

Dutch report, only 54% were actively employed. In general, the North American survey group seemed to be less socially affected by the disease than the earlier Dutch group. Although 52% did report experiencing some sort of social or financial effect of the disease, this was much less than in the Netherlands. The most frequent social complaints were nervousness when traveling, loss of self confidence, loss of social life, and the inability to accomplish tasks at home.

CONCLUSION

Analysis of the data showed that North American addisonians, with almost identical incidences of salt craving and hyperpigmentation as their Dutch counterparts, were better able to receive a diagnosis in a shorter period of time. This suggests that there is a greater degree of clinical suspicion of Addison's disease by North American primary physicians when the classic signs and symptoms are present, and there is a greater ease of specialty referral here.

Perhaps the most startling statistic drawn from this survey was the 76.7% incidence of autoimmune thyroid disease in those with autoimmune Addison's disease. 69.6% had hypothyroidism and 7.1% had hyperthyroidism. This not only strengthens the argument that autoimmunity is the predominant cause of Addison's disease, it also proves that APS-2 specifically is the most common genetic factor in the etiology of Addison's disease. The incidence of thyroid disease in APS-2 is more common than previously thought. The family history data shows that there is a high incidence of genetic susceptibility to thyroid disease in the relatives of addisonians.

The North American population appears to be highly informed on the treatment of their condition, handling the many facets of replacement therapy with knowledge and competency. However, the current use of oral glucocorticoids produces blood levels of hydrocortisone that deviate above or below the normal blood levels for significant portions of the day. The loss of normal automatic feedback between the adrenals and the pituitary contributes to the addisonians' complaints of fatigue. Our survey showed that even with this issue, most survey respondents reported being able to work and were less socially affected by the disease than their Dutch counterparts.

ACKNOWLEDGMENTS

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NATIONAL ADRENAL DISEASES FOUNDATION

NORTH AMERICAN SURVEY

PAUL L. MARGULIES, MD

Medical Director

JOYCE MULLEN

Executive Director, 1994–1999

In 1997, the National Adrenal Diseases Foundation (NADF) conducted the first survey of individuals with Addison's disease residing in North America. This survey was initiated as a service to addisonians in an effort to bring about greater understanding of life with this rare adrenal disorder. What is a typical daily dose of replacement therapy? What can the newly diagnosed expect in terms of quality of life over the long term? Which symptoms and stresses are "common" with this disease? In an attempt to find answers to these questions, NADF conducted the North American Survey. This survey consisted of twenty-four multi-part questions covering diagnosis, symptoms, medication, family history, quality of life issues and factors affecting mental and physical well-being. The survey was distributed to NADF members via the newsletter and to the general public via the NADF Web site.

NADF modeled its survey after the report from the Dutch Addison Society entitled, "Addison Patients in the Netherlands." That study, begun in 1990, was based on 155 questionnaires, with 143 responding. Of those, 133 were reported to have Addison's disease. The Dutch attempted to have personal examinations of all the respondents: 93 were examined, and 91 were found to have definite Addison's disease. Their statistics were based on the answers and findings of these 91 individuals, and the report was published in two parts in 1993 and 1994.

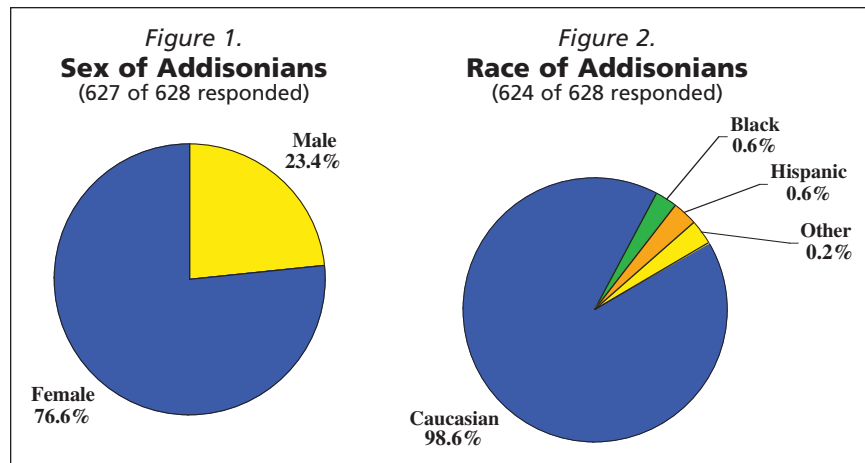
The NADF Survey received 700 responses; 665 of these individuals had Addison's disease. The responses were collected over several months. September 1, 1997 was used as a baseline for calculating the age of respondents and their age at diagnosis. Extensive statistical analysis of the survey results was performed. Some of the questions and answers proved to be unusable because some questions may have been too vague, or the answers (such as dosage of Florinef) too difficult for many of the respondents to answer precisely. Personal interviews and physical examinations were not feasible in this national survey, so all answers were presumed to be correct without direct confirmation. Some of the respondents left questions unanswered, so the denominator for the percentages for each question varies. Despite these

limitations, we believe the results of this survey provide a useful and fairly accurate view of the Addisonian population in North America.

GENERAL STATISTICS

SEX DISTRIBUTION:

Of 699 respondents, 23.7% were male and 76.3% were female. After excluding other adrenal diseases in the survey, leaving only the people identified as having Addison's disease, 23.4% were male and 76.6% were female [Figure 1].



RACE DISTRIBUTION:

Of 695 respondents, 98.3% were Caucasian, 0.6% Black, 0.6% Hispanic and 0.6% other. The Addison's respondents were virtually the same, with 98.6% Caucasian, 0.6% Black, 0.6% Hispanic and 0.2% other [Figure 2].

AGE OF ADDISON'S DISEASE RESPONDENTS:

There was a very even bell-shaped distribution of age of the respondents, with a peak in the 40-60-year age range [Figure 3].

AGE AT DIAGNOSIS FOR ADDISON'S DISEASE RESPONDENTS:

The age at diagnosis shifted toward the earlier years, with a peak in the 20-50-year age range [Figure 4].

and cortisone acetate over prednisone and dexamethasone is no different. The use of Florinef is similar. The doses of glucocorticoid and mineralocorticoid were also about the same in the two study groups. Because they were able to physically examine a significant number of their study participants, the Dutch Addison Society was able to look for any correlation between medication dosage and physical signs and persistent symptoms. They were unable to find any such association. They did complain that the availability of hydrocortisone in only the 20 mg. pill size limited the ability of their Addisonians to fine-tune their dosages. In North America, 10 and 20 mg. pills are more readily available. An interesting finding in the Dutch study was the high incidence of elevated plasma renin activity, suggesting that 37% of the Addisonians were under-replaced with Florinef. The North American population at least appears to be more informed about the need for treatment, with 95.5% indicating that they did know to take extra medication when acutely ill, and 89.9% wearing Medic Alert bracelets or necklaces, higher percentages than in the Dutch study.

