Idiopathic Pulmonary Fibrosis: The Role of Pathobiology in Making a Definitive Diagnosis

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Idiopathic Pulmonary Fibrosis: A Challenging Disease

Interstitial lung disease is characterized by diffuse fibrosis and scarring of the interstitium—the lace-like network of tissue that extends around the air sacs of the lungs.[1] Idiopathic pulmonary fibrosis (IPF) is one of the most common interstitial lung diseases, with an increasing prevalence and high mortality.[2,3] IPF has a histopathological pattern of usual interstitial pneumonia (UIP), but, as its name suggests, is of unknown etiology.[3] It is a chronic, progressive disease characterized by fibrosis and worsening dyspnea and lung function.[1] IPF is a complex disease that is challenging to diagnose and manage due to its nonspecific respiratory symptoms, unknown cause, need to exclude alternative diagnoses, varied clinical course punctuated by episodes of acute exacerbations, and an array of associated comorbidities.[3]

Epidemiology: Incidence and Mortality on the Rise?

The exact incidence or prevalence of IPF is unknown. The complexity of the diagnosis, variability in course, and evolving definition of the disease have made it difficult to conduct large-scale studies of the incidence or prevalence of IPF in the United States.[3] However, a variety of population-based cohort studies have estimated the prevalence to range from 14 to 42.7 cases per 100,000 individuals, using narrow and broad-based criteria to define IPF, respectively. The annual incidence of IPF is estimated at 6.8 and 16.3 per 100,000 people, using narrow and broad-based definitions, respectively.[4] These numbers have doubled over the past 3 decades.[3]

IPF primarily affects middle-aged to older adults.[1,2] In the Medicare population, the annual prevalence of IPF has increased steadily, from 202.2 cases per 100,000 individuals in 2001 to 494.5 cases per 100,000 individuals in 2011.[5] The majority of patients have a history of cigarette smoking.[1] Among newly diagnosed patients with Medicare, the majority were white (91%) and female (54%).

Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease of unknown etiology characterized by fibrosis of the interstitium, resulting in progressive respiratory insufficiency and shortened lifespan. Treatment focus tends to shift from disease-centered to symptom-centered as the disease progresses. Over the years, a number of pharmacologic strategies have been used to treat IPF, albeit without solid evidence demonstrating a beneficial impact on the disease course. The previously held theory that inflammation was the predominant underlying feature of IPF led to the use of corticosteroids and immunosuppressive therapy as the standard of care. However, a greater understanding of the pathogenesis of IPF has evolved and guidelines were developed using evidence-based criteria. Guided by the data, treatment guidelines developed in 2011 stated that no pharmacologic therapy showed a proven benefit for patients with IPF and issued recommendations against the use of most treatments. The treatment landscape changed in October 2014, when the FDA approved pirfenidone and nintedanib for the treatment of IPF. For the first time, clinicians have therapeutic options with demonstrated clinical efficacy to treat patients with IPF. To provide effective high-value care for patients with IPF, healthcare professionals require thorough knowledge and awareness about these medications, including their safety concerns.

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However, male sex was associated with a higher incidence of the disease and a shorter survival time after diagnosis.[5]

IPF is a progressive disease. Progression, however, is highly variable: most patients continue for years with a steady but gradual decline in lung function, while a minority stabilize or undergo a period of rapid decline. Some experience an acute exacerbation—a period of acute deterioration in respiratory function without a known cause or origin. IPF is typically fatal, with median survival estimated to be between 3 and 5 years after diagnosis.[6] Death rates are estimated at 61.2 deaths/million and 54.5 deaths/million for men and women, respectively.[7] Mortality, which increases with age, is consistently higher in men than women, and undergoes seasonal variation, even upon exclusion of infectious causes.[8] Evidence suggests that the incidence of IPF and its associated mortality are increasing, partly as a result of the aging population, and also because of an increased awareness of the disease among patients and physicians, as well as an improved ability to diagnose IPF.[7,9,10]

