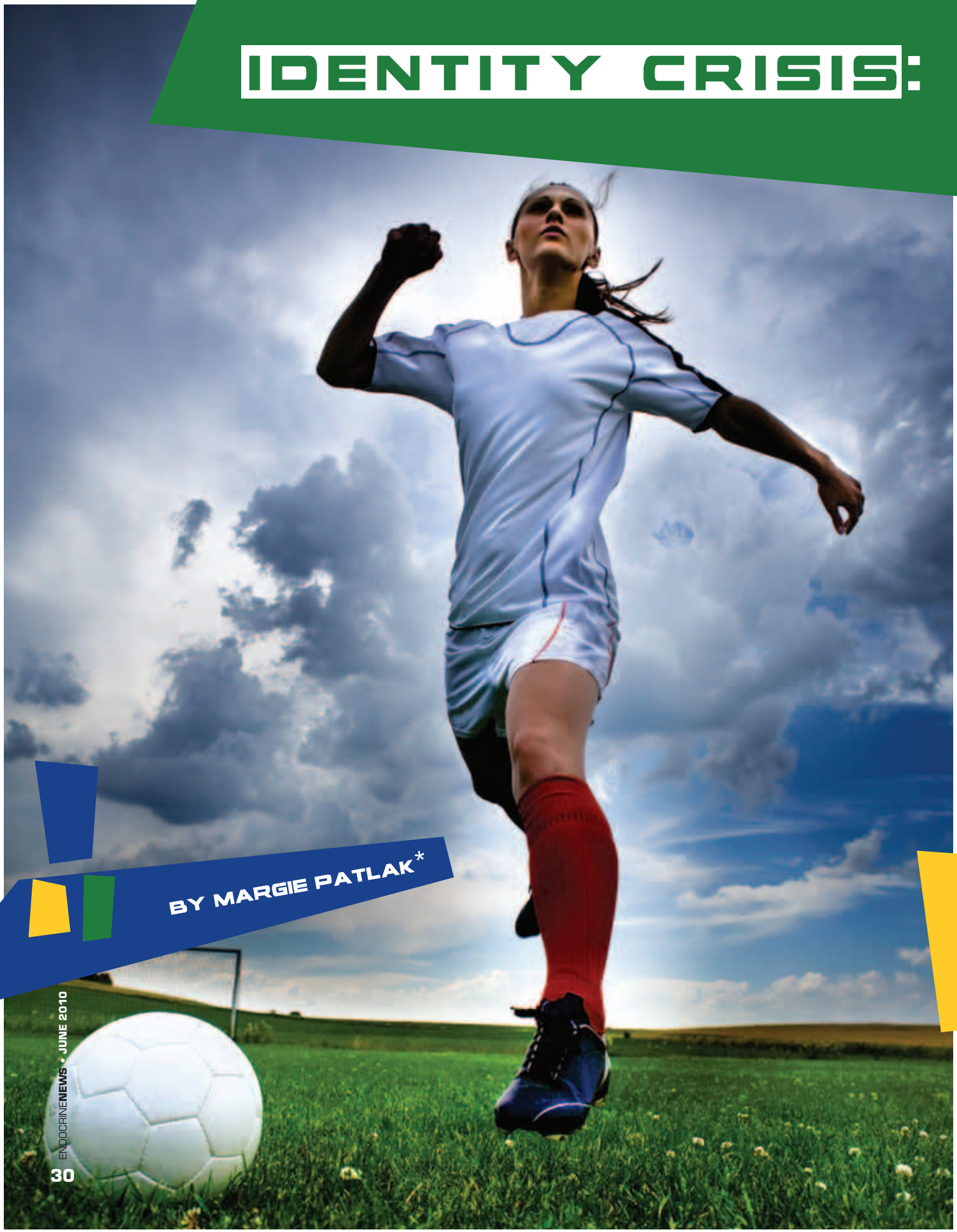
IDENTITY CRISIS:



BY MARGIE PATLAK*

WHAT DETERMINES GENDER?

What makes a man a man and a woman a woman? A simple answer to this question is no longer appropriate now that a deeper look into the underpinnings of gender has revealed a complex interplay of neural, hormonal, and genetic factors, which, along with social expectations, determine whether you see yourself as a woman or a man.