Unfortunately, there is no cure for Addison's disease. Even when the diagnosis is made and replacement treatment with glucocorticoids and mineralocorticoids is begun, the therapy itself remains less than ideal. The use of hydrocortisone or any of the other glucocorticoids plus Florinef does not duplicate the normal adrenal physiology that existed before the onset of the disease. As pointed out in the Dutch study, the current use of oral glucocorticoids produces blood levels of hydrocortisone that deviate above or below the normal blood levels for significant portions of each day. With the loss of the normal automatic feedback between the adrenals and the pituitary, oral dosing for typical days, and especially for stressful days, can only roughly approximate the needs of the Addisonian individual. It is therefore not surprising that people with Addison's disease report that they often do not feel well despite their medication. Given a long list of possible symptoms, the Addisonian population in the North American survey listed 16 frequent complaints that continued to be a problem while on appropriate replacement medication. The subjective sense of fatigue topped the list. A tendency to gain weight was second, suggesting unhappiness with the effect that glucocorticoid replacement was having on weight control. Easy bruising, ranked sixth, was another symptom that may reflect frequent over-treatment. Most of the other prevalent complaints were non-specific, and some of them may reflect concurrent hypothyroidism or menopause. The only symptom in this list of frequent complaints that suggests under-treatment is salt craving, ranked fifth.

Addison's disease did not prevent most of the North American survey respondents from actively working. Only 13.3% replied that they were not able to work, with 69.2% working, 17.2% retired and 0.3% students. In the

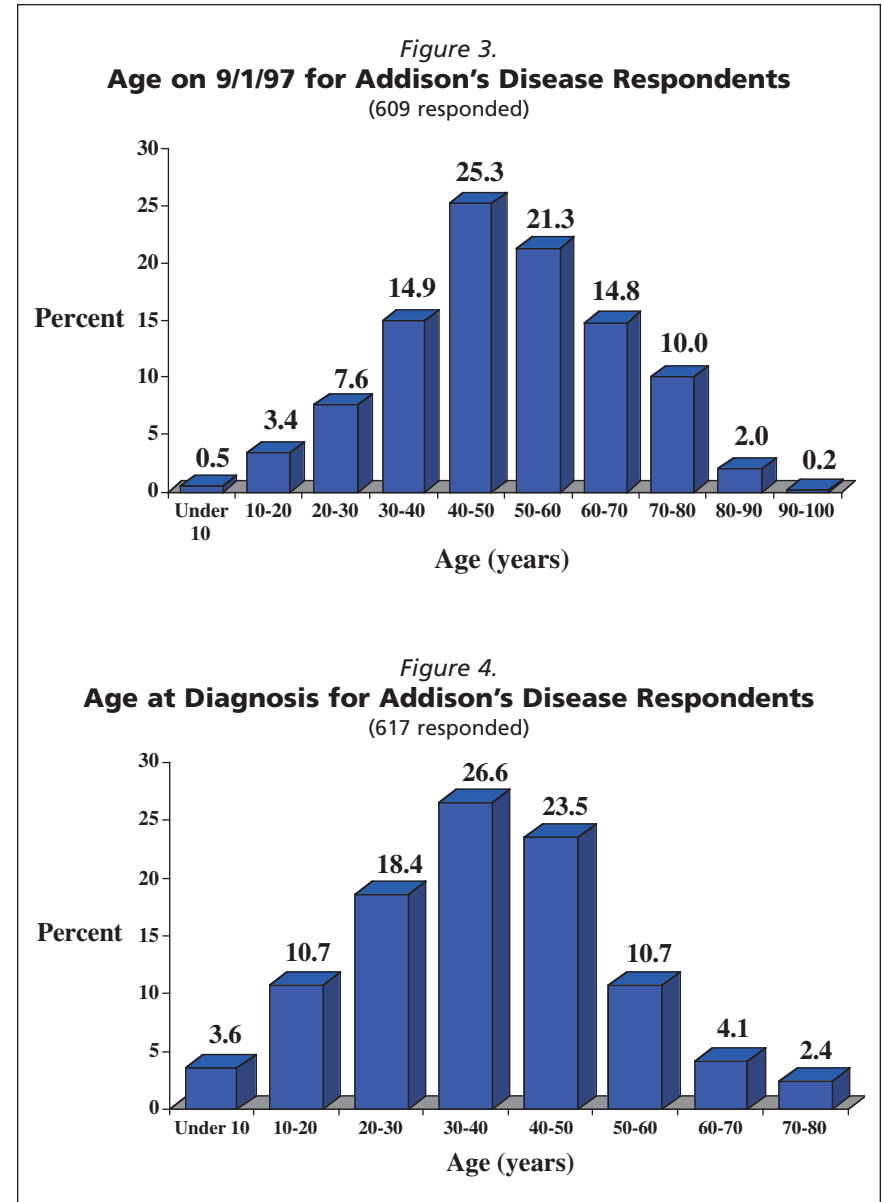
frequency of tuberculosis as a cause in the nineteenth century. As in the Dutch report, we found that the onset of the disease was most frequently in the 20- to 50-year age range. The sex ratio of 77% female to 23% male is slightly higher than the 66% female to 34% male balance in the Dutch report. However, this corresponds to the statistics published by the American Autoimmune & Related Diseases Association which indicate that autoimmune diseases, as a whole, affect women 3 times as often as men. Virtually all of our respondents were Caucasian, but the design of the survey does not permit any conclusions on race incidence in North America.

One striking difference between the Dutch report and our survey is in the ease of diagnosis. The Dutch found that on average it took 3 years from the onset of symptoms to the correct diagnosis. They concluded that this was due to the predominance of the use of general practitioners as the initial physician, and the lack of specificity of the presenting symptoms. They found that 99% of their addisonians complained of fatigue or weakness, but noted that as many as 97% also had hyperpigmentation, a very specific sign of Addison's disease. The other highly suggestive symptom, salt craving, occurred in 78% at presentation. In contrast, in our North American survey, 62.3% reported having the diagnosis made within the first year of symptoms.

The vast majority (80.6%) did need to see more than one doctor, and 34.5% required an endocrinologist to make the diagnosis. The incidence of hyperpigmentation in our population was only slightly lower, 89.2%, but the incidence of salt craving, 80.3%, was almost identical to the Dutch group. Indeed, the incidence of all the other presenting symptoms in the two groups is remarkably consistent. Therefore, the earlier diagnosis made in North America reflects a greater degree of clinical suspicion by the medical community and a greater ease of specialty referral, rather than any difference in the way the two groups present.

When the Dutch report was published, 47% of their Addison's disease population had at least one other autoimmune disorder, and the authors were surprised to find that as much as 20.5% had hypothyroidism. A significant observation in the North American survey is that a striking 76.7% had autoimmune thyroid disease, with 69.6% having hypothyroidism and 7.1% hyperthyroidism. The incidence of the other forms of autoimmune endocrine disease seen as part of the APS-2 family was also quite large. The incidence of autoimmune thyroid disease within APS-2 is simply more common than previously thought, and there may be some genetic differences between the Dutch population and the more heterogeneous North American group. The family history data reflects the individual statistics in showing a high incidence of genetic susceptibility to thyroid disease in these families.

