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THE EFFECTS OF AMPHETAMINE PRETREATMENTS

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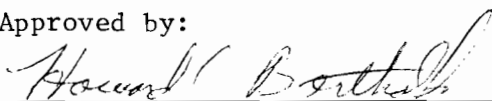
CHLORPROMAZINE INDUCED FOOD AVERSIONS

Kenneth Sibley

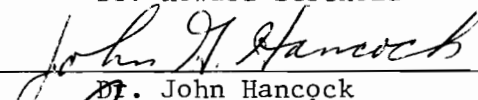
Lycoming College

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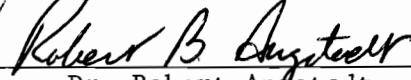
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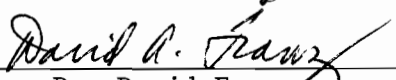
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This paper is divided into two sections. The first section, titled A Review of Some Current Monoaminergic Theories of Behavior, places special emphasis on theories of affective behavior. The second section, titled The Effects of Amphetamine Pretreatments on Chlorpromazine Induced Food Aversions, describes specific experiments examining the positively and negatively reinforcing aspects of shifts in affect resulting from injections of psychoactive drugs in rats.

A REVIEW OF SOME CURRENT MONOAMINERGIC
THEORIES OF BEHAVIOR

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The purpose of this paper is to review some current theories which attempt to explain how neurotransmitters influence behavior, with a particular focus on affective behavior. Most of these theories deal with the monoaminergic systems, since these neurotransmitters have been found to be the most relevant with regard to shifts in affect.

Emphasis will be given to describing several different theories, rather than giving a detailed account of the experimental support for each theory. However, enough experimental information will be given so that the origins of each theory can be understood.

The paper will begin with Jouvet's theory on the regulation of sleep. Following this will be the theories of minimal brain dysfunction, anxiety, aggression and depression. The last theories discussed will be on schizophrenia, since this disorder is a major focus of research.

As mentioned, the monoamine transmitters have been found to be most significant in the regulation of affective behavior. The monoamines can be divided into two groups; the indoleamines and the catecholamines. There are two brain catecholamine transmitters; dopamine and norepinephrine (also called noradrenaline). There is only one indoleamine transmitter; serotonin (or 5-hydroxytryptophan).

The primary goals of sleep research have been to determine the mechanisms involved in the induction of sleep

and to determine those mechanisms responsible for the alternation between slow wave and paradoxical sleep. Michel Jouvet has done much of the work in elucidating these mechanisms.

Evidence indicated that serotonin was the neurotransmitter responsible for the induction of slow wave sleep. IP injections of the serotonin precursor 5-hydroxytryptophan lead to a state which resembled slow wave sleep in cats, and treatment with the serotonin synthesis inhibitor p-chlorophenylalanine lead to insomnia (Jouvet, 1969). The raphe nucleus of the brainstem appeared to be the area responsible for this effect, since the destruction of 80-90% of this serotonin rich nucleus lead to continuous insomnia in cats. The triggering of paradoxical sleep is not as clearly understood, since pharmacological experiments indicate that acetylcholine, norepinephrine and a deaminated serotonin metabolite must all be present for paradoxical sleep to occur. However, bilateral lesioning of the locus coeruleus totally suppresses paradoxical sleep without altering slow wave sleep, suggesting that this noradrenergic area is at least one area required for the initiation of paradoxical sleep.

More recently, the hippocampus has been postulated as a subsidiary regulatory area in the sleep-wakefulness cycle. The hippocampus is unusual in that, while the rest of the brain is exhibiting a desynchronized EEG during paradoxical sleep, the hippocampus is displaying a 4 to 7 cycles per second wave called the theta rhythm.

In an experiment designed to test chemical changes in the hippocampus, Kovacevic and Radulovacki (1976) ablated the left hemisphere of cats after 20 minutes of slow wave sleep and analyzed specific brain areas for chemical changes which had occurred during sleep. A 143% increase in serotonin, a 289% increase in 5-hydroxyindoleacetic acid -- a catabolic product of serotonin -- and a 178% increase in dopamine was observed in the hippocampus. Kovacevic and Radulovacki proposed that this data, along with data from lesion studies, indicates a role for the hippocampus in the facilitation of both slow wave and paradoxical sleep. Perhaps this is the source of the deaminated serotonin catabolite Jouvett indicates as necessary in the triggering of paradoxical sleep.

Minimal brain dysfunction, or preadolescent hyperkinesis, is an intriguing behavior because it can be treated with the catecholamine agonist d-amphetamine, seemingly giving the opposite effect expected. However, an animal model for this behavior has recently been developed which tentatively accounts for this paradox.

Alpern and Greer (1977) selected long sleep and short sleep strains of mice as similar to normal and hyperkinetic populations. Neural excitability for these mice was determined by measuring the time to onset of flurothyl induced myoclonus. As expected, amphetamine treatments were found to reduce the neural excitability of immature short sleep mice and increase the neural excitability of immature long sleep mice. The amphetamine treatment increased neural excitability

in adults of both strains. A second experiment with the specific dopamine agonist apomorphine and the specific nor-epinephrine agonist clonidine was done in order to pinpoint the mode of action of d-amphetamine more precisely, since d-amphetamine is an agonist of both of these neurotransmitters. Results from this second experiment indicated that activation of the dopaminergic neurons was responsible for the decrease in neural excitability in immature short sleep mice, and that activation of noradrenergic neurons was responsible for the increase in neural excitability in all other cases.

What emerges is a model of preadolescent hyperkinesis where the noradrenergic system is relatively predominant over the dopaminergic system. Amphetamine ameliorates the symptoms by increasing the activity of the dopaminergic system, while further increases of the already overactive noradrenergic system are insignificant, possibly as the result of negative cooperativity between noradrenergic receptors. The symptoms appear to arise because the noradrenergic neurons mature before the dopaminergic neurons, and it is hypothesized that in some cases the development of the dopaminergic neurons may be excessively retarded (Kalat, 1976).

Anxiety is a complex state with both psychic and somatic components. Surprisingly, the locus coeruleus, mentioned as important in triggering paradoxical sleep, has been implicated as the area responsible for the heightened neural arousal resulting in anxiety. Lader (1974) particularly emphasizes the importance of the locus coeruleus in causing anxiety states.

The locus coeruleus sends noradrenergic neurons through the ascending reticular formation to the hypothalamus, cerebral cortex and cerebellar cortex. It appears to function as an arousal center, with overly high discharge rates resulting in anxiety. Studies have shown that stress causes an increased turnover of brain norepinephrine, and studies where animals were treated with catecholamine precursors also suggest that increases in catecholamines leads to anxiety states (Lader, 1974). Lader proposed the following model for the mechanisms behind psychic and somatic anxiety:

The perceptual analysis of the stimuli is presumed to take place in the association areas of the cortex, the arousal by corticofugal impulses which activate lower centers such as the locus coeruleus which in turn activate the entire cortex by noradrenergic neurons; the integration of the emotional response in behavioral and physiological terms takes place in the limbic system and hypothalamus. The peripheral changes are mediated by the autonomic system, in particular the beta-adrenoceptor system. Centrally acting anxiolytics mainly decrease arousal by inhibiting the noradrenergic neurons of ascending activating systems such as the locus coeruleus; peripheral anxiolytics block the beta-adrenoceptor system (Lader, 1974).

Lader's model is useful because it suggests a rationale for a treatment based on the observed symptoms. He admits that the model is speculative, but he is moving in the direction of a complete model, proposing both the relevant transmitters and the anatomical connections, which can easily be tested further.

Another theory of anxiety neurosis proceeds through an entirely different mechanism than that proposed by Lader. Pitts (1969) proposed that anxiety symptoms result from an increased flow of adrenalin, which increases the production

of lactate. It is proposed that lactate complexes calcium ions, thus interfering with the normal transmission of nerve impulses and producing the anxiety symptoms. Pitts had found that lactate infusions elicited some anxiety symptoms in control patients and anxiety attacks in a group of anxiety neurotics.

Pitts' theory is not completely incongruous with Lader's. In his paper Pitts emphasizes the somatic aspects of anxiety, comparing it with a state of extreme physical exertion. Pitts proposes that the anxiety neurosis may be treated with beta-adrenergic receptor blockers, which prevent adrenalin from increasing lactate production. Perhaps Pitts would interpret the psychic component of anxiety as a conditioned response, while Lader would interpret the effects of lactate as the next step in the mechanisms resulting in somatic anxiety. While Pitts has proposed a simpler theory, it does not give any insights into the central nervous system and does not account for the action of centrally active anxiolytic drugs.

Different models of aggressive behavior present a problem in interpretation because there are two different types of animal aggression; predatory and affective. Bernard (1975) characterizes predatory aggression as involving the ventral medial tegmentum, having no autonomic activation components and being inhibited by catecholamine agonists. Affective aggression is characterized as involving the brain central grey, having obvious autonomic activation components, being enhanced by catecholamine agonists

and inhibited by serotonin agonists. Bernard was interested in comparing three different models of aggression, shock-induced fighting, ranacide behavior and septal lesion induced hyperirritability, with the older theory that the catecholamines are the excitatory transmitters of the brain while serotonin is the inhibitory transmitter of the brain.

In Bernard's shock induced aggression study castrated rats were found to be less aggressive. It was found that the whole brain minus the hypothalamus of the castrate rats showed a great predominance of the catecholamines over serotonin. In the ranacide behavior experiment, the brains of those rats which were found to be frog "killers" also had a predominance of brain catecholamines over serotonin. These results are inconsistent with his original statement, since ranacide behavior is more predatory than affective. In the septal rat study, the opposite results were found. The septal rat brains showed increases in serotonin and decreases in norepinephrine when compared with sham operation controls. In his discussion of these results Bernard emphasizes that the old theories on the function of brain monoamines in aggression are obsolete. He emphasizes the need for precise definition of the behavior being studied before attempting to correlate the behavior with alterations in brain monoamines.

Research into the neurotransmitters involved in depression has implicated involvement of all three monoamines; dopamine, norepinephrine and serotonin. There are several different theories of depression, some dealing

specifically with one transmitter, while others deal with interacting systems. Tied to the models proposed for depression are often theories on manic behavior, which usually implicate chemical shifts to an opposite extreme. Blum et al. (1976) proposes two different models for depression; a catecholamine hypothesis and a serotonin hypothesis. Blum supports his catecholamine theory with pharmacological evidence showing that tricyclic antidepressants function by inhibiting the reuptake of norepinephrine from the synaptic cleft and that manic - depressive patients have a lower urinary excretion of norepinephrine and dopamine during the depressive state than at any other time. Blum supports the indoleamine hypothesis with post - mortem studies showing increases of serotonin in the brains of suicide victims and experiments where serotonin injections were used to induce hyperexcitability in rats. He emphasizes that these are two separate etiologies for depression, and makes the point that since a decrease in the availability of a neurotransmitter leads to an increased sensitivity of the receptor, patients can be characterized by either a heightened responsivity of the serotonin receptors or a heightened responsivity of the norepinephrine receptors. Vetulani and Sulser (1975) have similarly found that treatment with antidepressant drugs decreases the reactivity of the noradrenergic cyclic-AMP generating systems in the limbic forebrain of rats, since these receptors are then more constantly excited. Cyclic-AMP is generated when the norepinephrine receptor is activated by binding with norepinephrine, thus

it's production is a measure of receptor binding.

One neural area which has been implicated in the regulation of depression is, again, the locus coeruleus (Nyback et al., 1975). The tricyclic antidepressants function by inhibiting the reuptake of norepinephrine through the presynaptic membrane, making more norepinephrine available to the postsynaptic membrane and increasing the activity of this neuron. As a result, neuronal feedback mechanisms decrease the rate of firing of the presynaptic neurons in what normally would be a compensatory mechanism. This sort of inhibition by tricyclic antidepressants has been found in the cells of the locus coeruleus, which, based on its diverse anatomical connections, is a likely area for influencing depression.

The involvement of the serotonergic system has been supported in a study by Todrick and Tait (1974), who ranked antidepressant drugs and indicated that those drugs which are more sensitive to tests involving serotonin reuptake inhibition are the more effective antidepressants.

Reserpine has the ability to deplete brain serotonin, norepinephrine and dopamine. It had previously been thought that reserpine depression was the result of serotonin depletion in the brain, but studies with direct dopamine agonists such as apomorphine, which completely reverse the reserpine depression, indicate that dopamine is the transmitter involved in reserpine depression (Mennon, Clark and Masuoka, 1977). Based on these findings, the dopamine reversal test is frequently used to evaluate the dopaminergic potencies of

new drugs.

Recent studies have placed increasing emphasis on the importance of dopaminergic neurons in relation to depression. Randrup and Braestrup (1977) found that many of the newer antidepressants, such as butriptyline, maprotiline and ~~iprindole~~ have little effect on noradrenergic or serotonergic neurons. However, these drugs, as well as the classic tricyclic antidepressants, all inhibited the uptake of dopamine in crude striatal synaptosomes. Randrup et al. (1975) emphasizes that dopamine may be functioning in conjunction with norepinephrine and serotonin. Randrup believes that dopamine has been neglected in the study of monoamines and behavior, while in fact it plays a key role in all the major endogenous psychoses.

There has been a shift in emphasis from norepinephrine to dopamine as the key neurotransmitter in the regulation of eating, reproduction, stress-related aggression and electrical self stimulation of the brain. Antelman and Caggiula (1977) have proposed an elegant theory where dopamine and norepinephrine are dynamically interrelated in the control of the so called "dopamine behaviors", which would be useful for us to review now before beginning our discussion of the dopamine hypothesis of schizophrenia.

Antelman and Caggiula propose that under those circumstances when the activity of the noradrenergic nervous system is inhibited, behaviors mediated by the dopaminergic system are facilitated in the presence of stressful or activating stimuli, and those same behaviors show either ne

change or depression in the absence of stressful or activating stimuli. All of the behaviors they considered to be dopamine mediated depended on the functional integrity of the dopaminergic systems. Inhibition of both the dopaminergic and noradrenergic systems was less debilitating than inhibiting the dopaminergic system alone, while inhibition of the noradrenergic system potentiated dopaminergic behavior. However, it is critical to realize that the non-debilitating effect of depleting the noradrenergic system occurred only in the presence of activating or stressful stimuli.