"It's no longer a matter of whether or not you have a penis," said sex researcher Milton Diamond, Ph.D., who directs the University of Hawaii's Pacific Center for Sex and Society. "For gender, it's not what's between your legs that's important, but what's between your ears."

In fact the latest findings in neuroscience suggest gender identity may be engraved in the brain prenatally, regardless of how puberty unfolds. These findings, along with hormonal and surgical treatments aimed at turning one sex into the other (and the patients who request them), raise a number of thorny biological and ethical questions with which endocrinologists increasingly must wrestle.

Some of those questions reached center stage recently, when the International Olympic Committee (IOC) subjected South African runner Caster Semenya to sex testing, the results of which are pending. The runner is rumored to have, as well as female genitalia, undescended testes, which provide her with three times the normal female level of testosterone.

Boys Will Be Boys

Gone are the days when infants were assumed to come into this world with a blank gender identity slate. This naïve view, promoted in the 1970s by the late John Money, Ph.D., at Johns Hopkins University, Baltimore, Md., led many endocrinologists and pediatricians to advocate raising as girls infants with missing or defective sex organs, or those with both male and female sex organs. Physicians could surgically create a vagina easier than a penis, and they assumed that even children with the sexually distinctive Y chromosome would easily adapt to the female gender role if they were treated like girls.

That approach backfired 20 years later, when Dr. Money learned that his own poster child for gender identity malleability had never accepted the female role his parents and doctors assigned to him after a botched circumcision as an infant left him without a penis. Despite also having his testicles removed, receiving female hormones, and being raised as a girl with no knowledge that he started life as a boy, this person insisted that "she" was a boy during childhood, going to the extreme of ripping off any dresses put on him and insisting on urinating standing up. As an adult, he reclaimed his male identity, with the aid of transsexual hormonal and surgical treatments.

Studies of XY chromosome children with missing genitalia due to cloacal exstrophies or penile ablations have added to the anecdotal reports that some boys will be boys regardless of whether they have the appropriate sexual apparatus. Due to Dr. Money's influence, most of these chromosomally male children were routinely raised as girls, but by adulthood about half reverted to being male. Presumably, even more might have opted to switch if not for parental or other pressures. One person waited until "she" was 52 and both "her" parents were dead before changing genders. Studies consistently found that whether or not a gender switch was made, most XY "girls" showed stereotypical male behaviors from the beginning, such as playing with toy trucks rather than dolls.

In contrast, studies of XY individuals with complete androgen insensitivity syndrome who were raised as girls reveal that the vast majority are comfortable with their gender assignment, presumably because the same lack of androgen receptors that prevented development of a penis, descended testicles, and other male features, also prevented androgens from masculinizing their brains.

Complementary research on XX girls with congenital adrenal hyperplasia revealed that the earlier in gestation the fetus was exposed to excess androgen, the more masculinized the girl became. Those masculine features weren't limited to penis-like clitorises and fused labia that resembled scrotums. These chromosomal females were also more likely to have homosexual fantasies and to have levels of aggression and spatial visualizing abilities more typical of males.

All these gender-switching incidents have given researchers the opportunity to study the prenatal hormonal effects

on human gender identity and seem to confirm what animal and genetic studies had been revealing: Male prenatal hormones have a masculinizing effect on the brain. Conversely, the absence of those hormones leads to the female brain. Studies over the past 50 years in rodents, deer, and primates have consistently found that androgens made prenatally by chromosomal males trigger irreversible brain changes, producing stereotypical male behavior and mating habits.

His and Her Brains

Searching for physical evidence of gender-determining brain changes in humans, Dick Swaab, M.D., PhD., and his colleagues in the Netherlands showed that adult male and female brains have differing topographies in the hypothalamus and adjacent areas, and that adult transsexuals who denote themselves as females, despite having male genitalia at birth, have brain topography more like that of typical females than of typical males. The one female-to-male transsexual these researchers studied had hypothalamus topography typical of males.

By including post-menopausal women and castrated males in their studies, these scientists claimed that the brain differences they detected were not due to the effects of currently circulating hormones; prior hormonal treatment might have caused the differences. In addition, few individuals were studied by Dr. Swaab and his colleagues, and their findings have yet to be confirmed. However, complementing the findings are functional brain differences seen by other researchers in male-to-female transsexuals whose brain activation patterns in response to sniffing an estrogen-based pheromone found in sweat more resembled those of women.