The management of Addison's disease appears to be the same in North America as it is in the Netherlands. The predominant use of hydrocortisone

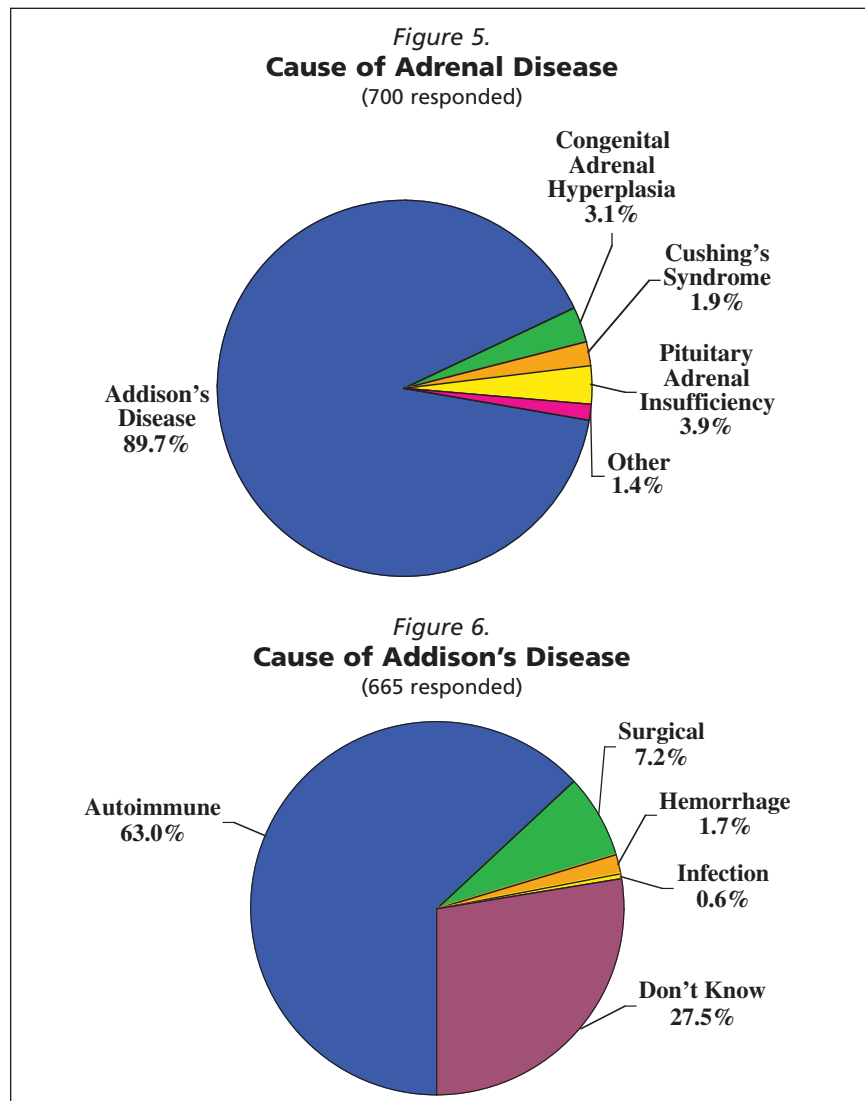


CAUSE OF ADRENAL DISEASE:

All 700 respondents answered this question. 89.7% indicated that they had Addison's disease (primary adrenal insufficiency), or 628 individuals [Figure 5].

CAUSE OF ADDISON'S DISEASE:

The cause of Addison's disease was 63.0% autoimmune, 7.2% surgical, 1.7% hemorrhage, 0.6% infection, and 27.5% did not know the cause [Figure 6]. 665 individuals answered this question, even though only 628 indicated that they had Addison's in the previous question. Using the larger figure, 418 individuals indicated that they had autoimmune Addison's disease. This denominator was used in calculating the associated autoimmune disease statistics and family history information.



were cited by at least 50% of the Addison's disease responders in the "sometimes" or "always" column. These most frequent current complaints are ranked in descending order. As with the symptoms enumerated at presentation of the Addison's disease, fatigue was the most common complaint in the currently treated population [Figure 27]. A tendency to gain weight was second, suggesting that difficulty with over-replacement of steroids causes a lot of concern. The only very specific symptom for Addison's disease to appear on this list of top complaints was salt cravings, ranked fifth.

SOCIAL ASPECTS

All respondents to the survey, regardless of the type of adrenal disease, were asked to indicate if they were experiencing difficulty in their social or financial life due to the disease. 52% replied yes, 48% no [Figure 28]. Those that answered yes were asked to check the type of problem they experienced from the following list: loss of self confidence, loss of social life, nervousness when traveling, nervousness when shopping, loss of reading/writing capacity, inability to work outside the home, inability to accomplish tasks at home, difficulty with relationships, fear of new experiences, and marital problems. None of these were cited by more than 30% of the respondents. The most frequent social complaints were nervousness when traveling, loss of self confidence, loss of social life, and inability to accomplish tasks at home [Figure 29]. When asked if they were able to work, 69.2% replied yes and 13.3% no; 17.2% were retired and 0.3% were students [Figure 30].

SUMMARY

This report presents the data collected in the first North American survey of Addison's disease. 700 individuals returned the completed survey questionnaire indicating that they had adrenal disease. Of these, 665 had Addison's disease. In the Dutch Addison Society report, 91% of the Addison's disease cases were autoimmune. In our survey, 63.0% listed autoimmune as the cause, with 7.2% surgical, 1.7% hemorrhage, and 0.6% infection. However, a large number of the respondents, 27.5%, did not know the cause of their Addison's disease. It is very likely that most of these would fit into the autoimmune category, but they were simply not informed adequately by their doctors about the etiology of their disease. Although it is impossible to conclude that the group would approach the 91% seen in the Dutch report, where each individual could be interviewed, it is clear that autoimmune Addison's disease is the predominant form seen today, in contrast to the

AUTOIMMUNE ADDISON'S DISEASE – ASSOCIATED CONDITIONS:

Figure 28.
Do You Feel You Have Experienced Difficulty in Your Social or Financial Life Due to Your Disease?