One particular experiment explained by Antelman and Caggiula helps describe a possible brain mechanism which would account for their findings, particularly the heavy dependence on activation. Animals with large unilateral lesions of the locus coeruleus display a strong, transient circling behavior in a direction away from the side of the lesion when given injections of amphetamine or the dopamine agonist apomorphine. The lesions obviously caused a reduction of locus coeruleus norepinephrine and the activity of its noradrenergic tracts, but also caused an elevation of striatal dopamine. It appears that the reduced activity of the locus coeruleus lead to a decreased activity and hence a buildup of dopamine in the nigrostriatal path. Circling behavior occurs in a direction away from the striatum in which dopamine receptors are most stimulated. The dopamine receptors on the lesioned side were hypersensitive due to a decrease of stimulation from the nigrostriatal path, and were therefore strongly stimulated by the dopamine agonists

amphetamine and apomorphine.

This experiment indicates that noradrenergic systems usually facilitate dopaminergic activity. When noradrenergic activity is decreased the dopaminergic activity decreases and excess dopamine is stored, but activating or stressful stimuli cause the release of the excess stored dopamine, restoring dopaminergic activity to normal. This type of mechanism explains why stress can cause the temporary relief of a dopamine deficiency disease, such as the paradoxical kinesia resulting when an akinetic Parkinson's patient is stressed (Antelman and Caggiula, 1977).

As mentioned, Parkinson's disease results from a decrease in activity of the dopaminergic neurons in the basal ganglia (Pincus and Tucker, 1974), resulting in tremor, rigidity and bradykinesia. Parkinson's patients are treated with dopamine precursors or dopamine reuptake inhibitors to compensate for the decreased amount of available dopamine, though occasionally these treatments lead to psychotic behavior (Pincus and Tucker, 1974).

This ties in with one of the most extensively researched, and therefore complex, monoamine theories of behavior; the dopamine hypothesis of schizophrenia. Briefly stated, this theory proposes that schizophrenic behavior is the result of overactivity of the dopaminergic systems. Attention has been assigned to this theory above all others because of the clinical significance involved in understanding the neurochemistry of schizophrenia.

Amphetamine psychosis has served as a useful model for

schizophrenia, since it produces symptoms similar to acute paranoid schizophrenia, and can be treated with antischizophrenic drugs such as the phenothiazines. Amphetamine causes the release of both norepinephrine and dopamine, but pharmacological evidence indicates that it is dopamine which is responsible for the induction of schizophrenia by amphetamine (Meltzer and Stahl, 1976). In fact, the potency of an antipsychotic drug is strongly correlated with it's binding affinity for a post-synaptic adenylate cyclase presumed to be the dopamine receptor (Creese, Burt and Snyder, 1976).

Another newer drug model for schizophrenia involves LSD, a substance well known for it's psychotomimetic properties. Originally, LSD was thought to effect behavior by mimicing serotonin. However, LSD has been found to stimulate the adenyl cyclase dopamine receptor (VonHungen, Roberts and Hill, 1974) and has been found to reduce the turnover of brain dopamine, probably as the result of negative feedback resulting from post - synaptic dopamine receptor stimulation (DaPrada, Saner, Burkard, Bartholini and Pletscher, 1975). It is worth noting that the dopamine adenyl cyclase receptor seems to have two binding sites; an agonistic or "dopamine" site and an antagonistic or "haloperidol" site (Creese, Burt and Snyder, 1976).

Although dopamine seems to be the primary neurotransmitter involved in schizophrenic behavior, acetylcholine has also been implicated. Davis (1974) proposed that the dopaminergic nervous system might be balanced by the cholinergic

nervous system regarding the regulation of schizophrenic behavior. He found that when psychosis was activated in schizophrenic patients with the potent dopamine releaser and reuptake blocker methylphenidate, the psychosis could be abolished with the cholinergic agonist physostigmine. When the physostigmine was given as a pretreatment, it prevented injections of methylphenidate from inducing psychosis.

In their review of schizophrenia, Meltzer and Stahl (1976) further elaborate this relation between acetylcholine and dopamine. It seems that nigrostriatal dopaminergic neurons and striatal cholinergic neurons inhibit each other so that the net outflow of the system results in smooth control of motor activities. Parkinson's disease is the result of a predominance of cholinergic over dopaminergic activity, while tardive dyskinesia -- buccal, lingual and facial movement disorders associated with a decline in psychotic behavior during neuroleptic drug treatment -- is associated with a predominance of dopaminergic over cholinergic activity. Metzler supports this theory with a variety of pharmacological evidence.

As may be evident by now, the nigrostriatal dopamine tract is the most thoroughly investigated tract in relation to schizophrenia. The somites for this tract are located in the substantia nigra and send their axons to the caudate - putamen of the neostriatum. It's major function is to regulate the extrapyramidal nervous system in the control of movements, but it has been suggested that this tract plays a role in memory and in goal directed behavior (Meltzer and

Stahl, 1976). As mentioned, it is the tract implicated in Parkinson's Disease and tardive dyskinesia.

The site of the antischizophrenic action of neuroleptics is not as concrete, although the meso-cortical and the meso- limbic dopaminergic systems have been implicated in addition to the nigrostriatal tract. Scatton, Glowinski and Julou (1976) have found that the meso- limbic and meso-cortical systems do not habituate to neuroleptic treatments, as does the nigrostriatal system. Since with continued drug treatment extrapyramidal effects subside while antipsychotic effects do not, this implicates these tracts as a possible site of action for antipsychotic drugs.

The mechanisms mediating schizophrenic behavior have been studied from a different approach; by looking at the reward systems of the brain. Dysfunction of reward systems would produce deficits in goal directed thinking, behavior and the ability to experience pleasure. Catecholamine agonists such as amphetamine have been found to facilitate self stimulation of brain reward systems, while drugs which are catecholamine antagonists, such as chlorpromazine, have been found to inhibit electrical self stimulation of the brain (Stein, Belluzzi, Ritter and Wise, 1974). Stein et al. indicate that the noradrenergic neurons projecting from the locus coeruleus in particular are responsible for self stimulation behavior.

The study of the reward systems has been reviewed more recently by Routtenberg (1978), who also emphasizes that the locus coeruleus, with it's projections to the cerebrum,

hypothalamus and cerebellum, plays an important role in reward mechanisms. Routtenberg, however, found that lesioning of the locus coeruleus did not eliminate self-stimulation, suggesting that another system may play a more important role in self-stimulation. Lesions involving the substantia nigra did reduce self-stimulation, indicating that the nigrostriatal dopaminergic system plays a key role in reward systems of the brain. These observations again emphasize the importance of the locus coeruleus in relation to affective states, the importance of the nigrostriatal path in relation to schizophrenia and the possibility of a dopamine-norepinephrine interaction in the brain.

Stein and Wise (1971) have proposed that schizophrenia evolves from a degeneration of the neurons originating in the locus coeruleus. This would lead to a state where the thoughts are not related or unified by any concept of a goal, and where emotional responsivity is eventually reduced to **indifference**. It is suggested that this degeneration is brought when dopamine beta hydroxylase incorrectly catalyzes the reaction of dopamine to 6-hydroxydopamine, which has been found to cause a specific poisoning of noradrenergic neurons. Normally, dopamine beta hydroxylase converts dopamine to norepinephrine, but it is possible that a simple genetic defect could alter the enzyme enough to catalyze an incorrect reaction (Kaufman, 1974).

Stein and Wise found that rats treated with 6-hydroxydopamine exhibited a great decrease in self-stimulation, and that an injection of the monoamine oxidase inhibitor

pargyline induced a catatonic like state they termed "waxy flexibility". In addition, pretreatments with chlorpromazine prevented 6-hydroxydopamine from damaging the noradrenergic neuron, possibly by preventing it's uptake into the neuron. This theory is the first to give a specific genetic cause for schizophrenia, and could be generalized to manic - depressive psychoses, which also may involve defects of the noradrenergic system.

The Stein and Wise theory proposes that schizophrenia results from inhibition of the noradrenergic nervous system, while the dopamine theory proposes that schizophrenia results from an overactivity of the dopaminergic nervous system. Present knowledge of dopamine - norepinephrine interactions suggests that these two different theories might amount to the same net effect when a schizophrenic is characterized by occasional psychotic episodes triggered by stressful or activating stimuli. Conversely, if the schizophrenia is characterized by a continual psychotic state, then these two theories are separate and distinct.

Much of the research on schizophrenia and other affective disorders reviewed stress the importance of several brain areas. The locus coeruleus seems to play a major role in the regulation of affective states, and some of this regulation appears to operate thru the nigrostriatal path. The nigrostriatal path has been implicated in the tremor disorders, and more importantly, as the critical path involved in reward.

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THE EFFECTS OF AMPHETAMINE PRETREATMENTS
ON
CHLORPROMAZINE INDUCED FOOD AVERSIONS

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The assumption that behavior can function to restore a physiological homeostasis is not new; this concept forms the base for Maslow's hierarch of needs in his holistic - dynamic theory of personality. Maslow points out that any imbalance in such aspects of the internal environment as salt concentration, pH, sugar concentration, calcium concentration and so on will motivate the organism to behave in a way that will restore homeostasis (Maslow, 1954).

This effect has been demonstrated more recently in an experiment by Neal Miller designed to test whether restoration of an optimum physiological level by a glandular response could function as a reward. Miller (1969) overloaded rats with water and placed them in a T-maze. The choice of one arm resulted in an injection of antidiuretic hormone, aggravating the rat's hypotonic state. The choice of the other arm resulted in a saline injection, which did not interfere with the rat's return to an isotonic state. As expected, the rats learned to pick the arm which resulted in a saline injection. Conversely, for rats with diabetes insipidus, loaded in advance with hypertonic NaCl, the arm which resulted in an injection of antidiuretic hormone was preferred. In both cases the rat was reinforced for the response which restored homeostasis and punished for the response which further upset homeostasis.

The purpose of the experiments described in this paper

was to see if the restoration of a normal behavioral state would also follow a homeostatic pattern. The means for altering an organisms behavioral state is provided through the use of numerous psychoactive drugs. If altering the normal behavioral state of an organism follows the patterns found in other homeostatic systems, such as blood pH, we would expect the administration of a psychoactive drug to be aversive; and this is indeed the case.

A strong food aversion can be conditioned in rats by treating them with psychoactive drugs at levels which do not show any signs of toxicity (Berger, 1972). By repeatedly following the presentation of a milk solution with an injection of a psychoactive drug, Berger found that an aversion to the milk was created. Fluid deprived rats were used and the dependent variable was the amount of time taken by the rat to drink 5 mls of the milk solution. Scopolamine HCl, Lorazepam, chlorpromazine HCl and d-amphetamine sulfate all created significant aversions to the milk solution when compared to rats which had received a saline injection only. Interestingly, when scopolamine was injected one-half hour before the presentation of the milk, no aversion was produced.

Parker, Failor and Weidman (1973) hypothesized that for need states for which the organism has no innate ability to recognize the needed substance the organism would develop a conditioned preference for food ingested prior to alleviation of the need. This sounds much like the homeostatically motivated type of behavior discussed earlier, except that the need state here refers to a morphine addiction.

By addicting rats to morphine and using morphine withdrawal as the need state, rats develop a conditioned preference for a sucrose-octa-acetate solution which was administered prior to the need repleting injections of morphine. Rats which had not been addicted to morphine developed a conditioned aversion to the sucrose-octa-acetate when it preceded the morphine injections.

Parker concluded that organisms develop a conditioned preference for substances associated with the repletion of artificially induced biological needs, essentially homeostatically motivated behavior. However, Cappell, LeBlanc and Herling (1974) explain the same results in a similar experiment with a tolerance theory. They concluded that chronic drug treatment -- addiction -- does not cause a conditioned preference for that drug but reduces its effectiveness as an unconditioned stimulus in gustatory conditioning. Thus far, the only means by which the aversiveness of a psychoactive drug, as measured by its capacity to produce a food aversion, has been reduced has been to addict the animal to that drug.

In order to test whether treatment with a psychoactive drug, and therefore the regulation of behavioral state, indeed follows the pattern expected for a homeostatically motivated behavior, a situation must be created where the drug injection is associated with the restoration of a normal behavioral state. Artificially induced biological needs may not be used, since the argument that only a tolerance is being produced will come into play. However, a drug injection

would restore a normal behavioral state if it followed an injection with an antagonistic drug. If the animal were being conditioned to associate the food with the second injection, it should develop a food preference when pretreated with the antagonist, and a food aversion when not pretreated with the antagonist.

Chlorpromazine HCl and d-amphetamine sulfate have been found to be antagonistic on the basis of neurochemical, behavioral, clinical and EEG evidence. Chlorpromazine is a phenothiazine which causes a central and peripheral blockade of the alpha adrenergic neurons of the sympathetic nervous system. Amphetamine also operates on the alpha adrenergic neurons, but acts as both a mimic and a releaser of endogenous catecholamines (Sutherland, 1970). The d-isomer of amphetamine is less active peripherally and more active centrally than the l-isomer (Ban, 1969). Both of these drugs have a similar effect on dopaminergic neurons. This effect ties amphetamine and chlorpromazine with the dopaminergic theory of schizophrenia, which, simply put, states that schizophrenia is brought about by an increase in dopaminergic activity. Amphetamine treated animals are a well known model for schizophrenic behavior, and chlorpromazine is the classic antischizophrenic drug (Meltzer and Stahl, 1976). Chlorpromazine can be used to treat amphetamine overdoses, and it has been observed that obese schizophrenic subjects on phenothiazine medication do not respond to a d-amphetamine weight loss treatment (Hansten, 1973). In terms of EEG evidence, amphetamine has been found to reverse the brain

wave synchronization produced by chlorpromazine treatments in rabbits (White and Boyajy, 1959). Not only are chlorpromazine and amphetamine an antagonistic pair of drugs, but either administered alone produces a significant food aversion, which is an important feature for a study of this type (Berger, 1972).

It has been emphasized during this discussion that the behavioral state of an organism may be subject to homeostatic regulation. Drugs which act to restore a normal behavioral state should be reinforcing and in fact cause a conditioned food preference. In the first experiment it was hypothesized that rats pretreated with d-amphetamine sulfate would have a higher preference for a food which precedes the administration of chlorpromazine than rats which had not been pretreated with amphetamine, and that rats which had not been pretreated with amphetamine would have a lower preference for a food which precedes the administration of chlorpromazine than would control groups which receive placebo injections only (see appendix A).

