The Adrenal Medulla & Adrenal Cortex | 20

(left margin, partial text from facing page)

ne to time
s sections
1 require-
tolerance.
ents gain
increased
nones that
the pres-
n patients

in experi-
cretion of
s alloxan-
. Somato-
c humans,
tion, there
nes. Thus,
rglucagon-
However,
i levels are
etics. Fur-
n secretion
itimulating
e of large
ed as being
a relative
nutes to the
st in some
in- and the

There are 2 endocrine organs in the adrenal gland, one surrounding the other. The inner **adrenal medulla** (Fig 20–1) secretes the catecholamines **epinephrine** and **norepinephrine;** the outer **adrenal cortex** secretes steroid hormones.

The adrenal medulla is in effect a sympathetic ganglion in which the postganglionic neurons have lost their axons and become secretory cells. The cells secrete when stimulated by the preganglionic nerve fibers that reach the gland via the splanchnic nerves. Adrenal medullary hormones are not essential for life, but they help to prepare the individual to deal with emergencies.

The adrenal cortex secretes **glucocorticoids,** steroids with widespread effects on the metabolism of carbohydrate and protein; a **mineralocorticoid** essential to the maintenance of sodium balance and ECF volume; and **sex hormones** that exert minor effects on reproductive function. Unless mineralocorticoid and glucocorticoid replacement therapy is administered postoperatively, adrenalectomy is followed by collapse and death. Adrenocortical secretion is controlled primarily by ACTH from the anterior pituitary, but mineralocorticoid secretion is also subject to independent control by circulating factors, of which the most important is angiotensin II, a polypeptide formed in the bloodstream. The formation of angiotensin is in turn dependent on renin, which is secreted by the kidney.

ADRENAL MORPHOLOGY

The adrenal medulla is made up of interlacing cords of densely innervated granule-containing cells that abut on venous sinuses. Two cell types can be distinguished morphologically: an epinephrine-secreting type that has larger, less dense granules; and a norepinephrine-secreting type in which the smaller, very dense granules fail to fill the vesicles in which they are contained (Fig 20–2). **Paraganglia,** small groups of cells resembling those in the adrenal medulla, are found near the thoracic and abdominal sym-

In adult mammals, the adrenal cortex is divided into 3 zones of variable distinctness (Fig 20–3). The outer **zona glomerulosa** is made up of whorls of cells that are continuous with the columns of cells which form the **zona fasciculata.** These columns are separated by venous sinuses. The inner portion of the zona fasciculata merges into the **zona reticularis,** where the cell columns become interlaced in a network. The cells contain abundant lipid, especially in the outer portion of the zona fasciculata. All 3 cortical zones secrete corticosterone (see below), but the enzymatic mechanism for aldosterone biosynthesis is limited to the zona glomerulosa, while the enzymatic mechanism for forming cortisol and sex hormones is found in the 2 inner zones.
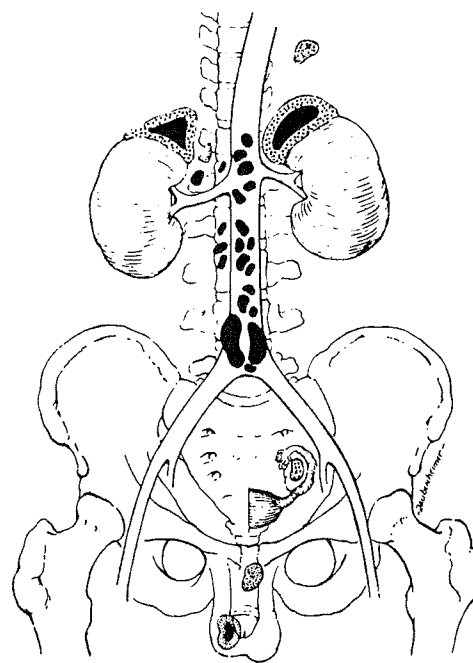