(681 responded)

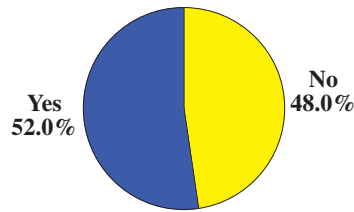


Figure 29.
If Yes, Indicate Whether Any of the Following Apply to You

(700 used as the denominator)

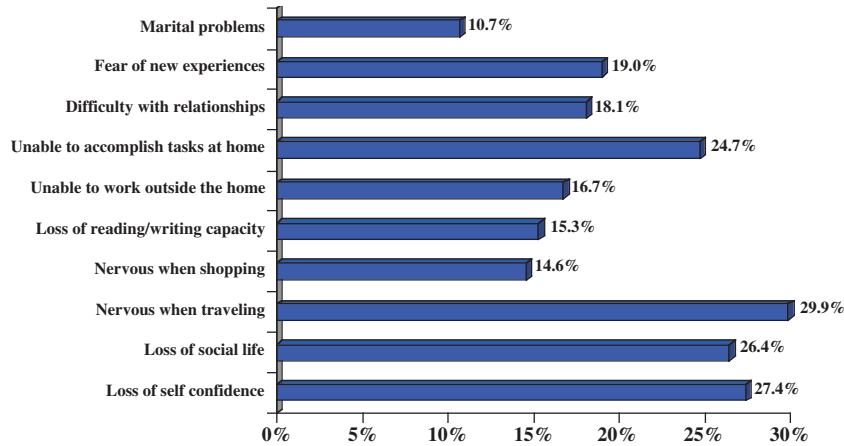
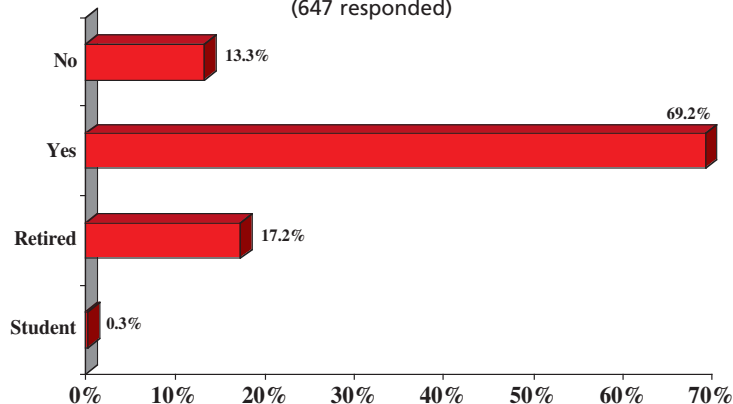


Figure 30.
Are You Able to Work?

(647 responded)



Autoimmune Addison's disease is usually a manifestation of a process that can affect other endocrine glands. In adults, the autoimmune polyglandular syndrome-2 (APS-2) is most common, with the other possible endocrine glands affected including the thyroid, pancreatic beta cells (producing juvenile or Type 1 diabetes mellitus), stomach cells that allow absorption of vitamin B12 (producing pernicious anemia), vitiligo from a loss of pigmented cells in the skin, and premature gonadal failure. Autoimmune Addison's disease can also be part of APS-1, a much less common syndrome presenting almost always in childhood, and including fungal infections of the tongue, skin and nails, hypoparathyroidism (causing low calcium levels), and failure of sexual maturation (primary hypogonadism). In the survey, we did not attempt to identify APS-1 or APS-2 individuals. Those with autoimmune Addison's disease were asked if they also had hypothyroidism, hyperthyroidism, Type-1 diabetes, pernicious anemia, hypoparathyroidism, primary gonadal failure (presenting as early menopause in our mostly female adult population) or vitiligo.

The results indicate a very large percentage with autoimmune thyroid disease. Those with hypothyroidism can be assumed to have Hashimoto's thyroiditis (autoimmune thyroid failure) and those with hyperthyroidism to have Graves' disease (autoimmune hyperthyroidism). The total with thyroid disease was 76.7%, 69.6% having hypothyroidism and 7.1% with hyperthyroidism. The other autoimmune disorders were much less common: 6.6% with Type-1 diabetes, 9.6% with pernicious anemia, 6.9% with hypoparathyroidism, 17.2% with primary gonadal failure, and 16.7% with vitiligo [Figure 7]. These figures suggest a very high incidence of APS-2 in the Addison's population. They also indicate a much higher incidence of autoimmune thyroid disease associated with Addison's disease than seen in the Dutch Addison Society study, where the incidence of hyperthyroidism was only 6.0% and hypothyroidism only 20.5%. Since the North American survey did not include a question on childhood fungal infections, it is difficult to estimate the number of individuals with APS-1.

FAMILY HISTORY:

Respondents who had autoimmune Addison's disease were asked to list family members who had autoimmune endocrine diseases. The first-degree relatives were separated out and grouped by sex. Many of the relatives had more than one endocrine disease and are listed more than once in the totals.

Figure 7.
Autoimmune Addison's Disease—
Associated Autoimmune Conditions
 (418 responders with autoimmune Addison's Disease)

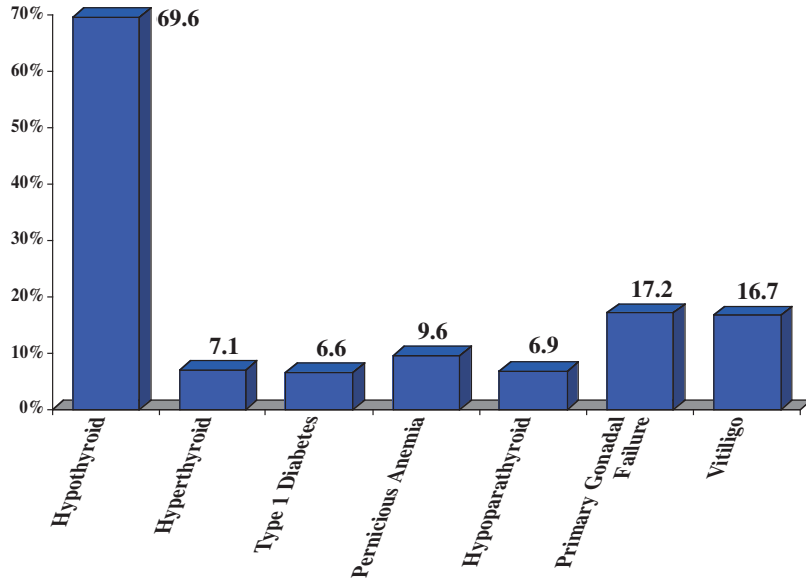


Figure 8.
First Degree Relatives with Autoimmune Diseases
 (Many had more than one and are listed more than once)