Experiment 1 Method

Subjects. The subjects were 24 male Sprague - Dawley rats, approximately 50 days old.

Apparatus. The treatment drugs were d-amphetamine sulfate (.6 mg/ml, prepared from .5 mg Dexedrine tablets; Smith, Kline and French) and chlorpromazine HCl (Thorazine, 25 mg/ml; Smith, Kline and French). Isotonic saline was used as a control injection and all injections were made with B-D 3/8 inch, 26 gauge, 1cc disposable tuberculin syringes.

The unconditioned stimulus solution (US) was one part of Borden Eagle brand sweetened condensed milk mixed with two parts of tap water. The US was presented in a Wahmann animal cage through Wahmann 100 ml graduated drinking cylinders. Preference or aversion for the US was tested in the same cage with both the US and tap water available from separate graduated drinking cylinders.

Procedure. For clarity, amphetamine will be abbreviated AMP, chlorpromazine will be abbreviated CPZ and saline will be abbreviated S.

The rats were randomly divided into four groups according to the injection preceding and the injection following presentation of the US. The groups were AMP-S, S-CPZ, AMP-CPZ and S-S. Six rats were randomly assigned to each group. The dose level for the AMP was 2.5 mg/Kg and the dose level for the CPZ was 5.0 mg/Kg. The volume of all pre-treatment injections was 4.16 ml/Kg and the volume of all posttreatment injections was .2 ml/Kg. The rats free fed and were on a 23 hour fluid deprivation schedule throughout the experiment.

The conditioning trials were administered once a day for seven days. Each rat was given the pretreatment injection one half hour before being placed in the experimental cage. After one hour in the experimental cage, where the rats were allowed free access to the US, the rat was removed and immediately given it's posttreatment injection before being returned to it's home cage. The amount of fluid consumed each day was recorded.

The testing trials were run once a day for the four days which followed the completion of the conditioning trials. Each rat was placed in the experimental cage and allowed free access to both the US solution and water for one hour. The positioning of the two cylinders on the right and left sides of the cages was counterbalanced. The volume consumed of each fluid was recorded at the end of each trial. The US preference ratio was computed as the total volume of milk solution consumed over four days divided by the total volume of both milk solution and water consumed over four days.

Results

The means and standard deviations of the US preference ratios for the four groups are recorded in table 1. The individual preference ratios are recorded in appendix B. The raw data is recorded in appendix D. A simple one way analysis of variance indicated significant differences

Insert table 1 about here

between the groups ($F=4.13$; $df=3,15$; $p<.05$).

The individual groups were compared with a one-tailed t-test for uncorrelated measures. The S-CPZ group was found to drink significantly less milk solution during the test trials than the S-S group ($t=3.23$; $df=8$; $p<.01$), and the AMP-S group was found to drink significantly less milk solution than the S-S group ($t=3.51$; $df=10$; $p<.005$).

No significant difference in milk consumption was found between the AMP-CPZ group and the S-CPZ group ($t=.382$; $df=5$; $p>.05$), and no significant difference was found between the AMP-CPZ and S-S group ($t=1.01$; $df=7$; $p>.05$).

Discussion

As hypothesized, the S-CPZ group developed a significant aversion to the milk solution. This essentially replicates Berger's findings (Berger, 1972) with the addition of a saline injection before the conditioning session.

It was not expected that the rats in the AMP-S group would develop a significant aversion to the milk solution. However, on further analysis this is completely reasonable and consistent with the assumptions of the experiment. The AMP injection requires one half hour to onset and the effects last for about three hours (Yasui, 1978). An aversion is produced because the effects of the AMP are present while the rat is in the presence of the US. Although in previous food aversion studies the injection of the psychoactive drug follows the exposure to the US, these results parallel those of Green and Garcia (1971). Green and Garcia found that when a noxious drug -- apomorphine -- was administered to rats prior to being placed in a cage with the US, the rats developed an aversion for the US when the presentation of the US coincided with the onset of illness. It appears that injections of psychoactive drugs will be associated with the US whether given before or after presentation of the US, contrary to previous findings (Berger, 1972).

The AMP-CPZ group, which was the experimental group, did not differ significantly from the S-S group, as was hypothesized. This, however, is support by accepting the null hypothesis. The AMP-CPZ group did not have a higher preference ratio than the S-CPZ group, which would be convincing

support of the hypothesis.

The raw data for the AMP-CPZ group, which had a high standard deviation, was very interesting. One rat's preference ratio was .83, a score even higher than the average score of .78 for the S-S group. Another rat in this group scored a preference ratio of .40, the lowest score in the entire sample. The rat which scored .83 drank a total of 60 mls of fluid during the seven days of conditioning, while the rat which scored .40 drank only eleven mls of fluid during the seven days of conditioning and died after the completion of the experiment. Rats in the S-S group consumed a mean of 95 mls total during the seven days of conditioning. It is typical of the rats which died during the experiment that they drank little or no fluid during the conditioning trials.

Of those rats which refused fluid during the conditioning trials, all were receiving AMP pretreatments. Of those rats which died of unknown causes, all belonged to the AMP-CPZ group and drank little or no fluid. It is tentatively possible that these rats did not adapt to the stress of the experiment, refused the fluid, their weights dropped and the CPZ injection became a lethal overdose. The CPZ was observed to have a very strong effect, with some rats falling asleep on their backs even when they had been pretreated with AMP. A dose this strong would be pulling the rat from one behavioral extreme to the opposite, not bringing it toward normal.

These results suggest several changes which should be made in order to lower the standard deviation and decrease

mortality in the experimental group. First, the CPZ injection should be diluted so that it may be measured with an accuracy of two significant figures, and the rats should be reweighed each day so that the injections may be recalibrated each day. Second, since drug injections prior to the conditioning session can cause food aversions, the CPZ injection may be administered just before the animal is placed in the conditioning chamber. This will bring the CPZ injection one hour closer to the AMP injection, so that the antagonistic effects of the CPZ injection would occur while the rat is in the presence of the US. Thirdly, the rats should be given four days of preference testing before the seven days of conditioning begins. This will both work the animals into the experiment more slowly, decreasing the stress, and provide useful baseline data. Finally, the CPZ dose is evidently too high, and should be decreased.

Experiment 2

The purpose of this experiment, essentially a pilot study, was to see if a 2.5 mg/Kg CPZ injection would be as effective as a 5.0 mg/Kg injection in conditioning a food aversion. Since the standard deviations for the last experiment were so small, a small number of subjects and no inferential statistics were used.

Method

Subjects. The subjects were 5 female Sprague - Dawley rats, approximately four months old. These rats had all been handled extensively during the lab sessions of a Learning Experimental Psychology course.

Apparatus. The apparatus was the same as that described in experiment 1. The chlorpromazine solution was diluted to 2.5 mg/ml with distilled water.

Procedure. The rats were conditioned for seven days and then tested for four days, as in experiment 1. No pretreatment injection was given. After removal from the conditioning chamber two rats received a 2.5 mg/Kg injection of CPZ, two rats received a 5.0 mg/Kg injection of CPZ and one rat received a saline injection of a volume proportional to the volume of the 5.0 mg/Kg CPZ injection.

Results

The mean preference ratios are recorded in table 2. No statistical operations were performed.

Insert table 2 about here

Discussion

No useful information on CPZ dosages was obtained from this experiment. In comparison with the control, the 5.0 mg/Kg rats seemed to develop a conditioned food preference, while the 2.5 mg/Kg rats developed neither a preference or an aversion. These results are inconsistent with the results of experiment 1. This is probably due to the much varied background and greater experience of these rats in comparison with the naive rats used in experiment 1, resulting in a greater deviation of preferences.

Experiment 3

In this experiment those changes in the design used in experiment 1 were made which were deemed necessary to produce significant results with respect to the AMP-CPZ group.

Most of these changes were explained in the discussion of experiment 1. Since there was no basis for decreasing the CPZ injection to 2.5 mg/Kg, it was decided that a slight decrease in the CPZ dose to 4.0 mg/Kg coupled with a small increase in the AMP dose to 3.0 mg/Kg would produce the net drug interaction desired without changing the dose of either drug enough so the administered alone they would not be capable of causing a conditioned food aversion.

It was hypothesized that the AMP-CPZ group would have a greater preference ratio than either the AMP-S group or the S-CPZ group, and that the S-S group would have a greater preference ratio than either the AMP-S group or the S-CPZ group.

Method

Subjects. The subjects were 23 naive male Sprague - Dawley rats, approximately 65 days old.

Apparatus. The apparatus was the same as that used in experiments 1 and 2. The treatment drugs were d-amphetamine sulfate (1.0 mg/ml in distilled water; Sigma), and Chlorpromazine HCL (2.5 mg/ml, Thorazine in distilled water; Smith, Kline and French).

Procedure. Six rats were randomly assigned to every group except for the S-S group, which was assigned five rats. The experiment consisted of four days of preference testing, seven days of conditioning and another four days of preference testing. The procedure for preference testing was the same as that used in experiment 1 and 2. Each conditioning trial consisted of a pretreatment injection, a one half hour wait,

another injection and one hour in the conditioning chamber. The AMP dose was 3.0 mg/Kg and the CPZ dose was 4.0 mg/Kg. The rats were weighed each day so that the drug dose could be recalculated.

Results

The means and standard deviations of the US preference ratios for the four groups, before and after conditioning, are given in table 3. The individual preference ratios are

Insert table 3 about here

recorded in appendix C. The raw data is recorded in appendix E, and graphs of individual feeding behavior are recorded in appendix F. The baseline preference ratio for the entire sample was .56. A simple one way analysis of variance indicated significant differences between the groups ($F= 4.25; df=3,19; p .05$).

An analysis of covariance indicated no significant differences between groups ($F= 2.43; df=3,19; p > .05$). However, since an analysis of variance did not indicate any significant differences between the baseline scores of the four groups ($F=.027; df=3,19; p > .05$) the reason for the insignificance of the analysis of covariance is not readily understandable.

A directional t-test for uncorrelated measures indicated no significant differences between the S-CPZ and S-S groups ($t=1.30; df=9; p > .05$) and no significant difference between the AMP-S and S-S groups ($t=1.50; df=9; p > .05$).

A non-directional t-test indicated a significant difference between the AMP-CPZ and S-S groups ($t=3.30; df=9; p < .01$), but this difference was in the opposite direction

hypothesized. A directional t-test indicated that the preference ratio for the AMP-CPZ group was significantly lower than the preference ratio for the S-CPZ group ($t=2.00$; $df=10$; $p<.05$) and significantly lower than the preference ratio for the AMP-S group ($t=2.04$; $df=10$; $p<.05$).

A significant correlation was found between the preference ratio and the total amount of fluid consumed by each rat during the conditioning trials ($r=.51$; $df=21$; $p<.02$).

Insert figure 1 about here

Discussion

The results of the experiment do not support the hypothesis. In this experiment AMP or CPZ administered alone did not cause a significant food aversion, as they did in experiment 1. Surprisingly, the AMP-CPZ group scored significantly lower than every other group. This in itself is interesting, because this means that AMP and CPZ added together, becoming more aversive than either drug administered alone, and there is such a substantial amount of literature which indicates that these two drugs are antagonistic. In terms of behavior, the dopaminergic theory of manic - depressive psychoses is yet another example of how these drugs antagonize each other. AMP increases dopaminergic activity, thus bringing on a manic like state. Phenothiazines decrease dopaminergic activity, and have both anti-manic properties and the capability of bringing on a depressive state (Randrup, Munkvad, Fog, Gerlach, Molander, Kjellberg and Scheel-Kruger, 1975).

The neurochemical effects of amphetamine and Chlorpromazine are not a perfect overlap, which could account for their additive effect in the ability to produce a food aversion. Chlorpromazine is more active on dopaminergic neurons than on noradrenergic neurons (Meltzer and Stahl, 1976) and amphetamine has a serotonergic effect as well as catecholaminergic (Randrup et al., 1975). If this is the case, then the conditioned taste aversion may be a more sensitive measure of subtle drug differences than the variables in the experiments cited which showed these drugs to be antagonistic, and might be a useful variable for identifying the mode of action of a new drug by pairing it with drugs of known action.

It is possible, then, that the many varied effects of AMP and CPZ were not matched well enough to totally counteract each other and thereby cancel the ability to condition a food aversion. This is consistent with the finding that, when administered together in one injection, AMP and CPZ do produce a food aversion (Cappell and LeBlanc, 1973).

Another possible explanation for the additive effect of chlorpromazine and amphetamine is that the incomplete overlap discussed caused a relative increase in noradrenergic activity and decrease in dopaminergic activity. According to Antelman and Caggiula (1977), dopamine depletion is less debilitating when it is accompanied by norepinephrine depletion. In the present study the amphetamine might have had the opposite effect due to its greater activity on noradrenergic neurons, leading to an even more debilitating balance of neurotransmitters.

A more precise neurochemical effect could be achieved by manipulating the metabolic pathways responsible for the synthesis of neurotransmitters. For example, the rate determining step in the conversion of tyrosine to 1-DOPA by tyrosine hydroxylase. Tyrosine hydroxylase is inhibited by alpha-methyltyrosine, resulting in a depletion of brain dopamine and norepinephrine. This depletion could be counteracted by administering 1-DOPA, thus bypassing the blocked synthetic step (Albers, Siegel, Katzman and Agranoff, 1972). If these two chemicals exerted an appropriate behavioral effect, and if when administered alone they both produced food aversions, then they would be suitable for this type of study.

There are also several drug pairs which have a more specific action than the AMP-CPZ pair. Reserpine is a dopamine ^{ant}agonist and apomorphine is a dopamine agonist (Menon, Clark and Masuoka, 1977). Both of these drugs have already been shown to condition food aversions in rats, although problems may be encountered because of apomorphine's capability to induce illness. Morphine is an agonist of brain opiate receptors, and naloxone is an opiate receptor antagonist which is capable of almost instantaneously reviving an animal at the point of death from a morphine overdose (Snyder, 1977). However, before a series of experiments with any drug pair is begun, it should be demonstrated that when given as a simultaneous injection they do not condition a food aversion. This will both aid in setting an appropriate drug dosage, and will eliminate any concern that there is not an adequate antagonism of effect between the two drugs during later

trials when the drugs are being administered separately.