Pathobiology

The pathogenesis of IPF is complex. The driving force behind disease progression is hypothesized to be the loss of cellular integrity in the alveolar epithelium, which results from a combination of factors that include injury, aging, genetic and epigenetic influences, and reactivation of developmental signaling pathways.[8,11] The distortion of the lung's architecture results in vascular remodeling, decreased oxygenation, respiratory failure, and, ultimately, death.[8]

The hallmark histopathologic feature of IPF is a heterogeneous, variegated appearance of the lungs, with alternating areas of healthy lung tissue adjacent to areas of fibrosis, with foci of fibroblastic activity (fibroblastic focus) and remodeled lung architecture manifested by the presence of honeycomb changes (cystic spaces surrounded by fibrous thickened walls that replace the normal lacelike structure of lung parenchyma) and scant interstitial inflammation.[12] These changes are thought to occur due to a relentless fibrotic process itself resulting from an inflammatory response or an epithelial/mesenchymal (fibroblastic) disorder that propels disease progression.[13,14] The currently accepted paradigm is that unknown endogenous or environmental stimuli disrupt the homeostasis of the alveolar epithelial cells that line most of the lung surface. When the lung is damaged, a key component of normal healing is to reestablish the epithelium. In IPF, there is excess epithelial cell apoptosis, while fibroblasts develop resistance to apoptosis, causing fibroproliferation. The damaged areas are repopulated by fibroblasts instead of epithelial cells, and these fibroblasts differentiate into myofibroblasts and secrete matrix proteins and collagen, leading to fibrosis.[12,13]

Another perspective on the pathophysiology of IPF also leads away from the thought that inflammation progressing to fibrosis is a key driver in IPF. IPF has been described as a neoproliferative, neoplastic disorder of the lung. This hypothesis is based on similarities in the pathogenicity of IPF and cancer, including genetic alterations, uncontrolled proliferation, resistance to apoptosis, tissue invasion by myofibroblasts, and altered cellular communications and intracellular signaling pathways.[14] The presence of cytogenetic alterations related to carcinogenesis have been demonstrated in patients with IPF, including the presence of a mutated *p53* gene, a tumor suppressor gene involved in apoptosis and cell proliferation, and the fragile histidine triad gene.[14-17] Even intracellular signaling pathways, such as Wnt/beta-catenin and the phosphatidylinositol 3-kinase/protein kinase B pathways crucial in the pathogenesis of cancer, are prominent in IPF.[14] If the similarities between the pathogenesis of IPF and cancer translate into a link between these diseases, it may provide researchers greater insight into the etiology of IPF, alter the treatment options and management strategies currently used in IPF, and improve the prognosis of patients with IPF.

Risk Factors

Despite its unknown etiology, there are a number of known risk factors associated with IPF. The most widely accepted is cigarette smoking, which increases the risk of IPF by approximately 2-fold.[18] Smoking is considered a major risk factor in patients regardless of genetic or familial factors, particularly in those with a history of more than 20 pack-years.[1] Other risk factors include occupational exposure (agriculture/farming, hairdressing, and textile manufacturing) and environmental exposure to contaminants, including textiles, coal dust, stone, and sand.[1,3,19] Metal dust (specifically brass, lead, and steel dust) and wood dust (pine) are also associated with IPF. Autopsy reports have also shown that patients with IPF had higher levels of inorganic particles, such as silicon and aluminum, in their hilar lymph nodes compared with controls.[1,19,20]

Epidemiologic study results show the prevalence of IPF is greater in industrialized regions versus rural regions within a nation.[21] Exposure to microbial agents and viral infections, particularly chronic viral infections with the Epstein-Barr virus and hepatitis C, is thought to

be associated with an increased risk of IPF. Due to the confounding factor of patients receiving immunosuppressive therapy, however, definitive conclusions cannot be made, making infection a potential complication of therapy rather than a factor in the presence of IPF.[1,19]

There is also increasing evidence for a genetic basis for IPF, with family history often indicating increased risk.[1,19] Although familial forms of IPF account for less than 5% of total patients with IPF, genetic studies have proven to be insightful when it comes to the pathogenesis of the disease.[1] Additionally, the presence of comorbid conditions, such as gastroesophageal reflux disease (GERD) (via microaspiration) and diabetes, may be considered risk factors for IPF.[1,3] Identification of risk factors and an early diagnosis is critical in developing prevention strategies and prompt treatment initiation.