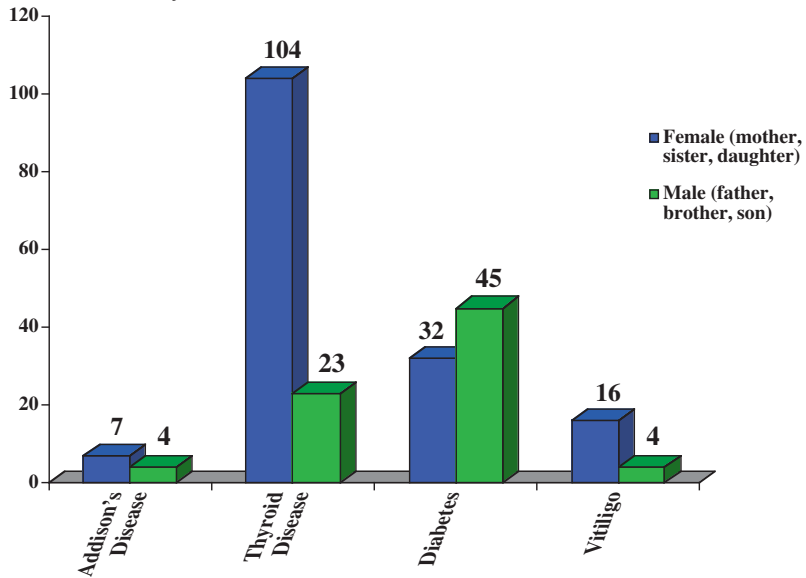
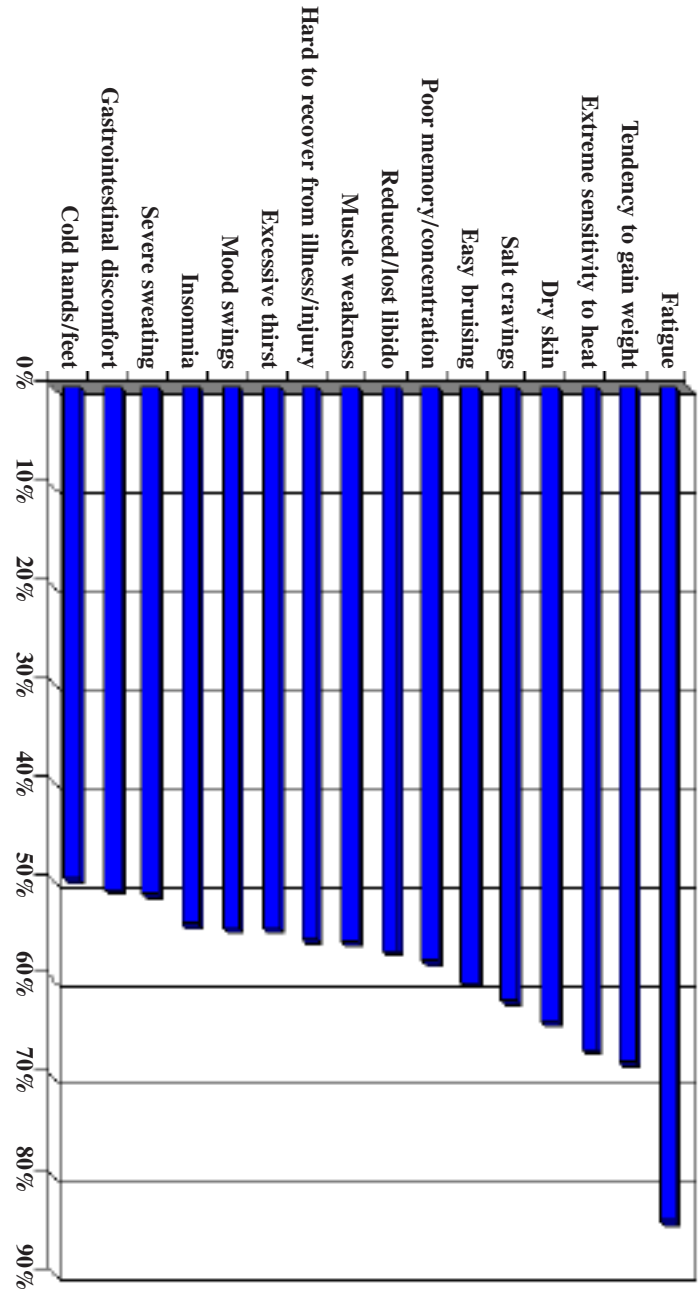
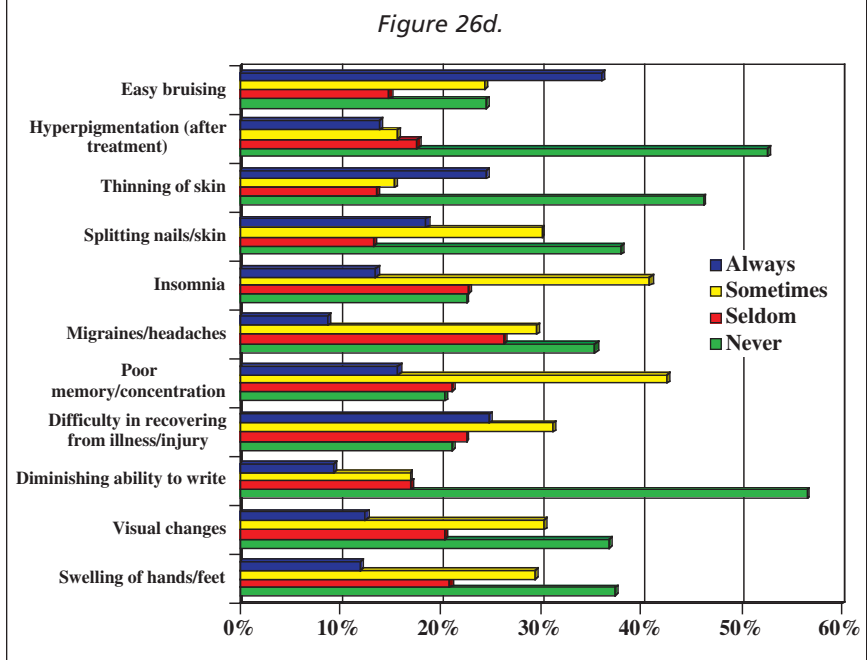
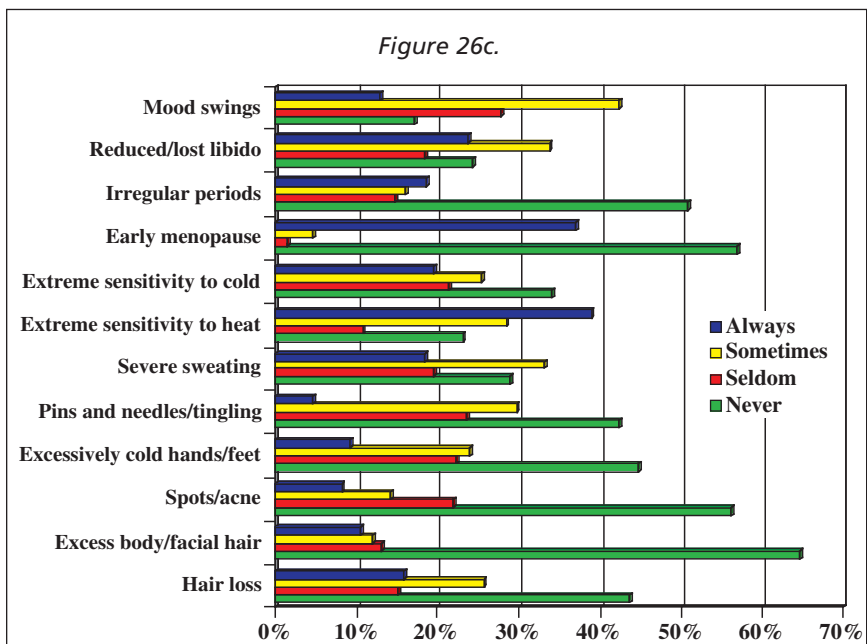


Figure 27.
Ranking of Those Symptoms That Were Listed as Present Sometimes or Always
at Least 50% of the Time