In the third experiment, there was a significant positive correlation between the preference ratio and the amount of fluid consumed during the seven conditioning sessions. It is possible that the amount of fluid the rat is able to consume during the conditioning sessions is a confounding variable. This possibility could be tested by conditioning fluid deprived animals for seven days so that the control group is allowed to drink for one hour and the experimental group is removed from the conditioning chamber after only a very small amount of fluid is consumed. If the amount of fluid consumed during the conditioning trials does effect the preference ratio, the preference ratio would be significantly less for the experimental group. This would indicate a severe problem with using a drug with anorexic effects, such as AMP, or any drug which significantly debilitates feeding behavior.

Stress seems to play an important role in these experiments. In experiment 1, the more stressful design, significant aversions were obtained with AMP and CPZ when they were administered alone, but the effect on the AMP-CPZ group was so severe -- this group had a 50% mortality -- that no significant data could be obtained. Only in the less stressful design was useful data obtained from the AMP-CPZ group. It is also interesting to note that there was no correlation between fluid consumed during conditioning and preference ratio obtained in experiment 1, as there was in experiment 3. Any effect due to the amount of fluid the rat is able to

Consume during the conditioning trials might be minimized as the situation becomes more stressful.

The main thrust of these experiments has been to extend homeostatic theories of motivation to the regulation of behavioral states. In conclusion it would be worthwhile to step back and again look at how this type of regulation would compare with the regulation of the body's internal environment.

For components of the internal environment such as water concentration there are intricate physiological mechanisms for maintaining homeostasis. The nervous system also has physiological mechanisms for maintaining normal activity; neurotransmitter receptor site concentrations decrease with increased concentration of the neurotransmitter (Dyson, 1978), the catecholamine receptors exhibit negative cooperativity between each other (Dyson, 1978), and several different single neuron and multiple neuron negative feedback systems exist (Meltzer and Stahl, 1976).

Just as with the physiological needs, it is advantageous for a behavioral mechanism to exist which would aid in helping to restore an optimum behavioral state; but this point has not yet been adequately demonstrated. Drug addiction studies can be difficult to interpret because of the question of tolerance, but in those cases where the addiction is due to changes in receptor densities (Dyson, 1978), these studies may indeed show that the drug has become reinforcing because it is returning the animal to what has become it's normal state. In non-addiction studies the deviation from a normal state appears aversive, but it has not been demonstrated that the restoration of a normal behavioral state by the drug is reinforcing.

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Table 1
Mean Preference Ratios and Standard
Deviations for Experiment 1

	<u>Group</u>			
	S-CPZ	AMP-CPZ	AMP-S	S-S
Mean	.57	.63	.62	.78
Standard Deviation	.095	.22	.051	.088

Table 2
Preference Ratios for Experiment 2

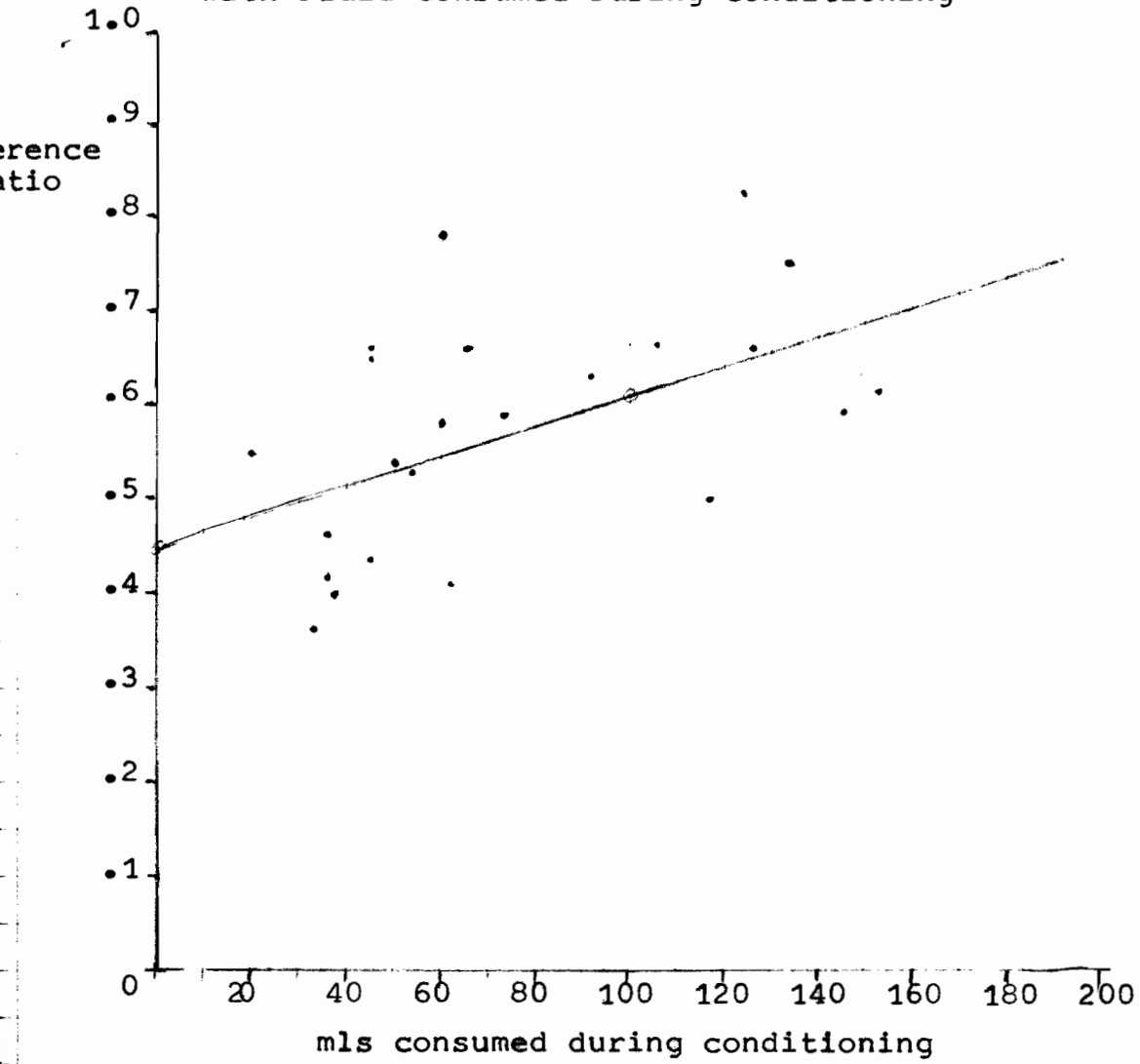
<u>Preference Ratios</u>		
<u>5.0 mg/Kg CPZ</u>	<u>2.5 mg/Kg CPZ</u>	<u>Saline Control</u>
.85	.76	.76
.80	.75	

Table 3
 Mean Preference Ratios and Standard
 Deviations for Experiment 3

	<u>Group</u>			
	S-CPZ	AMP-CPZ	AMP-S	S-S
Baseline Mean	.56	.56	.55	.56
Baseline Standard Deviation	.11	.051	.16	.084
Mean	.60	.46	.59	.69
Standard Deviation	.12	.087	.11	.099

Graph 1

Correlation of Drinking Preference
with Fluid Consumed During Conditioning



Appendix A

Expected Results for Subject Groups
in Experiment 1

Saline - Chlorpromazine (S-CPZ). This group compares the results of this study with the results of Berger's study. These rats should develop a conditioned food aversion.

Amphetamine - Chlorpromazine (AMP-CPZ). This is the experimental group. It is hypothesized that these rats will develop a conditioned food preference.

Amphetamine - Saline (AMP-S). Although drugs administered before the US have not caused rats to develop food aversions, they may have some effect on the rat's behavior. This group controls for any effects produced by the amphetamine.

Saline - Saline (S-S). Controls for any effects other than those caused by the drugs.

Appendix B

Preference Ratios for Experiment 1

<u>Preference Ratios</u>			
<u>S-CPZ</u>	<u>AMP-CPZ</u>	<u>AMP-S</u>	<u>S-S</u>
.65	.40	.64	.71
.46	.83	.61	.78
.51	.65	.59	.81
.64		.55	.93
		.64	.68
		.70	.78

Appendix C

Preference Ratios for Experiment 3

<u>Preference Ratios</u>			
<u>S-CPZ</u>	<u>AMP-CPZ</u>	<u>AMP-S</u>	<u>S-S</u>
.44	.46	.63	.83
.54	.58	.66	.59
.59	.42	.41	.66
.67	.40	.65	.75
.79	.55	.50	.62
.54	.36	.67	

Appendix D

Raw Data for Experiment 1

Group	Subject	mls milk consumed	mls water consumed
S-CPZ	1	-	-
	2	52	28
	3	39	45
	4	-	-
	5	40	38
	6	54	30
AMP-CPZ	7	25	38
	8	74	15
	9	-	-
	10	44	24
	11	-	-
	12	-	-
AMP-S	13	42	24
	14	43	28
	15	34	24
	16	56	46
	17	49	28
	18	65	28
S-S	19	60	24
	20	57	16
	21	57	13
	22	67	5
	23	73	35
	24	83	24

Appendix E

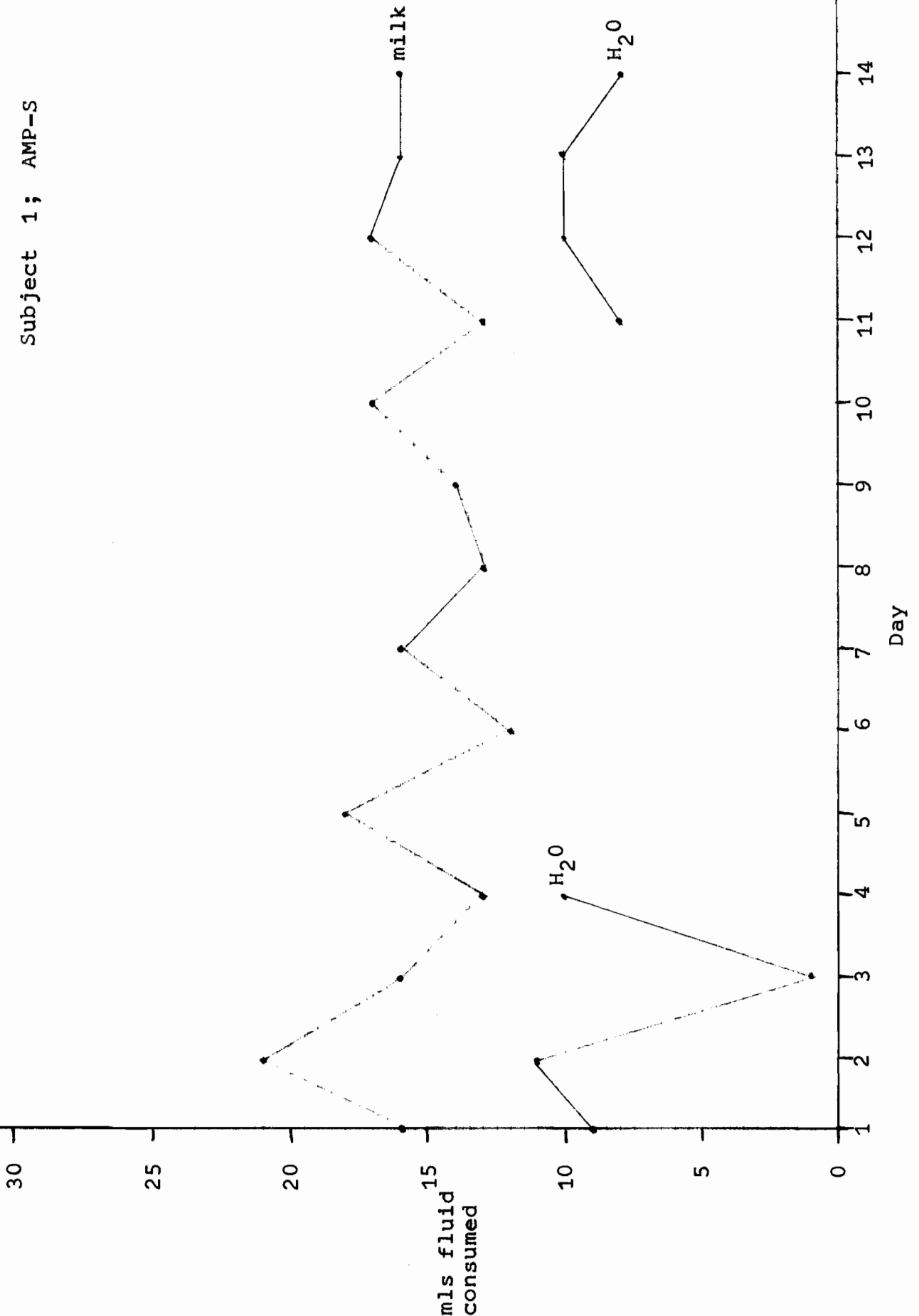
Raw Data For Experiment 3

Group	Subject	Pretest		Posttest	
		mls milk consumed	mls water consumed	mls milk consumed	mls water consumed
AMP-S	1	66	31	62	36
	2	23	52	73	37
	3	37	54	43	63
	4	64	33	71	39
	5	56	54	60	60
	6	70	30	65	32
S-CPZ	7	43	56	40	51
	8	60	42	57	49
	9	62	54	66	45
	10	76	32	74	37
	11	77	39	91	24
	12	56	65	70	60
AMP-CPZ	13	47	45	42	50
	14	50	35	63	45
	15	59	35	56	78
	16	28	22	36	55
	17	51	42	66	53
	18	37	38	37	65
S-S	19	50	31	78	16
	20	50	49	69	48
	21	54	63	117	61
	22	58	28	92	30
	23	57	45	69	42