Diagnosis

The clinical symptoms of IPF, which are cough and dyspnea, are nonspecific and could be readily attributed to other pulmonary diseases. IPF's histologic pattern, although currently defined as UIP, was previously often grouped with diseases now considered separate entities (nonspecific pneumonia and desquamative interstitial pneumonia). As a result, IPF may have been misdiagnosed as nonspecific interstitial pneumonia or desquamative interstitial pneumonia.[3] Accurate diagnosis involves a combination of clinical, laboratory, radiologic and/or pathologic data obtained from physical examination, laboratory (exclusionary serologic findings) testing, and diagnostic imaging.[6] A multidisciplinary approach with close collaboration among an array of health care professionals (ie, clinicians, radiologists, and pathologists) increases the accuracy of diagnosis.

Clinical Presentation

Evidence-based guidelines suggest that any patient presenting with unexplained chronic exertional dyspnea, cough, bibasilar inspiratory crackles, and finger clubbing be considered for the possible diagnosis of IPF.[1] The most common signs and symptoms include shortness of breath, with breathlessness during exercise, initially and at rest later in the course of the disease, and uncontrolled bouts of a constant dry, hacking cough.[2] Other signs and symptoms that may develop as the disease progresses include rapid and shallow breathing, gradual but unintended weight loss, fatigue or malaise, muscle aches, and clubbing of the fingers or toes. Progression of IPF has been associated with collapsed lung, lung infections, blood clots in the lungs, lung cancer, respiratory failure, pulmonary hypertension (PH), and heart failure.[2] However, around 5% of patients have no symptoms. Other diseases, especially collagen vascular disorders, may have similar pulmonary radiographic and histologic pictures that may precede the rheumatologic manifestations of these diseases, further complicating the diagnosis. The importance of performing serologic testing and eliminating alternative underlying diagnoses cannot be overemphasized.[4] Combined with the progressive nature of the disease, these factors can make it extremely challenging to obtain a definitive diagnosis of IPF[4] without the help of a multidisciplinary team.

Diagnostic Criteria

The clinical presentation of IPF is nonspecific and broad. The evaluation of a patient suspected of having IPF begins with the exclusion of other known causes. This includes a careful physical examination and a thorough individual and family history. Evaluations should focus on comorbidities, medication use, and occupational, avocational, and environmental exposures.[1,2]

Diagnostic tests include a chest x-ray, CT scan of chest along with a variety of lung function tests, such as spirometry, lung volume and diffusing capacity, pulse oximetry, the 6-minute walk test, a skin test to rule out tuberculosis, exercise testing, an electrocardiogram, and blood levels of oxygen and carbon dioxide (arterial blood gas test).[2]

Although no specific blood tests exist to help diagnose IPF, certain markers or serologic tests have been recommended to exclude connective tissue diseases that may have a similar presentation. Based on symptomatology and physical exam findings, the latter may include an expanded panel of rheumatologic markers to further establish an accurate diagnosis. Bronchoalveolar lavage cellular analysis and transbronchial lung biopsy are not helpful in establishing a diagnosis of IPF due to the small size of specimen, but may be useful in excluding other diagnoses. A surgical lung biopsy is more definitive in establishing the histologic pattern of UIP to support the diagnosis of IPF or an alternative diagnosis.[1,2] Not all patients are candidates for surgical biopsies due to limited reserve or increased morbidity. However, making a definitive diagnosis of IPF requires confirmation of the presence of a UIP pattern on high-resolution computed tomography (HRCT) in patients who do not undergo a surgical lung biopsy (see **Table 1**[1]) or specific combinations of HRCT and surgical lung biopsy patterns (see **Table 2**[1]) in patients who undergo a surgical lung biopsy (see **Table 3**[1]).[1]