Figure 20–1. Human adrenal glands. Adrenocortical tissue is stippled; adrenal medullary tissue is black. Note location of adrenals at superior pole of each kidney. Also shown are extra-adrenal sites at which cortical and medullary tissue is sometimes found. (Reproduced, with permission, from Forsham PH: *Textbook of Endocrinology,* 4th ed. Williams RH [editor]. Saun-
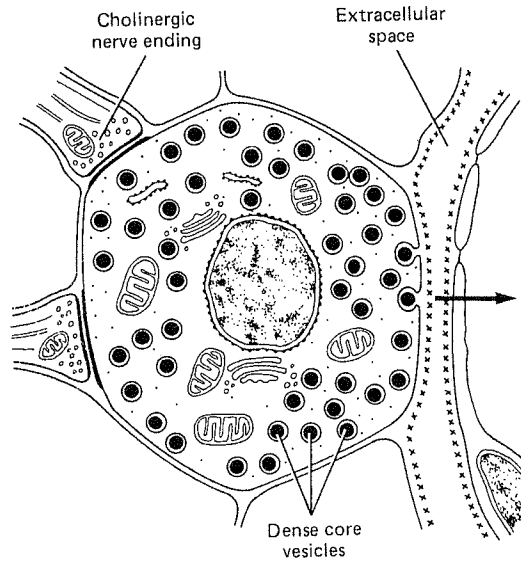
Figure 20–2. Norepinephrine-secreting adrenal medullary cell. The granules are released by exocytosis and the granule contents enter the bloodstream (arrow). (Modified from Poirier J, Dumas JLR: *Review of Medical Histology.* Saunders, 1977.)

Arterial blood reaches the adrenal from many small branches of the phrenic and renal arteries and the aorta. From a plexus in the capsule, blood flows to the sinusoids of the medulla. The medulla is also supplied by a few arterioles that pass directly to it from the capsule. In most species, including humans, there is a single large adrenal vein. The blood flow through the adrenal is large, as it is in most endocrine glands.

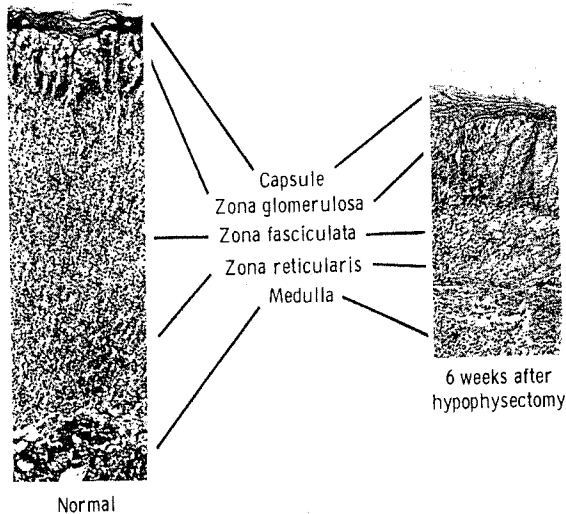During fetal life, the human adrenal is large and under pituitary control, but the 3 zones of the permanent cortex represent only 20% of the gland. The remaining 80% is the large **fetal adrenal cortex,** which undergoes rapid degeneration at the time of birth. A major function of this fetal adrenal is secretion of sulfate conjugates of androgens that are converted in the placenta to androgens and estrogens which enter the maternal circulation. There is no structure comparable to the fetal adrenal in laboratory animals. In the mouse, cat, rabbit, and female hamster, there is a layer of cortical cells called the **X zone** between the zona reticularis and the medulla. This zone is maintained by pituitary gonadotropins, and it degenerates when androgen secretion increases during puberty in the male and during the first pregnancy in the female.