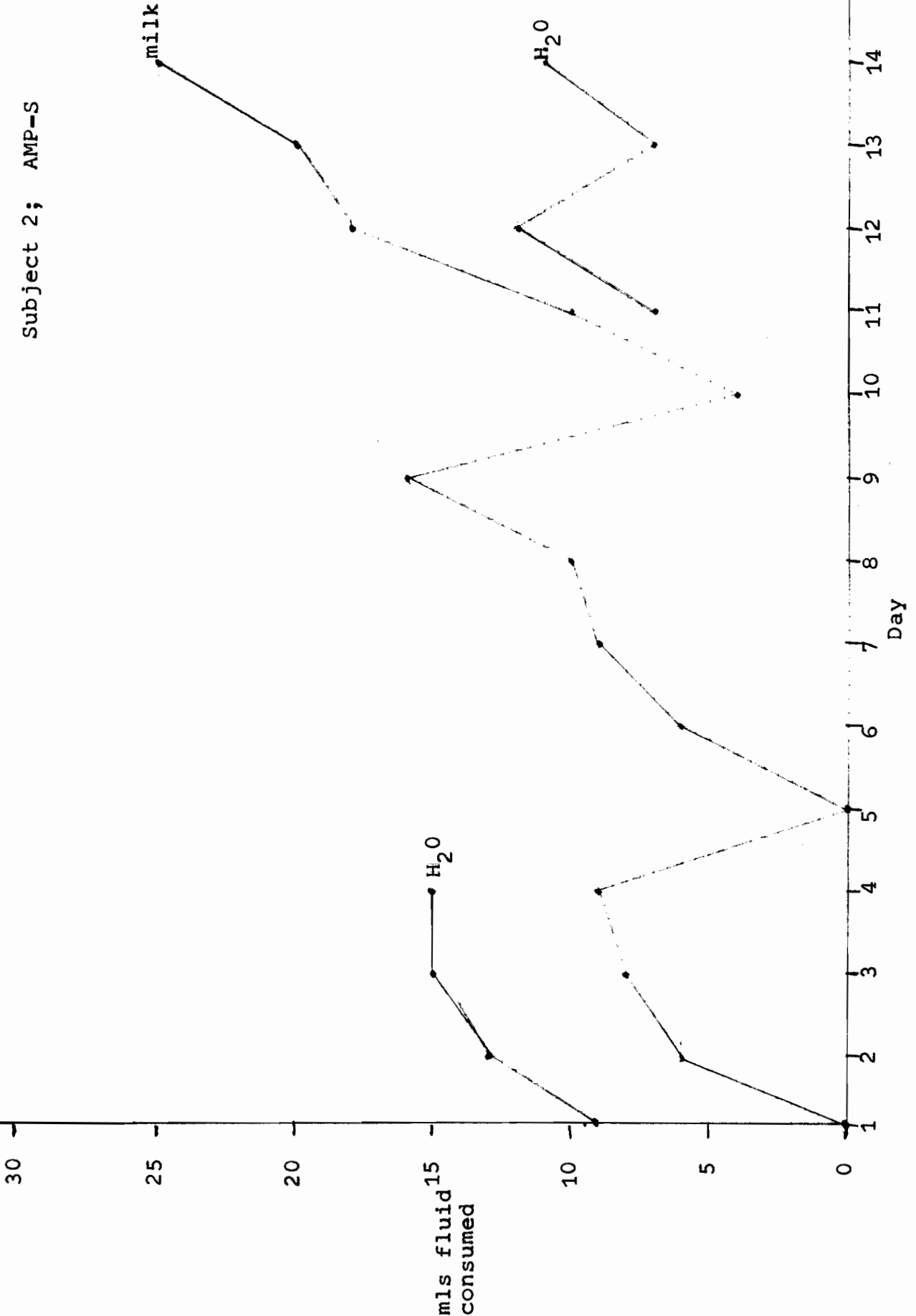
Appendix F

Graphs of Individual Subject Drinking
Behavior during Experiment 3

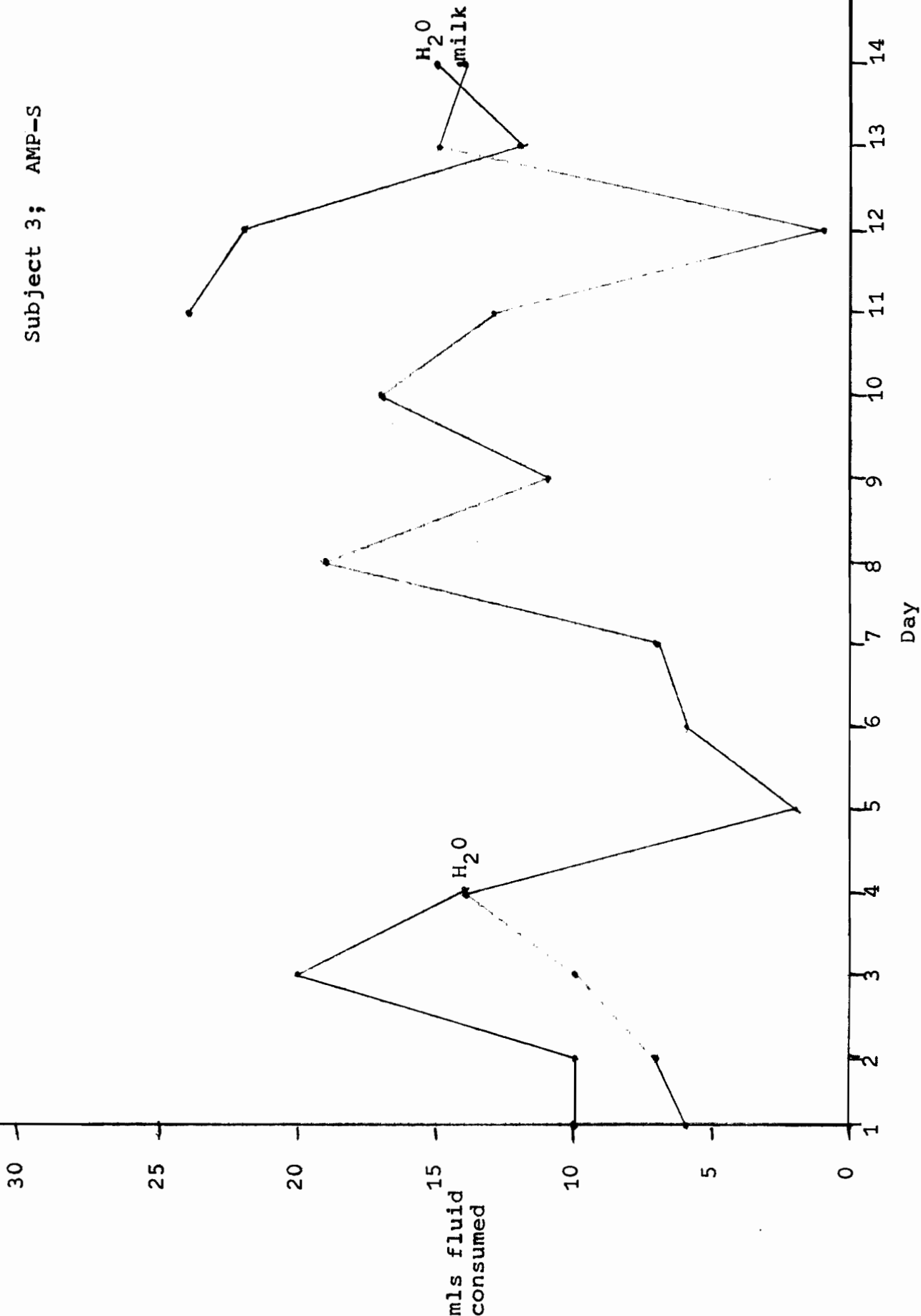
Subject 1; AMP-S



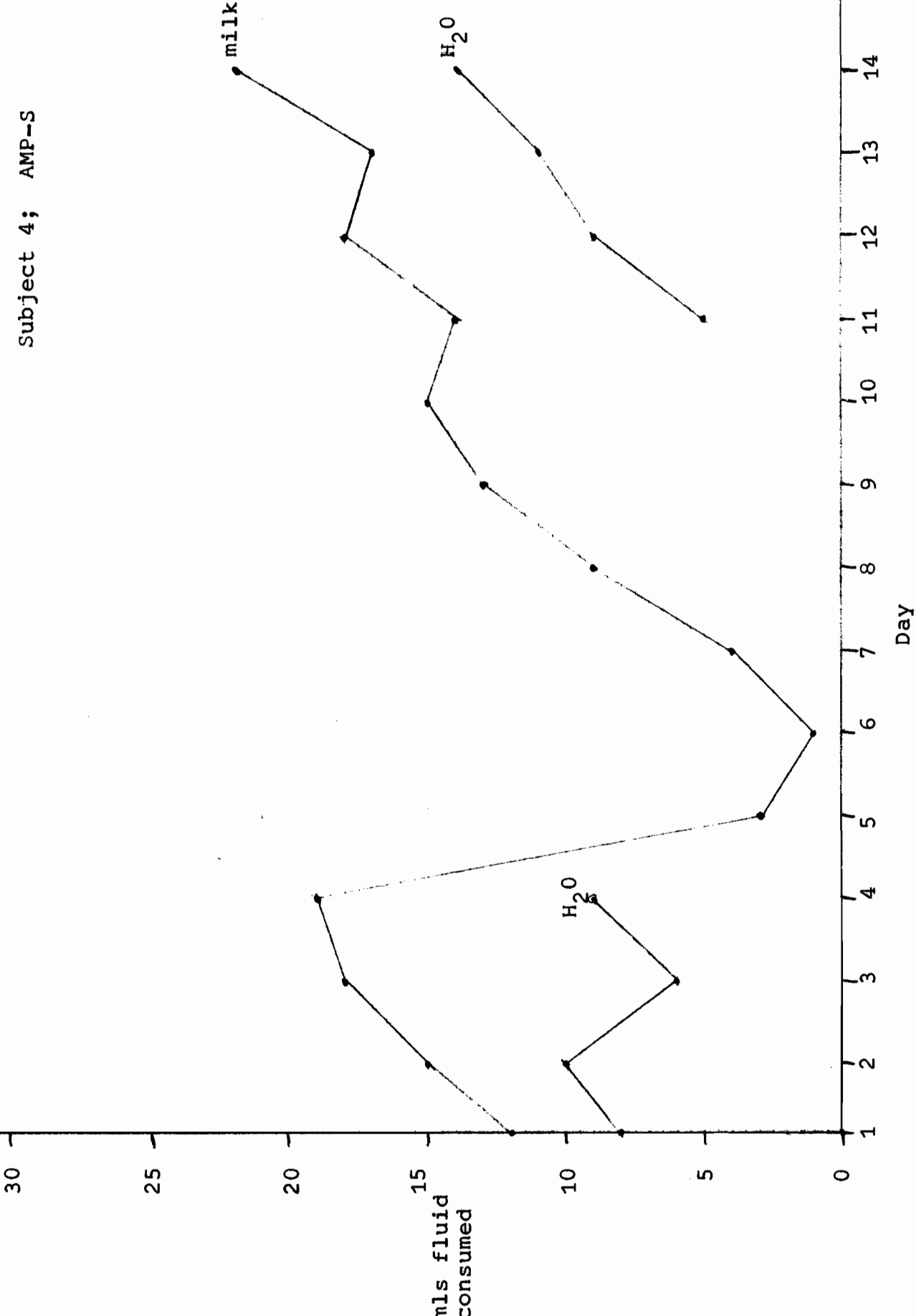
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