Table 1. HRCT Criteria for UIP Pattern[1]

UIP Pattern	Possible UIP Pattern	Inconsistent With UIP Pattern
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis ***and*** • Absence of features listed as inconsistent with UIP pattern (see third column)	• Subpleural, basal predominance • Reticular abnormality ***and*** • Absence of features listed as inconsistent with UIP pattern (see third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent greater than reticular abnormality) • Profuse bilateral micronodules (predominantly upper lobes) • Discrete multiple, bilateral cysts, away from areas of honeycombing • Diffuse, bilateral mosaic attenuation/air trapping in 3 or more lobes ***or*** • Consolidation in bronchopulmonary segment(s)/lobe(s)

HRCT indicates high-resolution computed tomography; UIP, usual interstitial pneumonia.

Histopathological criteria for a UIP pattern includes evidence of marked fibrosis or architectural distortion with or without honeycombing in a predominantly subpleural or paraseptal distribution, the presence of patchy involvement of lung parenchyma by fibrosis, the presence of fibroblast foci, and an absence of features against a diagnosis of UIP, suggesting an alternate diagnosis. Criteria suggesting an alternate diagnosis include hyaline membranes, organizing pneumonia, granulomas, marked interstitial inflammatory cell infiltrate away from areas of honeycombing, predominant airway-centered changes, or other features suggestive of an alternate diagnosis. However, the presence of hyaline membranes and organizing pneumonia may be associated with an acute exacerbation of IPF.[1] Confirmation of a UIP pattern using these criteria ensures that a differential diagnosis is limited to those that present with UIP in other clinical settings, such as connective tissue disease, chronic hypersensitivity pneumonitis, and pneumoconiosis.[1] In instances where a HRCT cannot confirm a diagnosis (see Table 2[1] for criteria inconsistent with a UIP pattern), a surgical lung biopsy is needed to ensure appropriate diagnosis.[1] In these instances, it is important to have a multidisciplinary discussion among experts in interstitial lung diseases that includes the potential for sampling error and re-evaluating the adequacy of the HRCT technique. The accurate diagnosis of IPF requires exclusion of diseases that may have similar radiographic and/or histologic patterns and may be treated differently. The multidisciplinary discussion enhances the accuracy of diagnosis and facilitates the initiation of appropriate therapy for IPF.[1]

Common Comorbidities

IPF is associated with a number of comorbidities that are responsible for a substantial proportion of morbidity and mortality. Among the most significant comorbidities is GERD, which is present in approximately 90% of patients with IPF; it is associated with a worsening or exacerbation of IPF.[22] Conversely, stabilization of pulmonary function and improved oxygen saturation levels have been demonstrated with the medical and surgical treatment of GERD. It has been suggested that more than 50% of patients with IPF have asymptomatic GERD.[22] Current guidelines recommend treating most patients with asymptomatic GERD.[1]

In patients with IPF evaluated for lung transplantation, more than one-third presented with PH at baseline. Over time, about 78% of patients who did not present with PH at baseline developed the condition. In addition, at the time of transplant, 86.4% of patients with IPF also had PH.[23] Concomitant PH tends to increase the incidence of dyspnea and impair exercise capacity.[6,24] Both of these, along with the diagnosis of PH itself, are known to increase risk of death within 2 years.[1]

Depression was observed in about a quarter of patients with IPF, and it is associated with increased dyspnea and pain, poor sleep quality, and reduced forced vital capacity (FVC).[25] Obstructive sleep apnea (OSA) was reported in up to 88% of patients with IPF, with 68% diagnosed with moderate to severe OSA. Because of the lack of strong

Table 2. Histopathological Criteria for UIP Pattern: Surgical Lung Biopsy[1]