An important function of the zona glomerulosa, in addition to aldosterone biosynthesis, is the formation of new cortical cells. Like other tissues of neural origin, the adrenal medulla does not regenerate; but when the inner 2 zones of the cortex are removed, a new zona fasciculata and zona reticularis regenerate from glomerular cells attached to the capsule. Small capsular remnants will regrow large pieces of adrenocortical tissue. Immediately after hypophysectomy, the zona fasciculata and zona reticularis begin to atrophy, whereas the zona glomerulosa is unchanged (Fig 20–3), because of the action of the renin-angiotensin system on this zone. However, in long-standing hypopituitarism, degenerative changes appear in the zona glomerulosa. In hypopituitarism, the
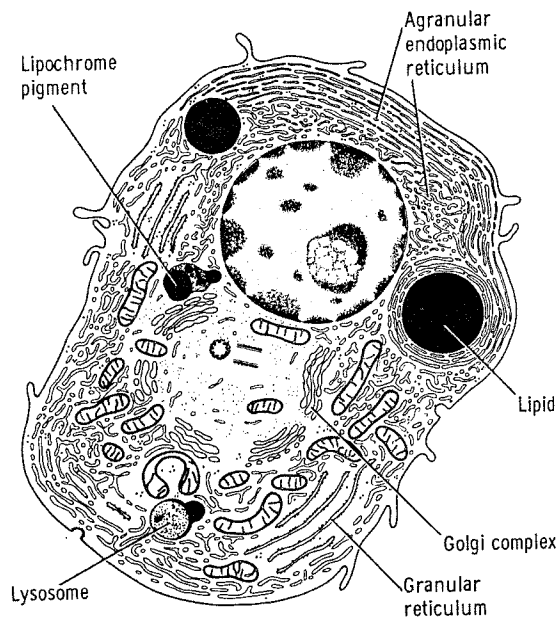

Figure 20–3. Effect of hypophysectomy on the morphology of the adrenal cortex of the dog. Note that the atrophy does not involve the zona glomerulosa. The morphology of the human adrenal is similar.

Figure 20–4. Diagrammatic representation of the cytologic features of steroid-secreting cells. Note the abundant agranular endoplasmic reticulum, the pleomorphic mitochondria, and the lipid droplets. (Reproduced, with permission, from Fawcett DW, Long JA, Jones AL: The ultrastructure of endocrine glands. Recent Prog Horm Res 25:315, 1969.)

ability to
tients wh
sterone c
and stim
produce
reticulari
glomerul

The
amounts
seems to
Other st
mitochor
is very si
tures of s

S

Biosynth

Nor
by the ad
secrete n
mans 80%
vein is e
circulatio

The
norepinep
ter 13 an
epinephri
ylation of
of norep
transferas
formation
found in
the adren
glucocort
draining
hypophys

In re
nephrine I
is a 50–10
nephrine i
but the ep
pg/ml (0.
epinephri
medulla a
from the l
The plasn
nmol/L),
dopamine
half the p
medulla,
comes fro
nents of tl

ability to conserve Na^+ is usually normal; but in patients who have had the disease for a long time, aldosterone deficiency may develop. Injections of ACTH and stimuli that cause endogenous ACTH secretion produce hypertrophy of the zona fasciculata and zona reticularis but do not increase the size of the zona glomerulosa.

The cells of the adrenal cortex contain large amounts of smooth endoplasmic reticulum, which seems to be involved in the steroid-forming process. Other steps in steroid biosynthesis occur in the mitochondria. The structure of steroid-secreting cells is very similar throughout the body. The typical features of such cells are shown in Fig 20–4.

ADRENAL MEDULLA

STRUCTURE & FUNCTION OF MEDULLARY HORMONES

Biosynthesis, Metabolism, & Excretion

Norepinephrine and epinephrine are both secreted by the adrenal medulla. Cats and some other species secrete mainly norepinephrine, but in dogs and humans 80% of the catecholamine output in the adrenal vein is epinephrine. Norepinephrine also enters the circulation from adrenergic nerve endings.

The details of the biosynthesis and catabolism of norepinephrine and epinephrine are described in Chapter 13 and summarized in Figs 13–3 and 13–5. Norepinephrine is formed by hydroxylation and decarboxylation of tyrosine, and epinephrine by the methylation of norepinephrine. Phenylethanolamine-N-methyltransferase (PNMT), the enzyme that catalyzes the formation of epinephrine from norepinephrine, is found in appreciable quantities only in the brain and the adrenal medulla. In the medulla, it is induced by glucocorticoids in the large amounts found in the blood draining from the cortex to the medulla. After hypophysectomy, epinephrine synthesis is decreased.