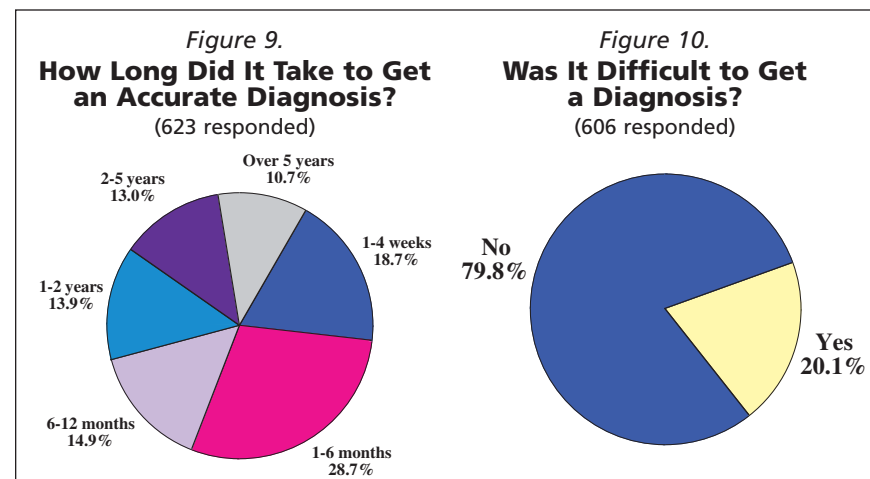


Percent incidence could not be calculated. Female first-degree relatives had more associated endocrine diseases than male relatives, with thyroid diseases predominating. From the high numbers listed with diabetes, we suspect that many respondents included relatives who actually had insulin-requiring Type-2 diabetes (adult onset) with those who had insulin-dependent Type-1 diabetes (juvenile onset) [Figure 8].

DIFFICULTY WITH DIAGNOSIS

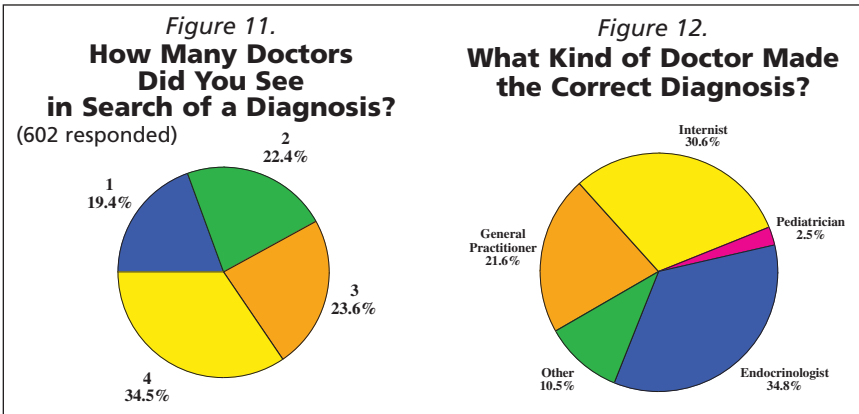
TIME TO DIAGNOSIS:

All Addison's disease respondents were asked how long it took to arrive at the diagnosis: 1-4 weeks for 18.7%, 1-6 months for 28.7%, 6-12 months for 14.9%, 1-2 years for 13.9%, 2-5 years for 13.0% and over 5 years for 10.7% [Figure 9]. When asked whether it was difficult to get the diagnosis of Addison's disease, only 20.1% replied yes, 79.8% no [Figure 10].



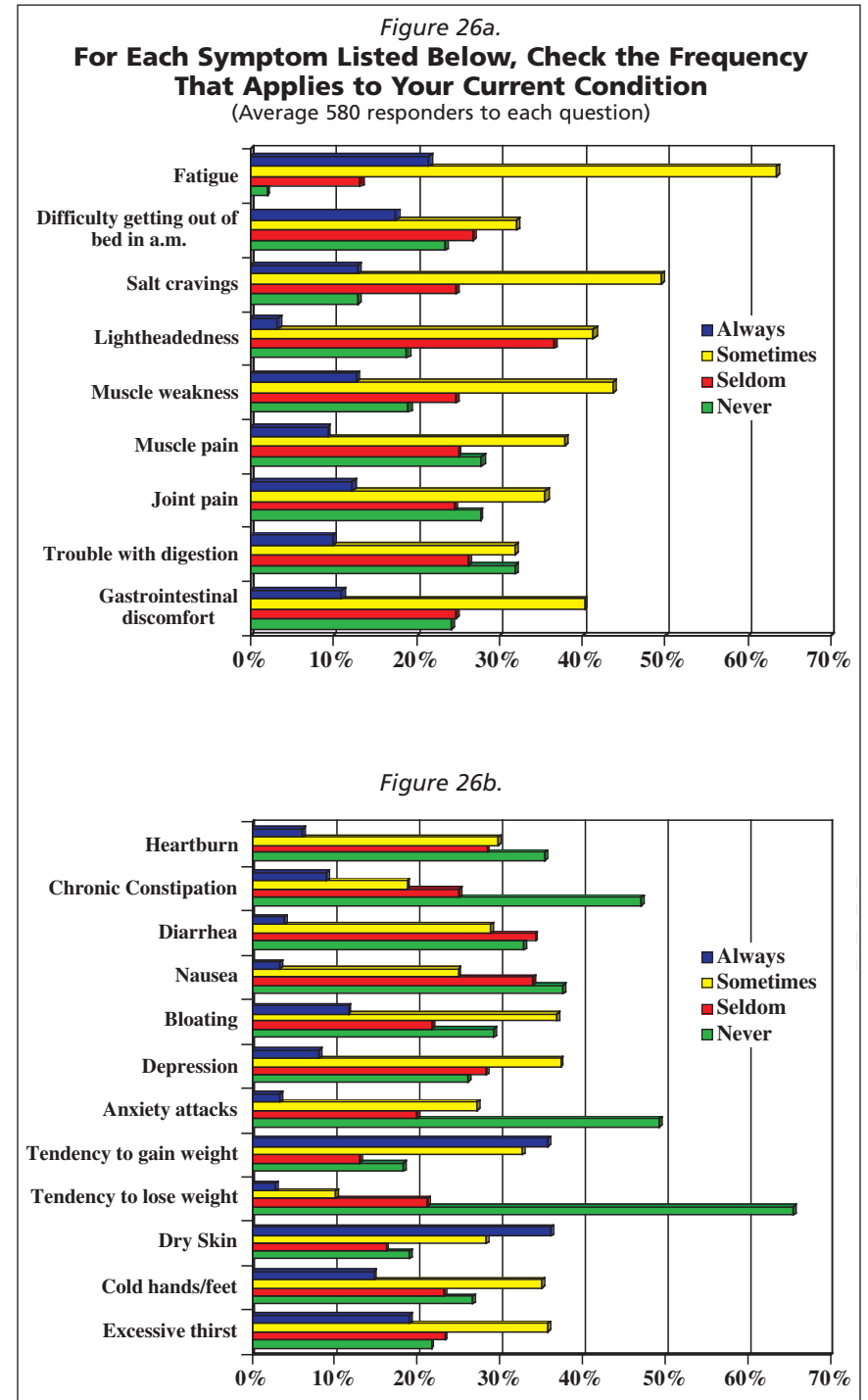
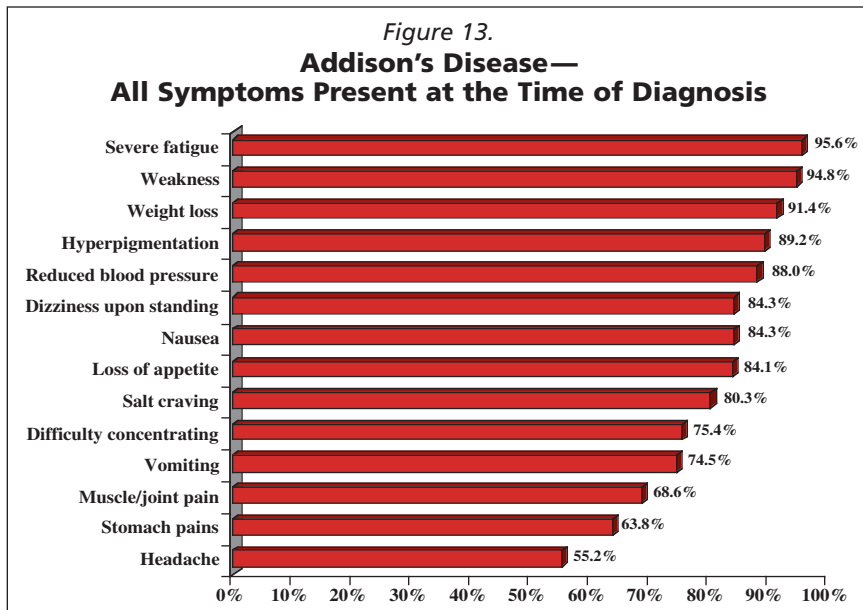
PHYSICIAN MAKING THE CORRECT DIAGNOSIS:

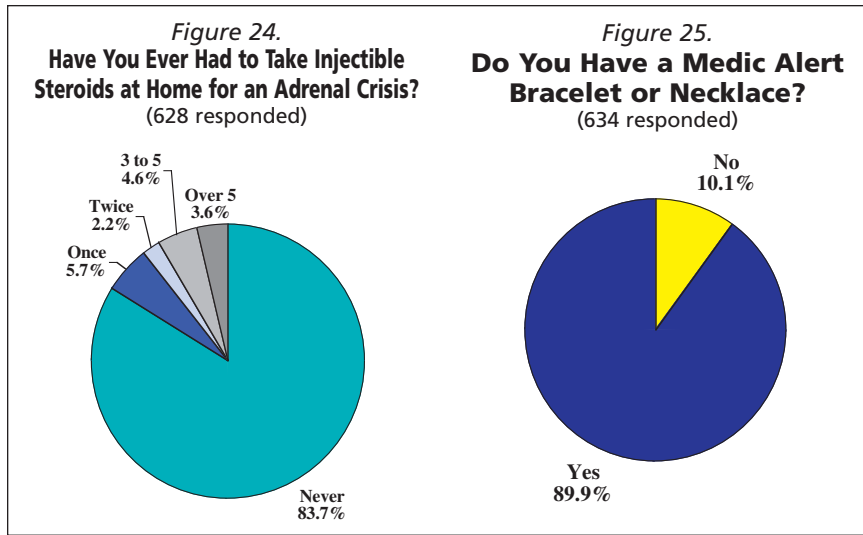
All Addison's disease respondents were asked how many doctors they had to see before the diagnosis was made, and what type of doctor made the correct diagnosis. For 19.4% it was one doctor, for 22.4% it was two, for 23.6% it was three, and for 34.5% it was four [Figure 11]. The type of doctor was a general practitioner for 21.6%, an internist for 30.6%, a pediatrician for 2.5%, an endocrinologist for 34.8%, and 10.5% other [Figure 12].



INITIAL PRESENTING COMPLAINTS:

All Addison's disease respondents were asked to check off which symptoms were present at the time of diagnosis from the following list: hyperpigmentation of skin and/or gums, severe fatigue, weakness, weight loss, salt craving, dizziness upon standing, loss of appetite, nausea, vomiting, stomach pains, muscle/joint pains, reduced blood pressure, headache, and difficulty concentrating. The totals were then ranked by incidence from 1 to 14 [Figure 13]. The vague complaints of severe fatigue, weakness and weight loss were





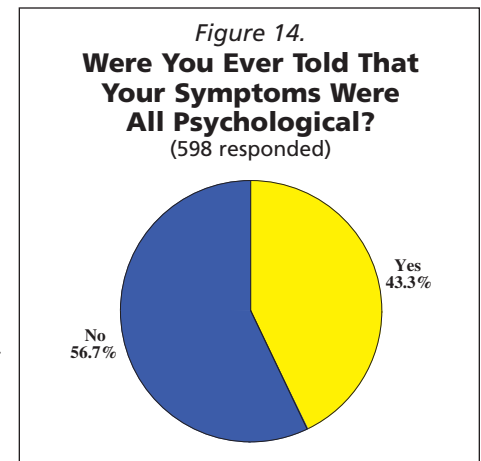
EMERGENCY MANAGEMENT:

Respondents were asked to check off how many times they had been to an emergency room or been admitted to a hospital for their Addison’s disease. 26.6% checked never; 27.7% once; 15.0% twice; 17.9% 3 to 5 times, and 12.8% over 5 times [Figure 22]. When asked if they take extra medication when acutely ill, 95.5% answered yes, only 4.5% no [Figure 23]. When asked the number of times they had to take injectible steroids at home for an adrenal crisis, 83.7% replied never, 5.7% once, and the remaining more than once [Figure 24]. Medic Alert bracelets or necklaces are worn by 89.9% of the respondents [Figure 25].

CURRENT CONDITION

All Addison’s disease respondents were asked to check off the frequency of symptoms that apply to their current condition. The list included all the symptoms enumerated at the presentation of the Addison’s disease, plus many more that would reflect their current well-being. Some of the symptoms were meant to be specific for Addison’s disease, and some were meant to be symptoms of other aspects of the autoimmune polyglandular syndromes. Respondents were asked to check if a symptom was occurring “always”, “sometimes”, “seldom”, or “never”. Many respondents skipped over some of the symptoms. The average number of responders to each symptom was 580 [Figures 26a-d]. Of the 44 symptoms listed, there were 16 symptoms that