UIP Pattern	Probable UIP Pattern	Possible UIP Pattern	Not a UIP Pattern
• Evidence of marked fibrosis/ architectural distortion with or without honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci ***and*** • Absence of features against a diagnosis of UIP, suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis/ architectural distortion with or without honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP, suggesting an alternate diagnosis (see fourth column) ***or*** • Honeycomb changes only[a]	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (see first column) ***and*** • Absence of features against a diagnosis of UIP, suggesting an alternate diagnosis (see fourth column)	• Hyaline membranes • Organizing pneumonia[b] • Granulomas[b] • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes ***or*** • Other features suggestive of an alternate diagnosis

HRCT indicates high-resolution computed tomography; UIP = usual interstitial pneumonia.
[a]An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.
[b]This scenario usually represents end-stage fibrotic lung disease in which honeycombed segments have been sampled, but where a pattern of UIP might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by preoperative targeting of biopsy sites away from these areas using HRCT.

screening tools for OSA in these patients, it is recommended that a formal sleep evaluation and polysomnography or nocturnal oximetry at least be considered in patients with IPF.[26]

In addition to these comorbidities, several others are seen with IPF. Patients with IPF have a 7-fold increase in the risk of developing lung cancer, with squamous cell carcinoma being most common.[27,28] The risk of developing lung cancer was independent of the contribution of cigarette smoking on the development of lung cancer or IPF.[28] Finally, venous thromboembolism occurs at an incidence 34% higher than in the general population[29] and should be considered in patients with IPF who have declining respiratory status. Other common comorbidities include pulmonary infection, bronchitis, asthma, heart disease (including heart failure, myocardial infarction, atrial fibrillation, and coronary artery disease), and cerebrovascular disease. The presence of comorbidities negatively impacts patient outcomes and quality of life. Comprehensive evaluation for these comorbidities and aggressive management of them may lead to improved outcomes in patients with IPF.

Disease Progression: Acute Exacerbations

Although most patients continue for years with a steady but gradual decline in lung function, some patients with IPF undergo a period of rapid decline or an acute exacerbation. Acute exacerbations can occur at any time, and it remains unclear if they are the result of a respiratory complication or an acceleration of the biological processes underlying IPF. The reported incidence of acute exacerbations varies, but it may be as high as 60%. Patients with acute exacerbations have an especially poor prognosis, with retrospective study results reporting mortality rates between 69% and 96% in patients in intensive care units.[30-33] The most commonly reported cause of death in patients with IPF is respiratory complications, usually due to an acute exacerbation.[34] The criteria for diagnosing an acute exacerbation are typically unexplained breathing difficulty within the previous month, impaired gas exchange, new alveolar infiltrates on HRCT, and no apparent explanation for worsening symptoms.[1]

Disease Progression: Risk of Mortality

There are a variety of suggestions proposed for staging IPF, most based on resting pulmonary function test measurements or the extent of radiologic abnormalities. The process is complicated due to the range of comorbidities associated with IPF and unpredictable acute exacerbations. Clinicians may find staging helpful in framing decisions regarding disease management and transplant timing.

Table 3. Diagnosing IPF Using a Combination of HRCT and Surgical Lung Biopsy[1]

		HRCT Pattern		
		UIP	**Possible UIP**	**Inconsistent With UIP**
Surgical Lung Biopsy Pattern (when performed)	UIP	Yes	Yes	Possible
	Probable UIP	Yes	Yes	No
	Possible UIP	Yes	Probable	No
	Nonclassifiable fibrosis[a]	Yes	Probable	No
	Not UIP	No	No	No

HRCT indicates high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.
[a]Nonclassifiable fibrosis: biopsy may reveal a pattern of fibrosis that does not meet the above criteria for a UIP pattern and the other idiopathic interstitial pneumonias.
Adapted from Raghu G, Collard H, Egan J, et al. *Am J Respir Crit Care Med.* 2011;183(6):788-824.