In recumbent humans, the normal plasma norepinephrine level is about 300 pg/ml (1.8 nmol/L). There is a 50–100% increase upon standing. Plasma norepinephrine is generally unchanged after adrenalectomy, but the epinephrine level, which is normally about 30 pg/ml (0.16 nmol/L), falls to essentially zero. The epinephrine found in tissues other than the adrenal medulla and the brain is for the most part absorbed from the bloodstream rather than synthesized in situ. The plasma dopamine level is about 200 pg/ml (1.3 nmol/L), and there are appreciable quantities of dopamine in the urine. There is evidence that about half the plasma dopamine comes from the adrenal medulla, whereas the remaining half presumably

In the medulla, the amines are stored in granules bound to ATP and protein. Their secretion is initiated by acetylcholine released from the preganglionic neurons that innervate the secretory cells. The acetylcholine increases the permeability of the cells, and the Ca^{2+} that enters the cells from the ECF triggers exocytosis (see Chapter 1). In this fashion, the catecholamines, ATP, and proteins in the granules are all extruded from the cell.

The catecholamines have a very short half-life in the circulation. For the most part, they are methoxylated, then oxidized to 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid, VMA). About 50% of the secreted catecholamines appear in the urine as free or conjugated metanephrine and normetanephrine, and 35% as VMA. Only small amounts of free norepinephrine and epinephrine are excreted. In normal humans, about 30 μg of norepinephrine, 6 μg of epinephrine, and 700 μg of VMA are excreted per day.
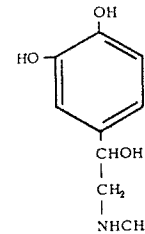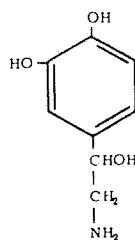
Effects of Epinephrine & Norepinephrine

In addition to mimicking the effects of adrenergic nervous discharge (Table 13–1), norepinephrine and epinephrine stimulate the nervous system and exert metabolic effects that include glycogenolysis in liver and skeletal muscle, mobilization of free fatty acids, and stimulation of the metabolic rate (Table 20–1).

Norepinephrine and epinephrine both increase the force and rate of contraction of the isolated heart. They also increase myocardial excitability, causing extrasystoles and, occasionally, more serious cardiac

Table 20–1. Comparison of the effects of epinephrine and norepinephrine on some physiologic parameters. Where pertinent, the activity of the more active compound has been indicated as ++++ and the activity of the other is compared to it on a scale of + to ++++.

Norepinephrine	Parameter	Epinephrine
Decreased (due to reflex bradycardia)	Cardiac output	Increased
Increased	Peripheral resistance	Decreased
++++	Blood pressure elevation	++
++++	Free fatty acid release	+++
++++	Stimulation of CNS	++++
+++	Increased heat production	++++

arrhythmias. Norepinephrine produces vasoconstriction in most if not all organs, but epinephrine dilates the blood vessels in skeletal muscle and the liver. This overbalances the vasoconstriction it produces elsewhere, and the total peripheral resistance drops. When norepinephrine is infused slowly in normal animals or humans, the systolic and diastolic blood pressures rise. The hypertension stimulates the carotid and aortic baroreceptors, producing reflex bradycardia that overrides the direct cardioacceleratory effect of norepinephrine. Consequently, cardiac output per minute falls. Epinephrine causes a widening of the pulse pressure; but, because baroreceptor stimulation is insufficient to obscure the direct effect of the hormone on the heart, cardiac rate and output increase. These changes are summarized in Fig 20–5.

The increased alertness that is produced by catecholamines is described in Chapter 11. Epinephrine and norepinephrine are equally potent in this regard, although in humans epinephrine usually evokes more anxiety and fear.

The one effect of epinephrine that is shared to only a small extent by norepinephrine, at least in some species, is its glycogenolytic action. Epinephrine activates phosphorylase in liver and skeletal muscle (see Chapter 17), and the blood glucose rises. The blood lactic acid also rises. The liver glycogen first falls and then rises as the lactic acid is oxidized (Fig 19–19). Plasma K^+ rises coincident with the glycogenolysis.