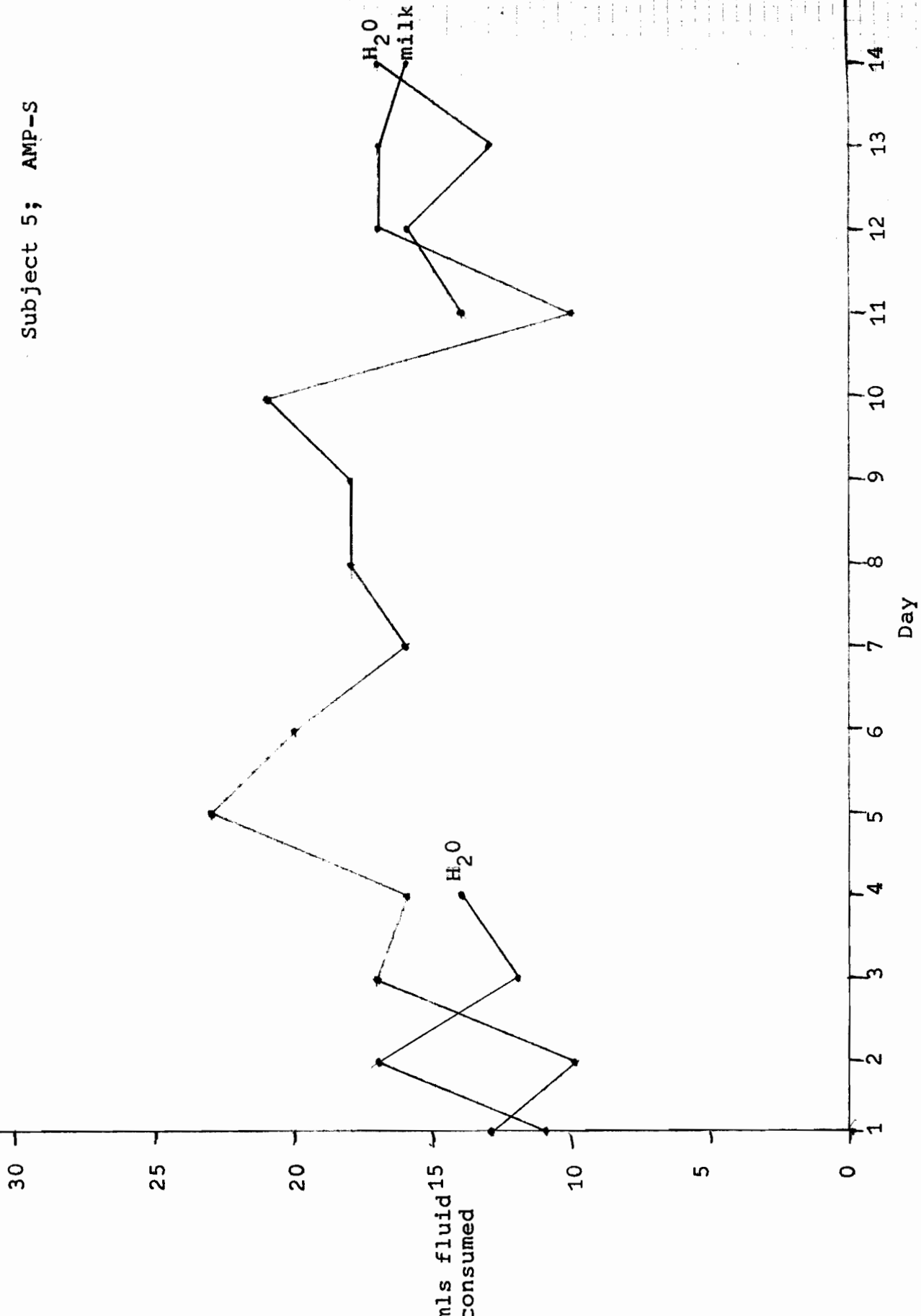
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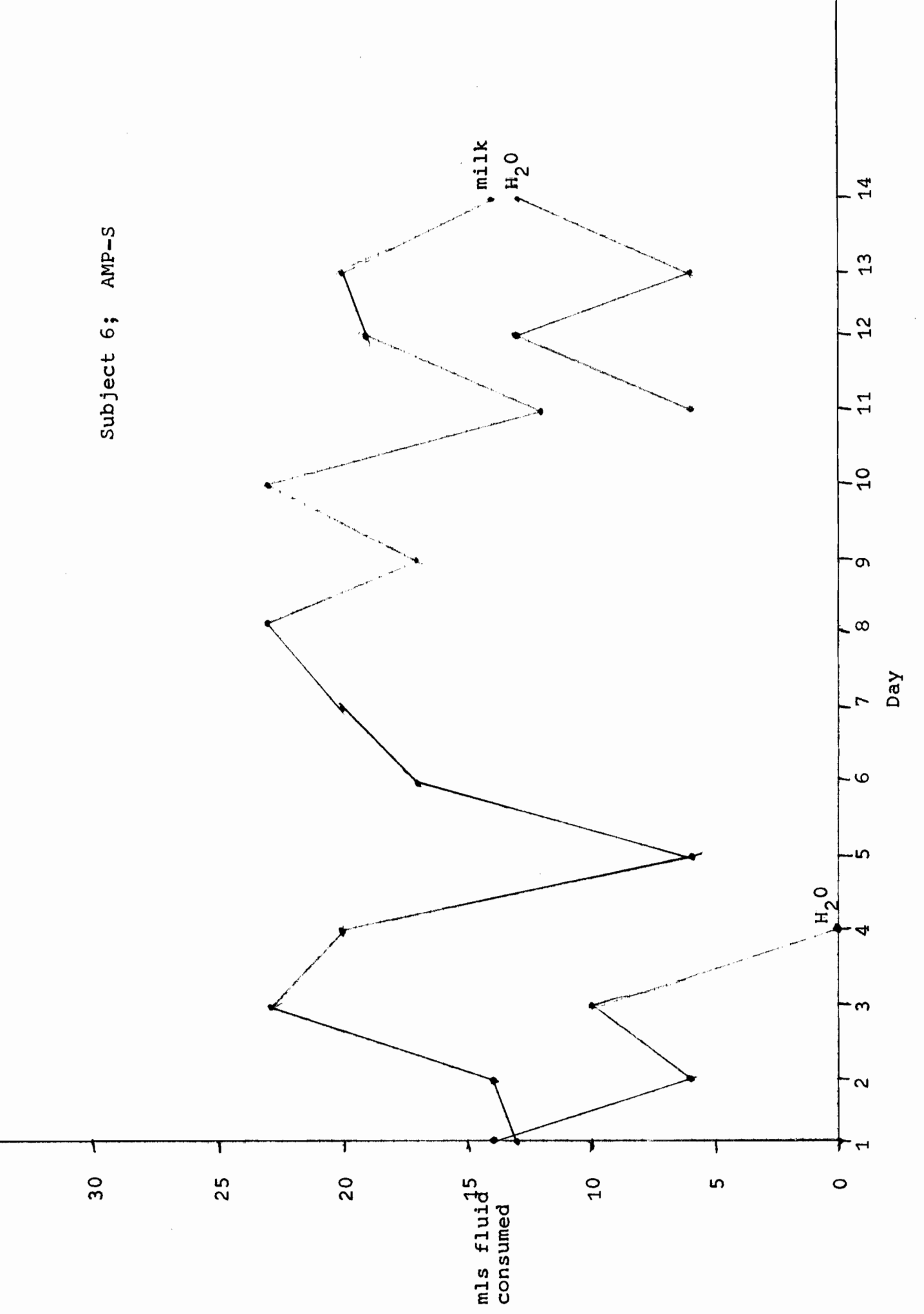
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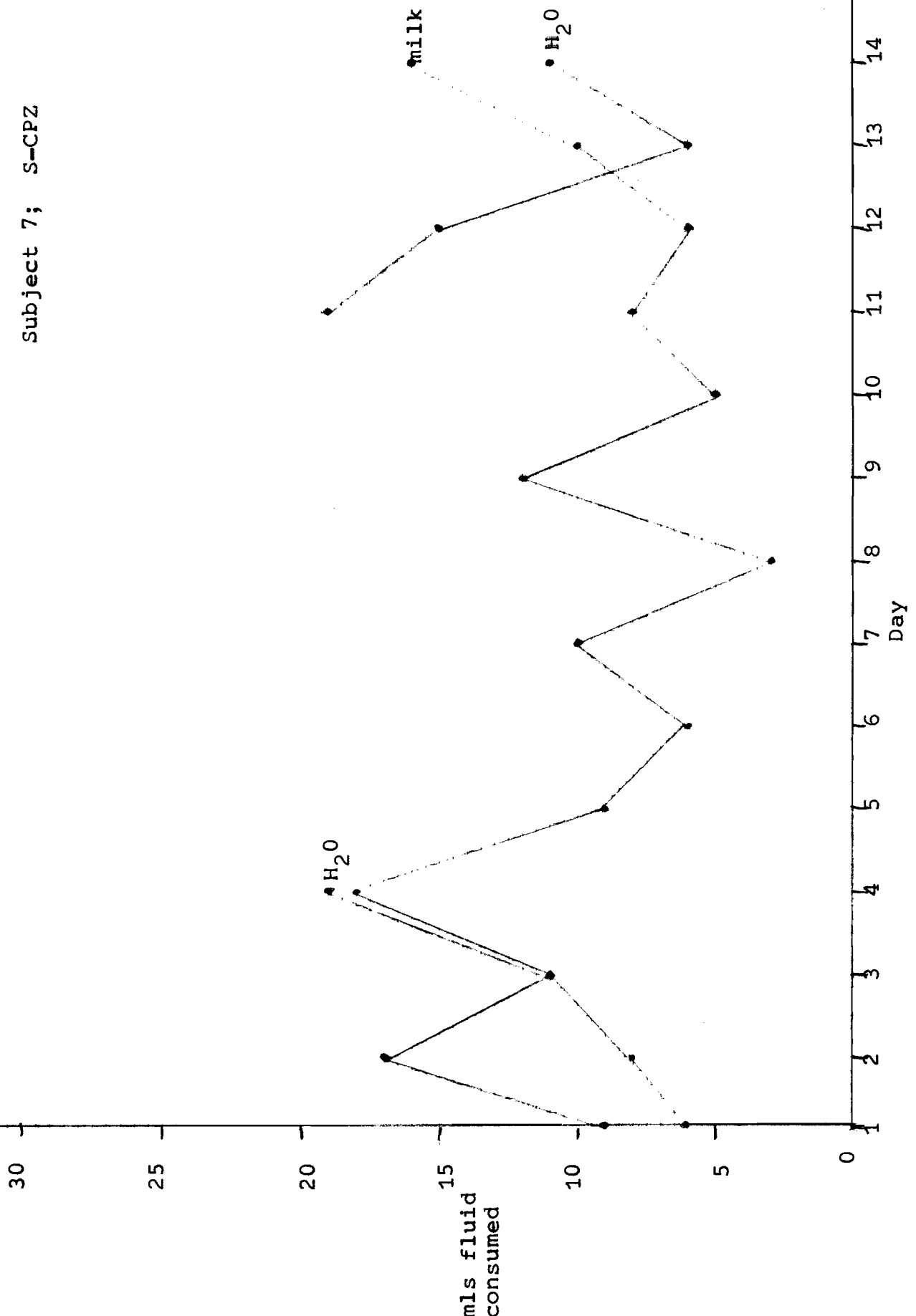
Subject 5; AMP-S