Identifying patients at risk of death within 2 years is critical in prioritizing patients for lung transplantation.[1] Currently, patients with IPF account for the largest proportion of patients on the lung transplant waiting list, with 46.1% classified as having restrictive lung disease (ie, IPF or re-transplants). Depending on the patient population, the country, and the era (before or after lung allocation score), a total of 14% to 67% of patients with IPF die while on the waiting list for a single or bilateral lung transplant.[35] Baseline factors associated with an increased risk of death in patients with IPF include greater levels of dyspnea, diffusion capacity for carbon monoxide (D_{LCO}) less than 40% predicted, oxygen desaturation of 88% or less during the 6-minute walk test, greater extent of honeycombing on HRCT, or PH.[1]

Longitudinal factors that increase the risk of death within 2 years include an increase in the level of dyspnea, a decreased FVC by at least 10% of absolute value, a decrease in D_{LCO} by at least 15% absolute value, or worsening of fibrosis on HRCT.[1] Physiologic parameters should be assessed at 3- to 6-month intervals.

Treatment of IPF

Once a diagnosis has been obtained, there are a number of management strategies that can be used; guidelines have also been developed to assist practitioners. Because IPF is a progressive disease, the goal of therapy is to improve the status of patients by slowing the progression of disease, managing comorbidities, and preventing acute exacerbations to optimize quality of life and increase survival. Management strategies are typically disease-centered (using pharmacologic and nonpharmacologic approaches to manage disease progression) or symptom-centered (palliative care that focuses on maximizing quality of life and reducing symptom burden from IPF or its comorbidities), with the latter increasing over time as IPF progresses.[1,36]

The recommendation is for patients to be considered for nonpharmacologic and pharmacologic therapies for IPF symptoms and treatment of comorbidities as soon as they are diagnosed, especially in cases of PH (challenging, as no approved pharmacologic therapy exists), OSA, and GERD. Currently, oxygen is the only modality recommended for the treatment of patients with PH who are hypoxemic at rest or with effort. Throughout the course of IPF, patients should be evaluated for their risk of death and suitability for a lung transplant. Lung transplantation remains the final treatment option over the course of the disease. However, not all patients are eligible for lung transplantation. In addition, even among those who undergo a transplant, median survival is only 4.5 years.[35]

The treatment guidelines for IPF were updated in 2015 to include the first 2 drugs approved for the treatment of IPF: pirfenidone and nintedanib.[37] Pirfenidone (Esbriet) is an approved antifibrotic and is an anti-inflammatory drug that has the potential to reduce the risk of disease progression by 30%.[38,39] In the pirfenidone group, compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC (P <.001).[40] Twenty-three percent of patients on pirfenidone had stable lung function, and pirfenidone reduced the decline in FVC by 193 mL compared with placebo.[41] A second drug, nintedanib (Ofev), is a small molecule tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor.[42] Nintedanib has demonstrated a

45% to 68% reduction in the annual rate of FVC decline compared with placebo,[42-44] as well as a significant reduction in the time to first acute exacerbation in patients with IPF (but only in 1 of 2 trials conducted in parallel).[42] Together, these results potentially indicate a slowing of IPF progression.[42] Both agents require close monitoring due to significant adverse events.

As a result of the varied course of IPF, the presence of comorbidities, the periods of acute exacerbations that may necessitate aggressive treatment, and the lack of updated treatment guidelines, there is no unified IPF treatment strategy. IPF management should continually evolve over the course of the disease in an effort to prevent disease progression and maximize quality of life and health status. Discussion with patients as to goals of therapy, expected benefits, and potential adverse effects and interventions to mitigate these are imperative before initiating treatment with specific therapeutic agents. It is essential, therefore, that all members of the healthcare team, from the primary care physicians to the pharmacy benefits managers, understand the course and evolution of the disease, the range of comorbidities, and the potential for acute exacerbations. All of these factors need to be assessed to develop a comprehensive and effective drug formulary for IPF and ensure a timely shift in management strategy to counter any adverse events or worsening of symptoms. Furthermore, there is a significant potential for drug interactions with increasing polypharmacy as treatment evolves and comorbidities appear. Through drug utilization reviews, prescriptions should be monitored to ensure that old medications that are no longer needed or do not appear to be effective will not continue to be used in error; in addition healthcare professional should ensure compliance with medications to promote optimal well-being.

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