety of slower administration must be sacrificed to meet an urgent demand for rapid action, a preparation with a rapidly rising curve is indicated. The other pertains to the time that should elapse between doses of a drug. If further medication is given before the full effects of the preceding dose have accumulated, toxicity is invited.

The biological effects upon the heart of the different preparations wane and disappear at variable rates, as has been abundantly demonstrated by many observations in man and animals. The reasons for the differences are obscure. Little enough is known of the distribution, degradation, and excretion of digitoxin; practically nothing is known by direct measurement of these functions of the other glycosides. The comparative order is the same as for the development of effects, with digitoxin the most persistent and acetyl strophanthidin the most transient. The decline curves of figure 1 vary even more from individual to individual than do the upward curves. They are of special clinical significance with respect to maintenance requirements, duration of toxicity, and re-digitalization. A preparation with a very rapid decline curve is not suitable for long term use because adequate stability of digitalization level is impossible to achieve. A rapid decline curve correlates with relatively large daily maintenance requirements and a relatively short duration of toxicity, if it occurs. When digitalization has been achieved, and then allowed to lapse, the amount of any preparation required to re-establish digitalization will vary in accordance with the glycoside originally used and the time elapsed since its administration. The decline curves provide some indication of the probable requirements.

(To be concluded in the August issue)
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