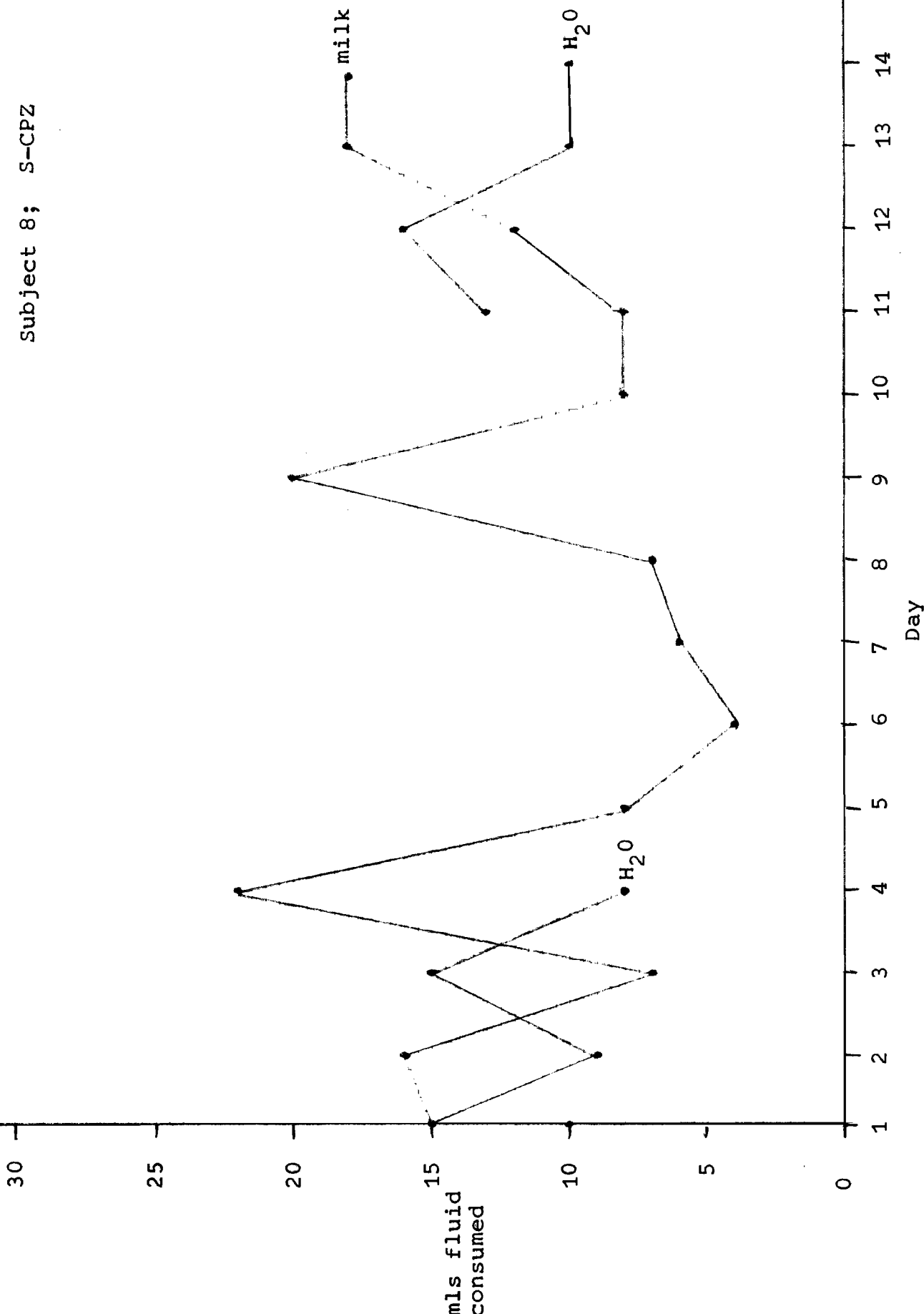
Subject 6; AMP-S



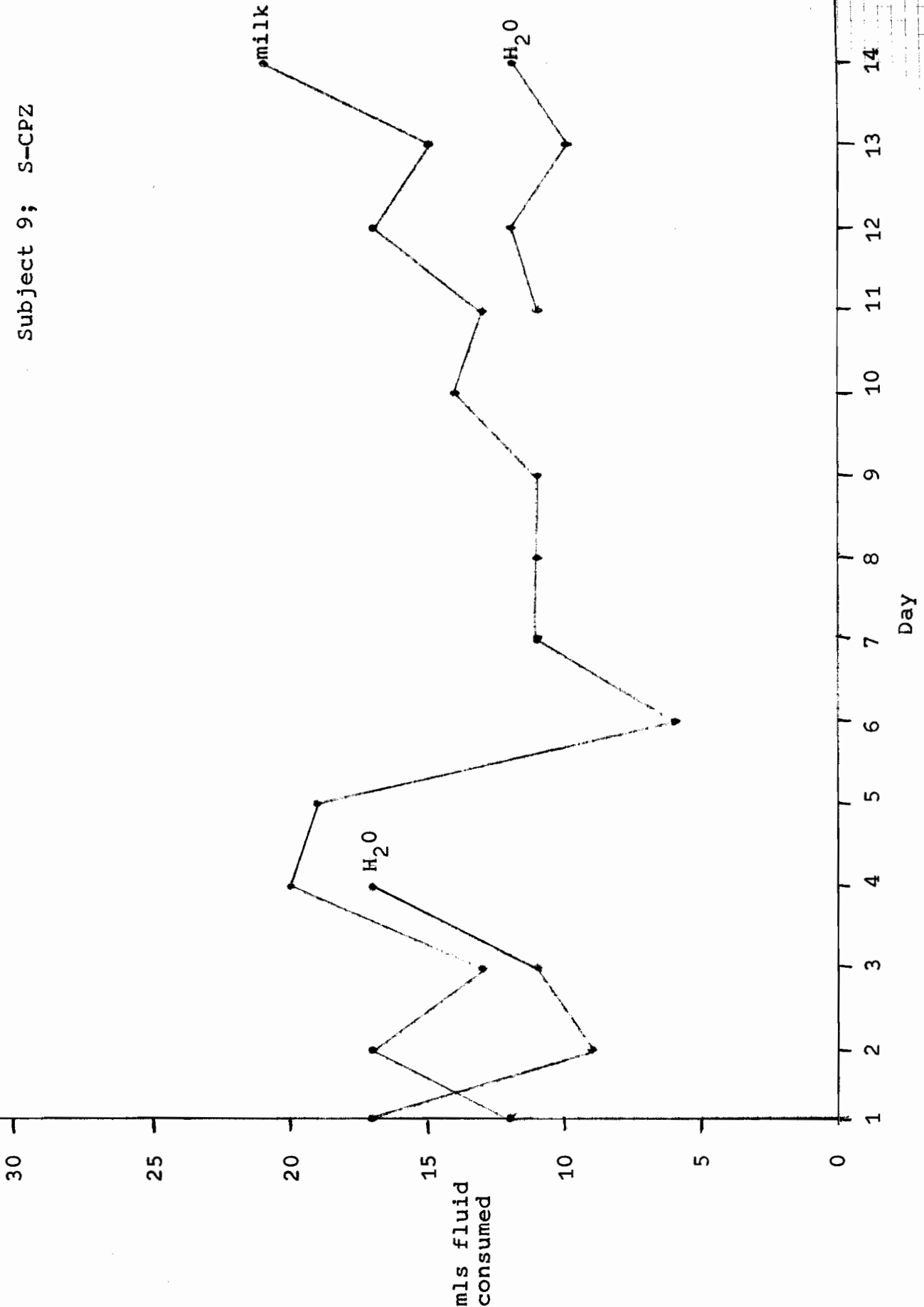
Subject 7; S-CPZ



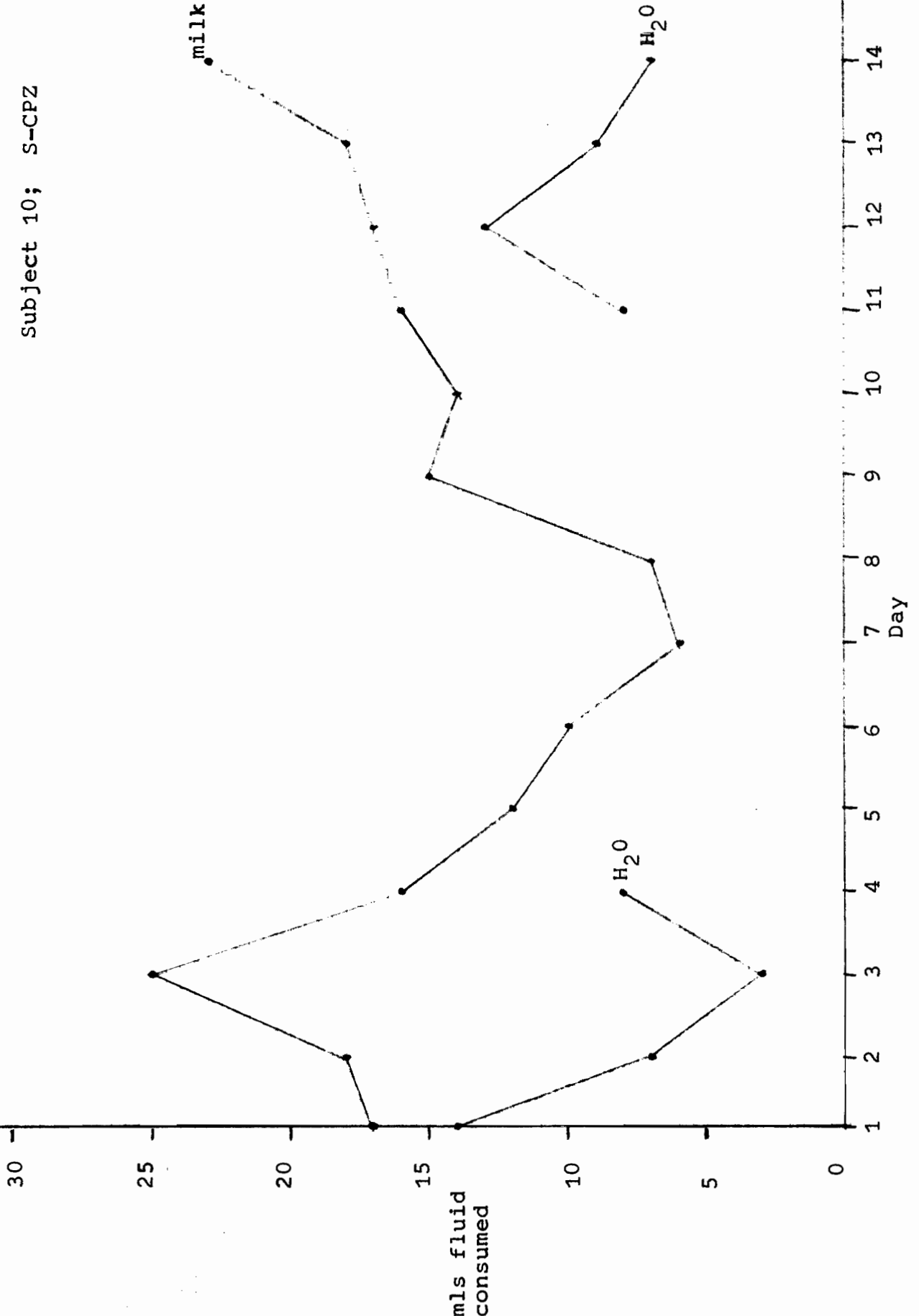
Subject 8; S-CPZ



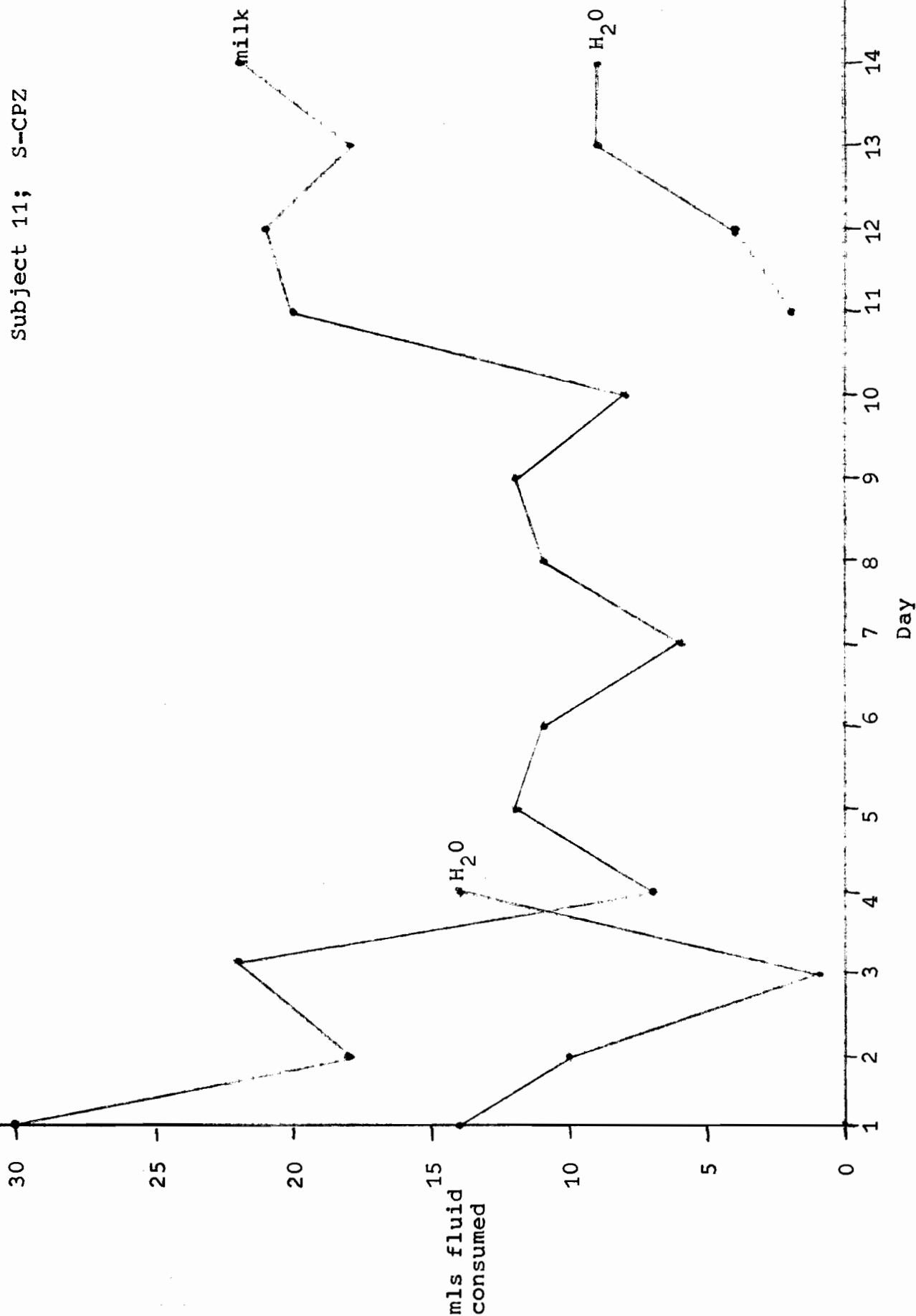
Subject 9; S-CPZ



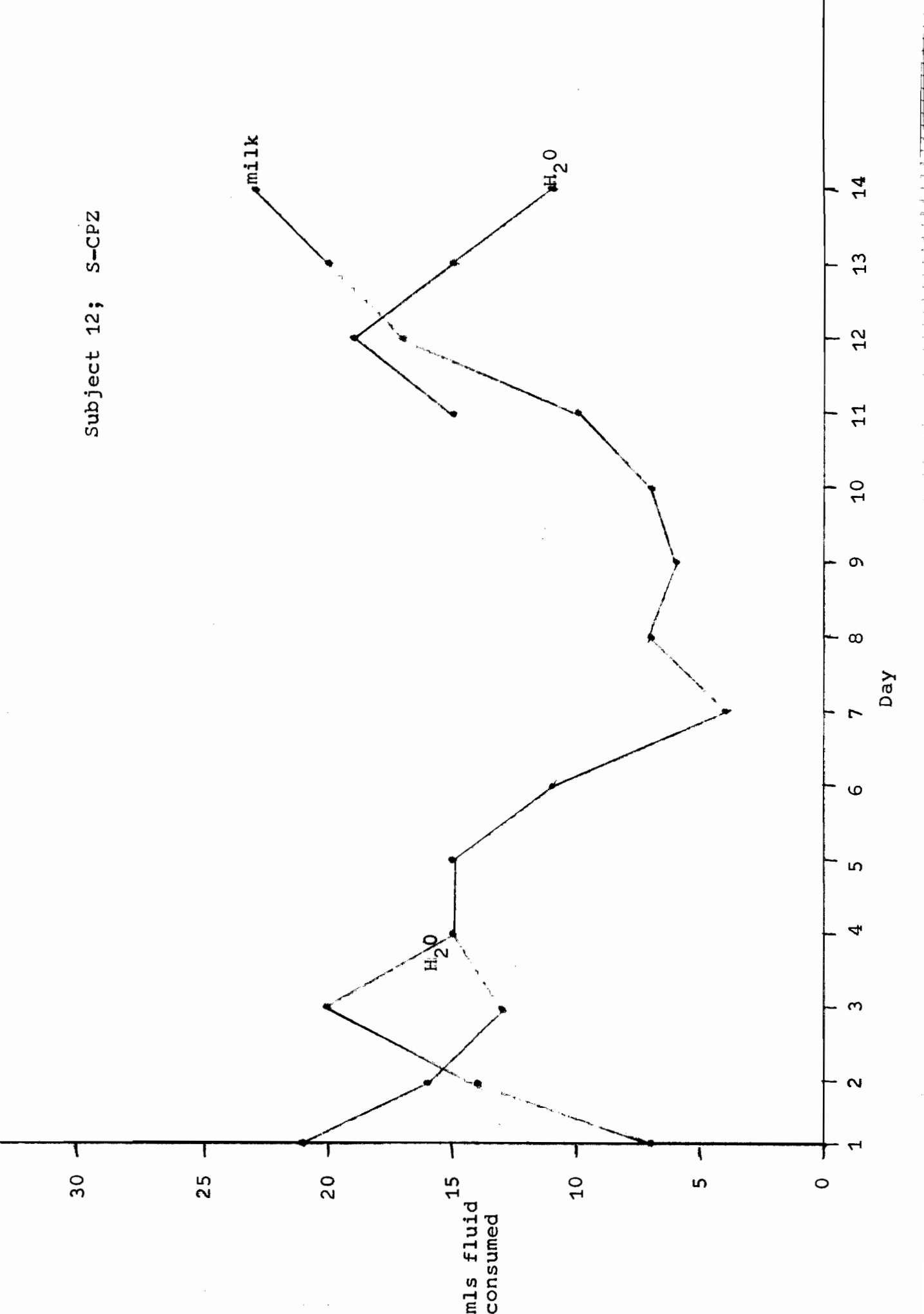