Norepinephrine and epinephrine are almost equally potent in their free fatty acid–mobilizing activity (see Chapter 17) and their calorigenic action. They produce a prompt rise in the metabolic rate which is independent of the liver and a smaller, delayed rise which is abolished by hepatectomy and coincides with the rise in blood lactic acid. The calorigenic action does not occur in the absence of the thyroid and the adrenal cortex. The cause of the initial rise in metabolic rate is not clearly understood. It may be due to cutaneous vasoconstriction, which decreases heat loss and leads to a rise in body temperature, or to increased muscular activity, or to both. The second rise is probably due to oxidation of lactic acid in the liver.

On the basis of their differential sensitivity to drugs, the effects of epinephrine and norepinephrine have been divided into 2 groups. Those in one group are brought about by catecholamines interacting with α receptors in the effector organs, whereas those in the other group are brought about by catecholamines interacting with β receptors (see Chapter 13 and Table 13–1). Drugs that are α blockers inhibit actions such as the pressor effects of the catecholamines. Drugs that are β blockers generally inhibit actions such as the chronotropic and inotropic effects of catecholamines on the heart and their glycogenolytic and free fatty acid–mobilizing effects. β-Mediated effects are due to stimulation of adenylate cyclase, with resultant increased formation of cyclic AMP (see Chapter 17).

REGULATION OF ADRENAL MEDULLARY SECRETION

Neural Control

Certain drugs act directly on the adrenal medulla, but physiologic stimuli affect medullary secretion through the nervous system. Catecholamine secretion is low in basal states, but the secretion of epinephrine and, to a lesser extent, that of norepinephrine is reduced even further during sleep.

There is evidence that adrenal medullary secretion is increased when the ''cholinergic sympathetic vasodilator'' system discharges at the start of exercise, the increased epinephrine secretion reinforcing the vasodilatation produced by sympathetic vasodilator fibers to skeletal muscle (see Chapter 31).

Increased adrenal medullary secretion is part of the diffuse adrenergic discharge provoked in emergency situations, which Cannon called the ''emergency function of the sympathoadrenal system.'' The ways in which this discharge prepares the individual for flight or fight are described in Chapter 13. It is worth mentioning, however, that when adrenal medullary hormones are injected into control animals in the amounts secreted in response to splanchnic nerve stimulation, they exert effects on the musculature of the skin, kidneys, and spleen that are only 10–20% as great as the effects produced by comparable stimulation of the
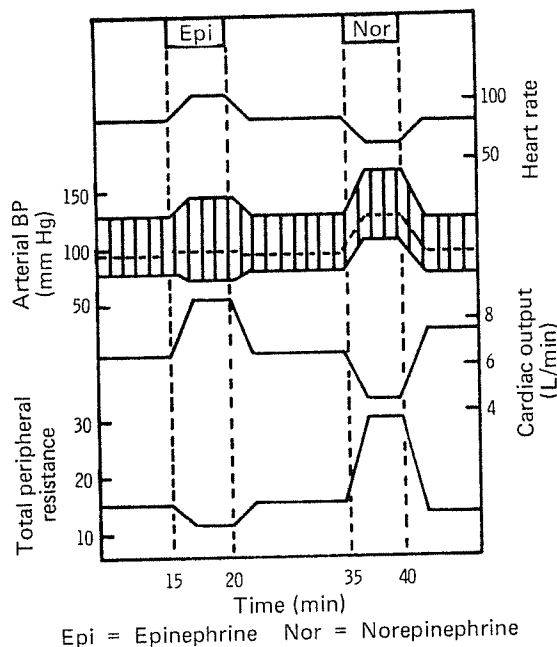

Figure 20–5. Circulatory changes produced in humans by the slow intravenous infusion of epinephrine and norepinephrine. (Modified and reproduced, with permission, from Barcroft H, Swan HJC: *Sympathetic Control of Human Blood Vessels.* Arnold, 1953.)

sympathetic innervation of these structures. Thus, the action of secreted catecholamines in augmenting the effects of adrenergic nerve discharges on the vascular system is relatively slight.