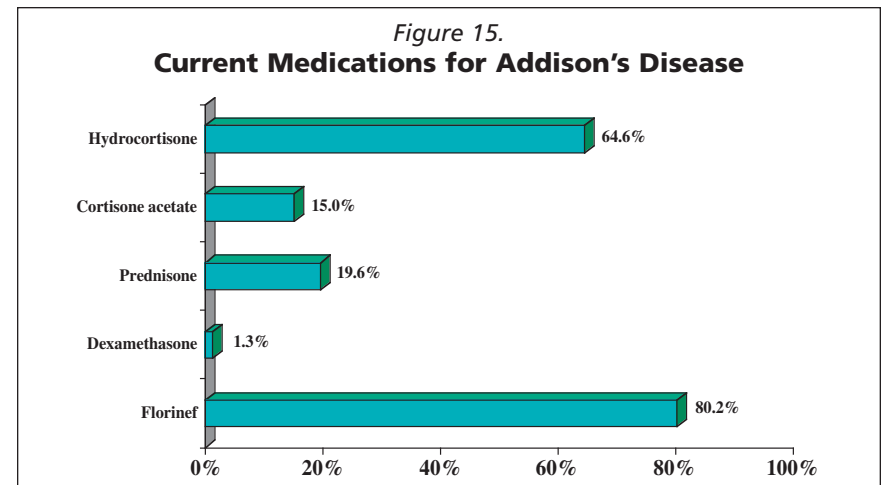
the most common, all above 90%. The more specific symptoms that might lead to the suspicion of the diagnosis of Addison’s disease were slightly less universal, but still very common: hyperpigmentation, reduced blood pressure, dizziness upon standing, nausea, loss of appetite, and salt craving all appeared more than 80% of the time. When asked if they were ever told that their symptoms were all psychological, 43.3 % replied yes, 56.7% no [Figure 14].

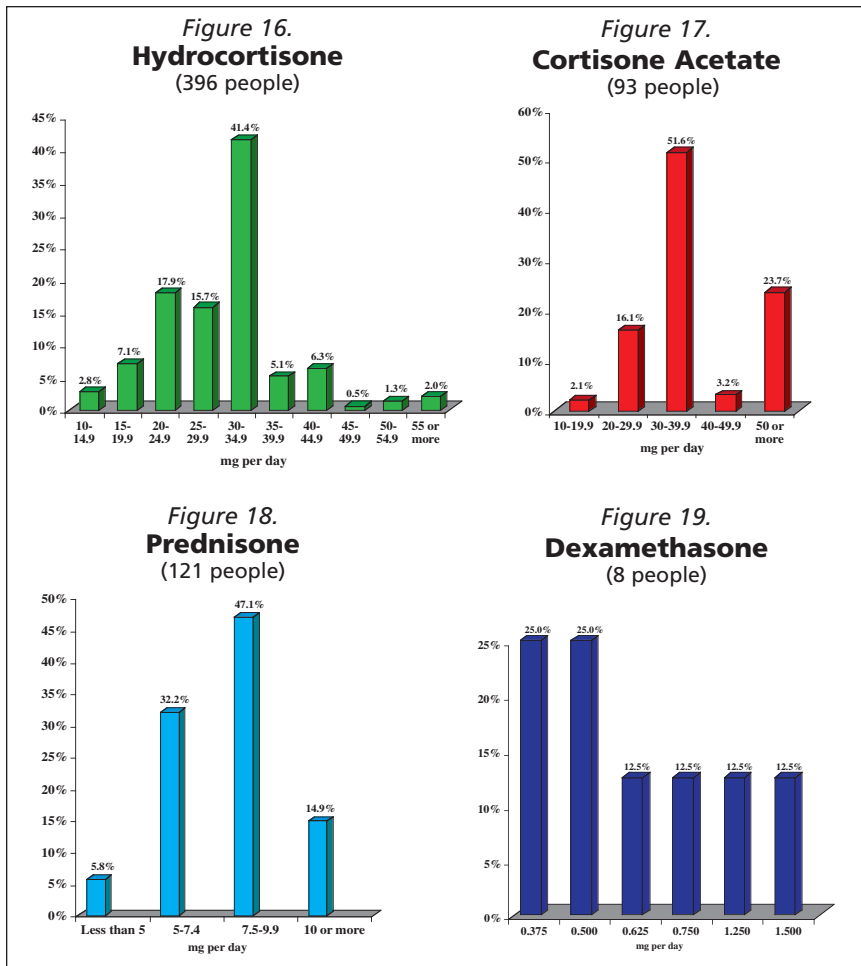


CURRENT TREATMENT

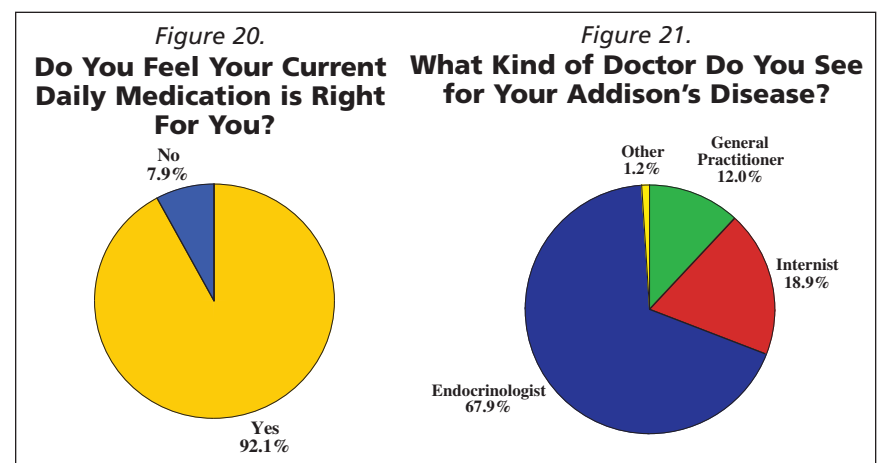
CURRENT MEDICATION:

All Addison’s disease respondents were asked to check off the medications they currently take from the following list: hydrocortisone, cortisone acetate, prednisone, dexamethasone (the glucocorticoids), and Florinef. They were then asked to indicate the dosage in milligrams of each medication taken as the first dose, second dose and third dose, with the time of day of each dose, plus the dose of Florinef, if used. The overwhelming majority,





64.6%, take hydrocortisone as their glucocorticoid. 15.0% use cortisone acetate, 19.6% use prednisone, and only 1.3% use dexamethasone. Florinef is also used by 80.2% of Addison's respondents [Figure 15]. The results on dosages were difficult to calculate by time of day because of the variability in the way the answers were written. However, the total dosage for each glucocorticoid per day indicates that most people with Addison's disease take a daily dosage near the textbook physiologic replacement dosage. For hydrocortisone, that is near 30 mg [Figure 16]. For cortisone acetate, that is near 37.5 mg [Figure 17]. For prednisone it is about 7.5 mg [Figure 18]. Only 8 individuals indicated that they use dexamethasone as their glucocorticoid, so the numbers in each dosage lack significance [Figure 19]. Unfortunately, there was much confusion over the decimal point placement in the milligram dosage of Florinef used. The only tablet made is the 0.1 mg pill, but many individuals listed daily doses of 1 and 2 mg by mistake. Therefore, an



accurate breakdown of the Florinef dosage for the Addison's population could not be calculated. When asked if they felt the current daily medication was right for them, 92.1% replied yes, with only 7.9% indicating no [Figure 20].

CURRENT DOCTOR:

Respondents were asked to check off which type of doctor they currently see for their Addison's disease. 67.9% see an endocrinologist, 18.9% see an internist, 12.0% see a general practitioner, and 1.2% some other type of doctor [Figure 21].