"The gender-determining factor is the peak in fetal testosterone and the reaction to that by the brain," said Dr. Swaab, who directs the Netherlands Institute for Brain Research, and is a professor at the University of Amsterdam.

He noted that genitalia develop during the first trimester of pregnancy, whereas sexual differentiation of the brain doesn't start until the second half, with some brain features that differ between men and women, such as the stria terminalis, not fully developing until early adulthood. Although in most people the brain's sexual differentiation follows the same pathway previously set by the genital development, Dr. Swaab postulated that gender identity disorders occur when a mismatch exists between the two. Supporting this theory are findings that most transsexuals in adulthood report strong feelings of being in the wrong body from early childhood onward.

It is not known exactly what degree of brain changes, if any, is needed to tip the balance of gender identity from one sex to another. In fact, a continuum of changes might exist between identifying as male or female, with some people falling in the middle—a sort of grey zone. Dr. Swaab agreed that there probably is an identity grey zone, but said he suspects the proportion of people in it is small.

In contrast, Dr. Diamond argued that many belong in the grey zone, at least on a molecular level, because thousands of genes might be contributing to gender. "Biology loves differences, but society hates them," he said, pointing out that society often tries to put people into black-or-white, us-or-them categories, rather than accept a multitude of variations. "Our society accentuates the differences between men and women rather than the similarities," Dr. Diamond stressed. He called for more acceptance of variation in gender identity and a recognition that not all newborns, or even adults, will fit into pink or blue categories. In agreement with this view, an increasing number of hermaphrodites and pseudohermaphrodites are adopting the "intersex" label and are seeking greater social acceptance for their unique variations on the gender theme.

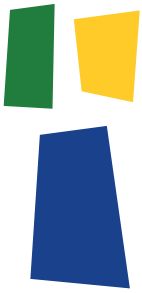
Experts also caution against asserting that gender in humans could be completely determined prenatally, with no social influences. They cite a meta-analysis that found, like Dr. Money, only about half of XY individuals with missing male genitalia who were raised as girls chose to reverse their gender. Dr. Diamond believes that prenatal hormonal influences create a "bias" toward becoming a specific gender, but this is not written in stone because social forces can also create strong biases, particularly in societies that don't accept gender variations. Asked why more people don't change their sex if they feel their gender identity is at odds with their genitalia, Dr. Diamond responded, "They don't want to lose their husbands, parents, kids, or religion. This is not a simple decision."

Cases of Mistaken Identity

So what's a physician to do when a child is born with ambiguous genitalia or an adult comes to the office claiming to be a male stuck in a female's body, or vice versa? Each year, 1 in 1,500–2,000 intersex babies with ambiguous genitalia are born, according to the Intersex Society of North America. Dutch surveys suggest that as many as 3 in 100 adults are not comfortable with their gender.

Pediatricians feel the heat most when parents of children whose genitalia are not obviously male or female ask for medical help in shaping their child to fit a more socially acceptable and physically obvious gender category. The latest American Academy of Pediatrics (AAP) consensus statement on managing intersex disorders stresses preserving female fertility and sexual functioning, lowering the malignancy risk, and minimizing the need for surgery when making gender assignments and prescribing treatment. Cosmetic appearance is low on the totem pole of priorities. This statement also considers the likelihood that individuals will be satisfied with their assigned genders, based on the underlying cause of their intersex

"FOR GENDER, IT'S NOT WHAT'S BETWEEN YOUR LEGS THAT'S IMPORTANT, BUT WHAT'S BETWEEN YOUR EARS."



conditions, prenatal androgen exposures, and the outcomes of the few studies that assess long-term satisfaction with gender assignments in intersex individuals.

Unlike the AAP consensus study, the focus of The Endocrine Society's recent guideline on transsexual treatment was children and adults without any known genetic, hormonal, intersex, or chromosomal abnormality. These are people whose genitalia match their sex but not their psyche. The guideline noted that for these people, prenatal androgen exposures do not reliably predict gender, nor can current circulating levels of sex steroids. The only way to determine if a patient has the right gender is to assess how the person feels about his or her gender. The guideline panel recommended gender reassignment only if a patient satisfies the criteria set by mental health experts for gender identity disorder. These criteria are that the patient strongly identifies more with the opposite sex, has persistent discomfort with his or her current gender role, and the disturbed sense of gender causes the patient to have clinically significant distress or impairment in social or work situations.