The metabolic effects of circulating catecholamines are probably more important, especially in certain situations. The calorigenic action of catecholamines in animals exposed to cold is an example. Animals with denervated adrenal glands shiver sooner and more vigorously than normal controls when exposed to cold. The glycogenolysis produced by epinephrine in hypoglycemic animals is another example. Hypoglycemia is a potent stimulus to catecholamine secretion, and insulin tolerance appears to be reduced when adrenal medullary secretion is blocked.

Selective Secretion

When adrenal medullary secretion is increased, the ratio of epinephrine to norepinephrine in the adrenal effluent is generally unchanged or elevated. However, asphyxia and hypoxia increase the ratio of norepinephrine to epinephrine. The fact that the output of norepinephrine can be increased selectively has unfortunately led to the teleologic speculation that the adrenal medulla secretes epinephrine or norepinephrine depending upon which hormone best equips the animal to meet the emergency it faces. The fallacy of such speculation is illustrated by the response to hemorrhage, in which the predominant catecholamine secreted is not norepinephrine but epinephrine, which lowers the peripheral resistance. Norepinephrine secretion is increased by emotional stresses with which the individual is familiar, whereas epinephrine secretion rises in situations in which the individual does not know what to expect.

ADRENAL CORTEX

STRUCTURE & BIOSYNTHESIS OF ADRENOCORTICAL HORMONES

Classification & Structure

The hormones of the adrenal cortex are derivatives of cholesterol. Like cholesterol, bile acids, vitamin D, and ovarian and testicular steroids, they contain the **cyclopentanoperhydrophenanthrene nucleus** (Fig 20–6). The adrenocortical steroids are of 2 structural types (Fig 20–7): those that have a 2-carbon side chain attached at position 17 of the D ring and contain 21 carbon atoms (''C 21 steroids''), and those that have a keto or hydroxyl group at position 17 and contain 19 carbon atoms (''C 19 steroids''). Most of the C 19 steroids have a keto group at position 17 and are therefore called **17-ketosteroids**. The C 21 steroids
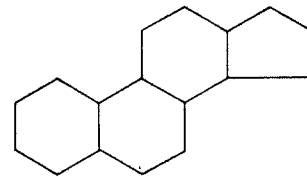

Figure 20–6. The cyclopentanoperhydrophenanthrene nucleus.

tion to the side chain are often called 17-hydroxycorticoids or 17-hydroxycorticosteroids.

The C 19 steroids have androgenic activity. The C 21 steroids are classified, using Selye's terminology, as mineralocorticoids or glucocorticoids. All secreted C 21 steroids have both mineralocorticoid and glucocorticoid activity; **mineralocorticoids** are those in which effects on Na^+ and K^+ excretion predominate, and **glucocorticoids** those in which effects on glucose and protein metabolism predominate.

Steroid Nomenclature & Isomerism

For the sake of simplicity, the steroid names used here and in Chapter 23 are the most commonly used trivial names. A few common synonyms are shown in Table 20–2. The details of steroid nomenclature and
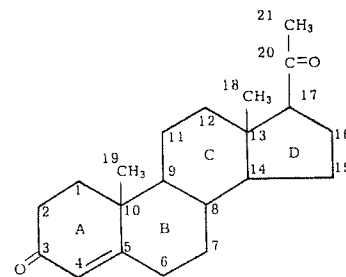
''C 21'' steroid (progesterone)
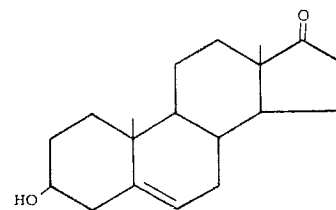
''C 19'' steroid (dehydroepiandrosterone)

Figure 20–7. Structure of adrenocortical steroids. The letters in the formula for progesterone identify the A, B, C, and D rings; the numbers show the positions in the basic C 21 steroid structure. The angular methyl groups (positions 18 and 19) are usually indicated simply by straight lines, as in the lower formula. Dehydroepiandrosterone is a ''17-ketosteroid'' formed by cleavage of the side chain of the C 21 steroid 17-hydroxypregnenolone and its replacement by an O atom. Similar conversion of other C 21

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.

fastcase®
Smarter legal research.