One telltale sign of gender identity disorder is disgust at developing breasts, facial hair, or other sex-distinguishing characteristics once puberty ensues. For this reason, as well as because of the findings that most children's dissatisfaction with their gender disappears once they enter puberty, the panel recommended holding off on sex change treatments until after puberty has started. At that point, it recommended suppressing puberty with gonadotropin-releasing hormone analogs. This will allow delaying the decision to irreversibly switch gender until the age of 16, when patients will likely be mature enough to make such a life-changing decision, yet not so developmentally advanced that transgender treatments are unlikely to be completely effective. In many countries, 16-year-old people are legal adults for medical decisions. The guideline recommends, nonetheless, deferring transsexual surgery until a patient is at least 18 years of age.

As for the current controversy about defining gender for athletic competitions, "From a medical standpoint, persons raised as women should compete with others raised as women," said Wylie Hembree, M.D., of Columbia University and chair of the Society's transsexual treatment panel. This advice contrasts with that given by a panel of medical experts convened by the IOC, which recommended that athletes who identify themselves as women, but have medical disorders that blur gender boundaries, should not be allowed to compete as women until after their medical disorders are treated with hormones or surgery.

Other experts call for categorical distinctions aimed at making athletic competitions fair. These distinctions could depend on height, testosterone levels, and several other gender-related factors, rather than solely on simple sex determinations. Some urge making gender determinations based on prenatal factors, such as hormonal effects on the brain. Dr. Swaab is currently searching for biomarkers that indicate gender identity early in development, which could be helpful for this.

Dr. Hembree believes that what should determine gender in athletic competitions is more of a social or political question than a biological one, so any answer to it will be somewhat arbitrary. "Biology, as we know it, has not evolved based upon a doctrine either of fairness or homogeneity," he said.

Although the IOC's eventual recommendation may solve the problem of what to do about athletes like Ms. Semenya, it still leaves unanswered the questions, "What makes a woman a woman?" and "What makes athletic competitions fair?" Until there are answers, treatment of athletes with ambiguous gender will be toward an undefined goal—one that may actually be a moving target, as more research findings file in. ■

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* Margie Patlak is a free-lance science writer living near Philadelphia, Penn.

To read about The Endocrine Society's current and upcoming clinical practice guidelines or to order individual or compendium copies, please visit *www.endo-society.org/guidelines/index.cfm*.

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NovoLog® is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog® or one of its excipients. NovoLog® has a more rapid onset and shorter duration of action than regular human insulin. An injection of NovoLog® should be immediately followed by a meal within 5 to 10 minutes. Because of the short duration of action of NovoLog®, a longer-acting insulin also should be used in patients with type 1 diabetes and may be needed in patients with type 2 diabetes. **When used in an external subcutaneous insulin infusion pump, NovoLog® should not be mixed with any other insulin or diluent.** Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulins. Any change of insulin dose should be made cautiously and only under medical supervision. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy. As with all insulin preparations, the time course of action of NovoLog® may vary in different individuals or at different times in the same individual and is dependent on many conditions, including injection site, local blood supply, temperature, and level of physical activity. Severe, life-threatening generalized allergy, including anaphylactic reaction, may occur with any insulin product, including NovoLog®. Adverse reactions observed with NovoLog® include hypoglycemia, allergic reactions, local injection site reactions, lipodystrophy, rash, and pruritus. Insulin, particularly when given intravenously or in settings of poor glycemic control, may cause hypokalemia. Like all insulins, NovoLog® requirements may be reduced in patients with renal impairment or hepatic impairment. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy.

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WARNINGS AND PRECAUTIONS: Administration: NovoLog® has a more rapid onset of action and a shorter duration of activity than regular human insulin. An injection of NovoLog® should immediately be followed by a meal within 5-10 minutes. Because of NovoLog®'s short duration of action, a longer acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy. Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. As with all insulin preparations, the time course of NovoLog® action may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, temperature, and physical activity. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages. Insulin requirements may be altered during illness, emotional disturbances, or other stresses. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure. **Hypoglycemia:** Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog®. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., patients who are fasting or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycemia. **Hypokalemia:** All insulin products, including NovoLog®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, and patients receiving intravenously administered insulin). **Renal Impairment:** As with other insulins, the dose requirements for NovoLog® may be reduced in patients with renal impairment. **Hepatic Impairment:** As with other insulins, the dose requirements for NovoLog® may be reduced in patients with hepatic impairment. **Hypersensitivity and Allergic Reactions:** *Local Reactions* - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of NovoLog® injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog®. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoLog®. *Systemic Reactions* - Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin product, including NovoLog®. Anaphylactic reactions with NovoLog® have been reported post-approval. Generalized allergy to insulin may also cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis. In controlled clinical trials, allergic reactions were reported in 3 of 735 patients (0.4%) treated with regular human insulin and 10 of 1394 patients (0.7%) treated with NovoLog®. In controlled and uncontrolled clinical trials, 3 of 2341 (0.1%) NovoLog®-treated patients discontinued due to allergic reactions. **Antibody Production:** Increases in anti-insulin antibody titers that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog®. Increases in anti-insulin antibodies are observed more frequently with NovoLog® than with regular human insulin. Data from a 12-month controlled trial in patients with type 1 diabetes suggest that the increase in these antibodies is transient, and the differences in antibody levels between the regular human insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. These antibodies do not appear to cause deterioration in glycemic control or necessitate increases in insulin dose. **Mixing of Insulins:** Mixing NovoLog® with NPH human insulin immediately before injection attenuates the peak concentration of NovoLog®, without significantly affecting the time to peak concentration or total bioavailability of NovoLog®. If NovoLog® is mixed with NPH human insulin, NovoLog® should be drawn into the syringe first, and the mixture should be injected immediately after mixing. The efficacy and safety of mixing NovoLog® with insulin preparations produced by other manufacturers have not been studied. Insulin mixtures should not be administered intravenously. **Continuous Subcutaneous Insulin Infusion by External Pump: When used in an external subcutaneous insulin infusion pump, NovoLog® should not be mixed with any other insulin or diluent.** When using NovoLog® in an external insulin pump, the NovoLog®-specific information should be followed (e.g., in-use time, frequency of changing infusion sets) because NovoLog®-specific information may differ from general pump manual instructions. Pump or infusion set malfunctions or insulin degradation can lead to a rapid onset of hyperglycemia and ketosis because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required [*see Warnings and Precautions*]. NovoLog® should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog® that will be used in a pump should not be mixed with other insulin or with a diluent** [*see Warnings and Precautions*].

ADVERSE REACTIONS: ***Clinical Trial Experience:*** Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. *Hypoglycemia:* Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog® [*see Warnings and Precautions*]. *Insulin initiation and glucose control intensification:* Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy. *Lipodystrophy:* Long-term use of insulin, including NovoLog®, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. *Weight gain:* Weight gain can occur with some insulin therapies, including NovoLog®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria. *Peripheral Edema:* Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. *Frequencies of adverse drug reactions:* The frequencies of adverse drug reactions during NovoLog® clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (Adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

	NovoLog® + NPH N= 596		Human Regular Insulin + NPH N= 286	
Preferred Term	**N**	**(%)**	**N**	**(%)**
Hypoglycemia*	448	75%	205	72%
Headache	70	12%	28	10%
Injury accidental	65	11%	29	10%
Nausea	43	7%	13	5%
Diarrhea	28	5%	9	3%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL with or without symptoms.

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (except for hypoglycemia, adverse events with frequency ≥ 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

	NovoLog® + NPH N= 91		Human Regular Insulin + NPH N= 91	
	N	**(%)**	**N**	**(%)**
Hypoglycemia*	25	27%	33	36%
Hyporeflexia	10	11%	6	7%
Onychomycosis	9	10%	5	5%
Sensory disturbance	8	9%	6	7%
Urinary tract infection	7	8%	6	7%
Chest pain	5	5%	3	3%
Headache	5	5%	3	3%
Skin disorder	5	5%	2	2%
Abdominal pain	5	5%	1	1%
Sinusitis	5	5%	1	1%

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms.

Postmarketing Data: The following additional adverse reactions have been identified during postapproval use of NovoLog®. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Medication errors in which other insulins have been accidentally substituted for NovoLog® have been identified during postapproval use.

OVERDOSAGE: Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

More detailed information is available on request.

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