Subject 10; S-CPZ



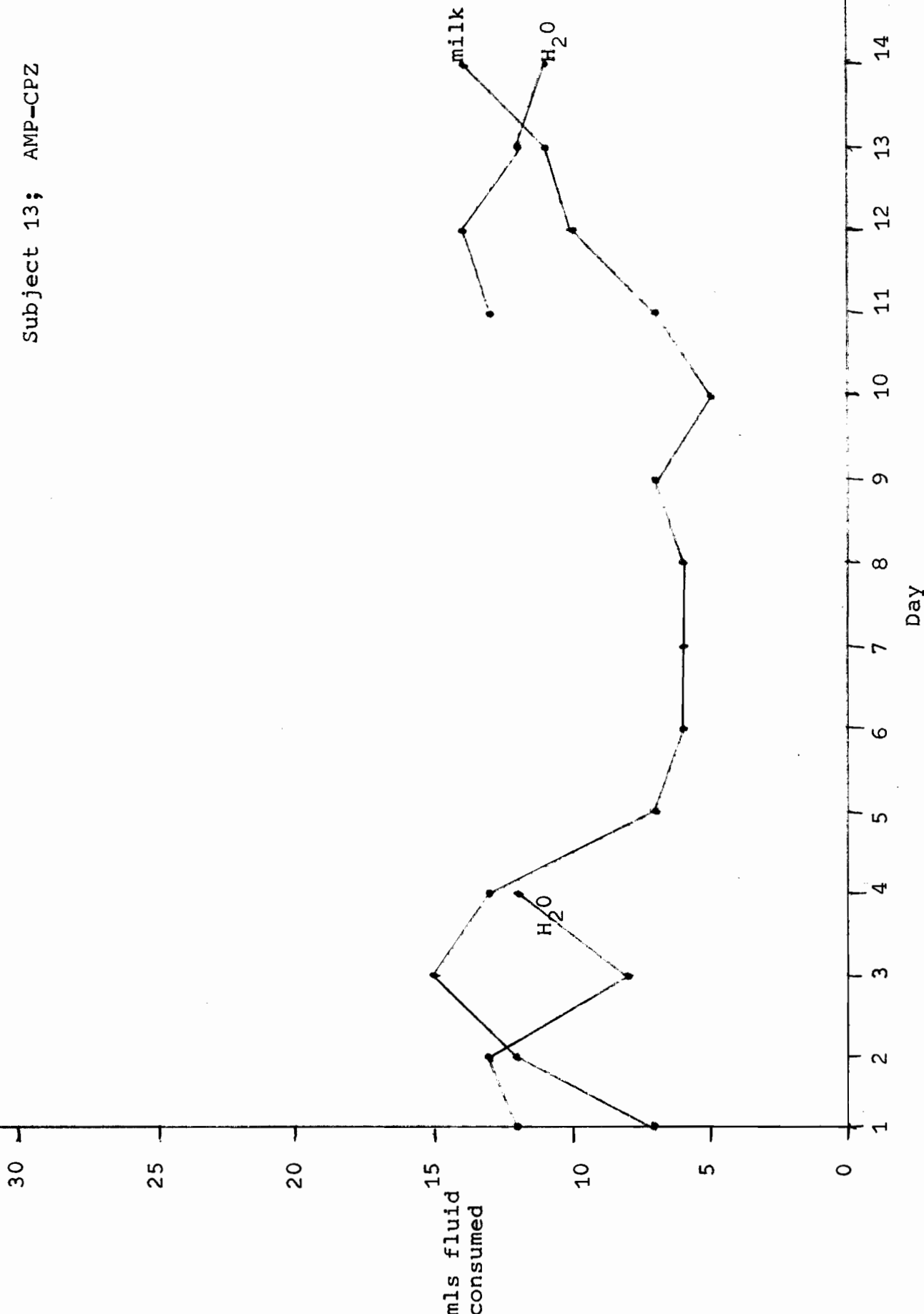
Subject 11; S-CPZ



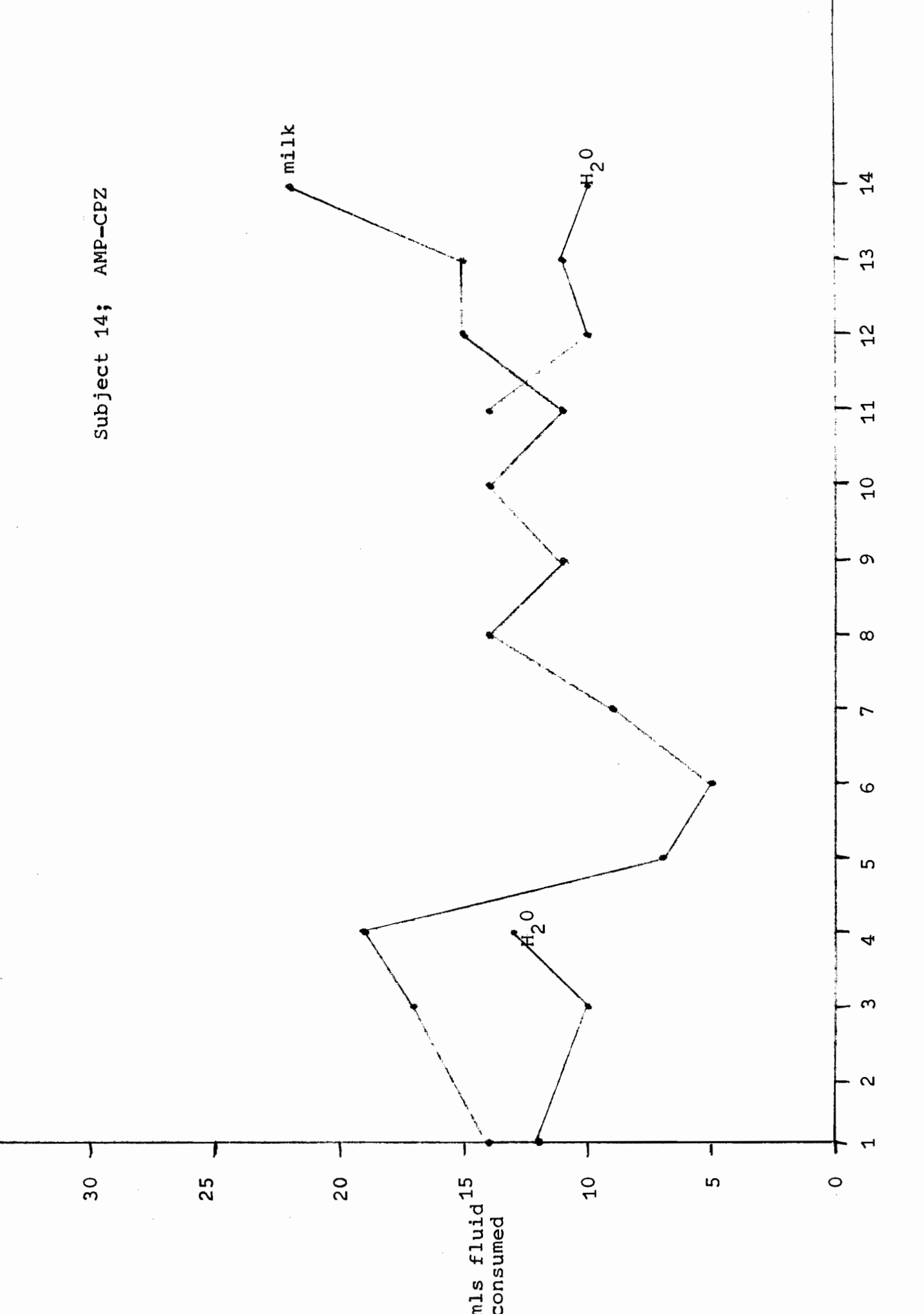
Subject 12; S-CPZ



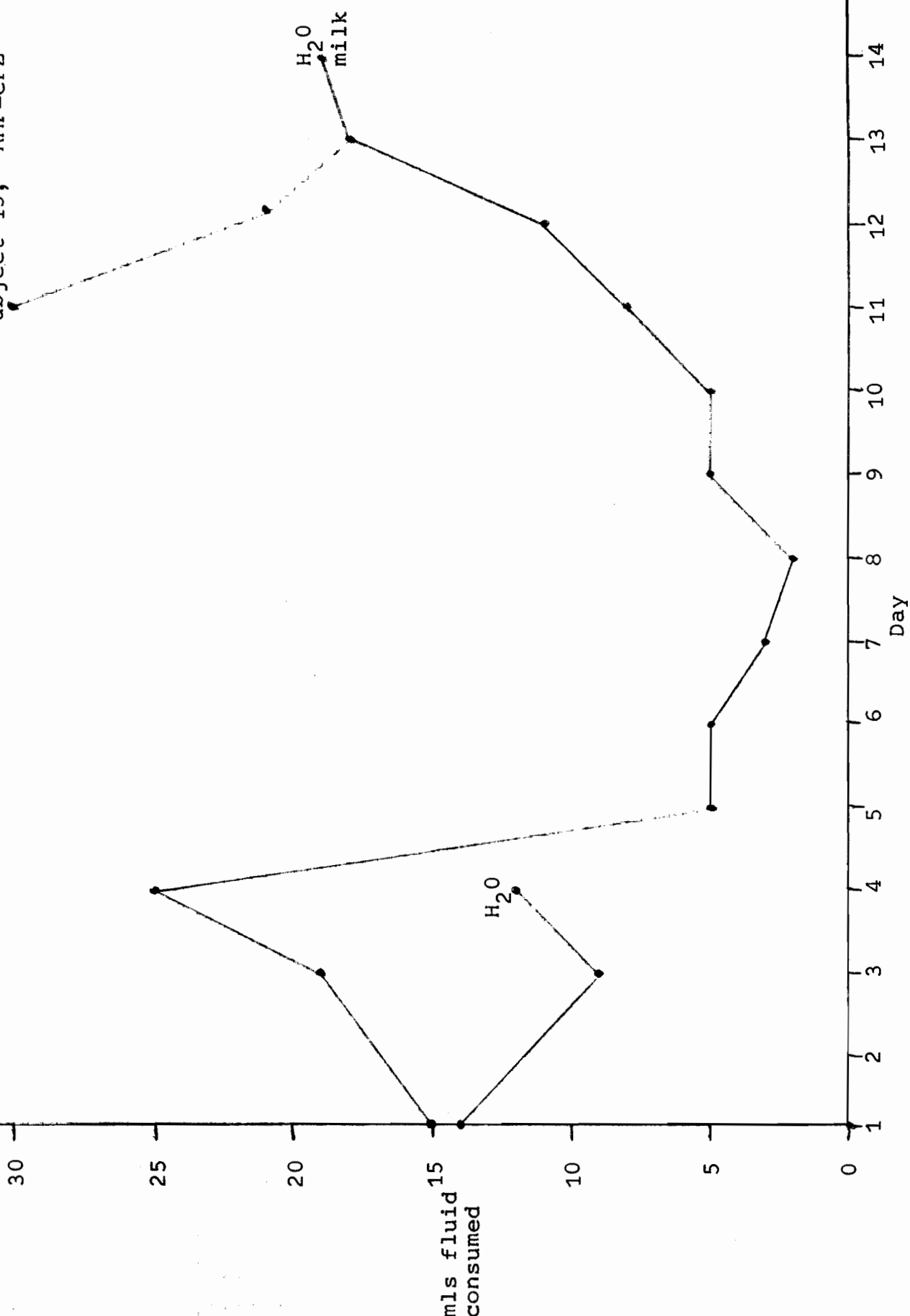
Subject 13; AMP-CPZ



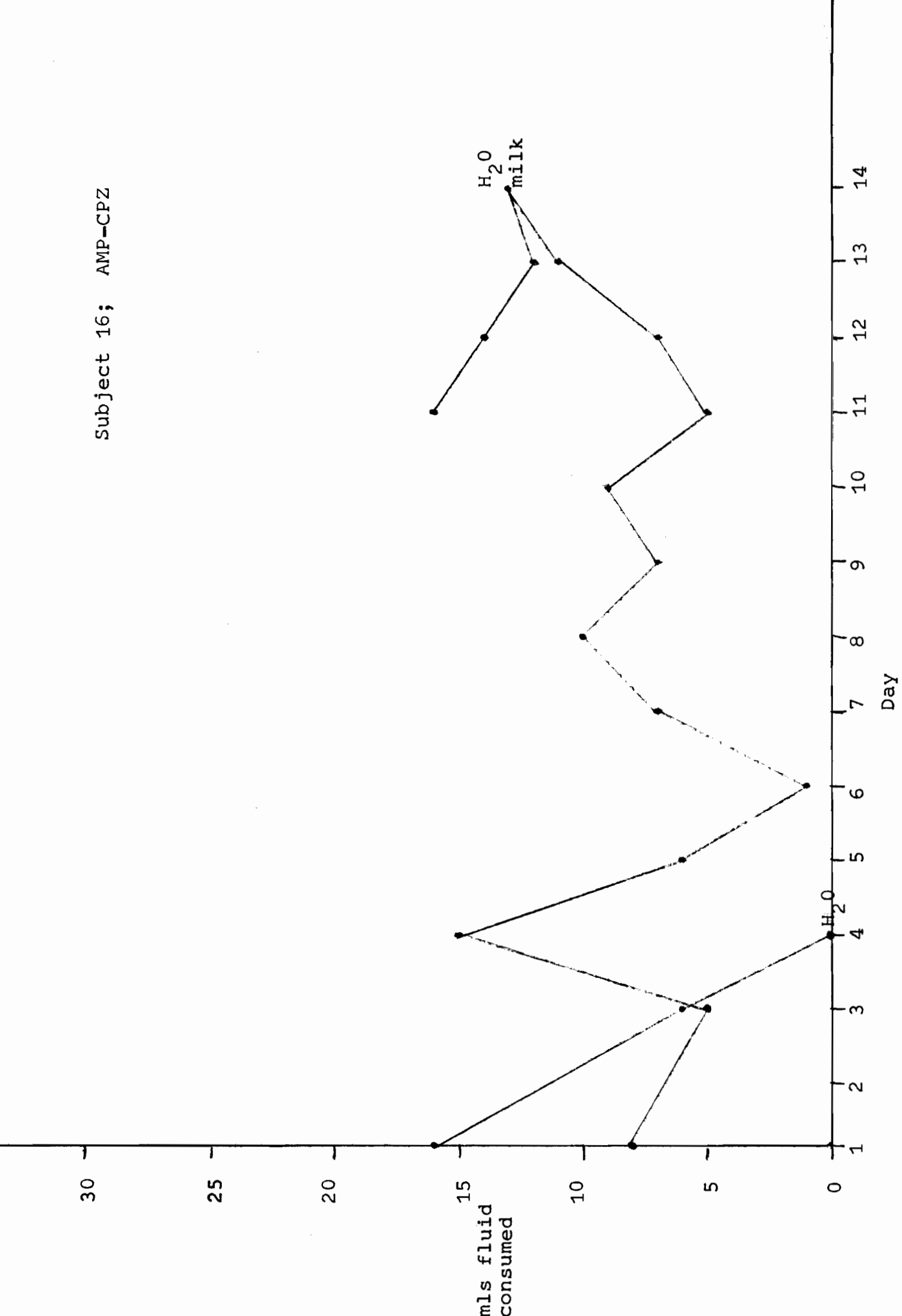
Subject 14; AMP-CPZ



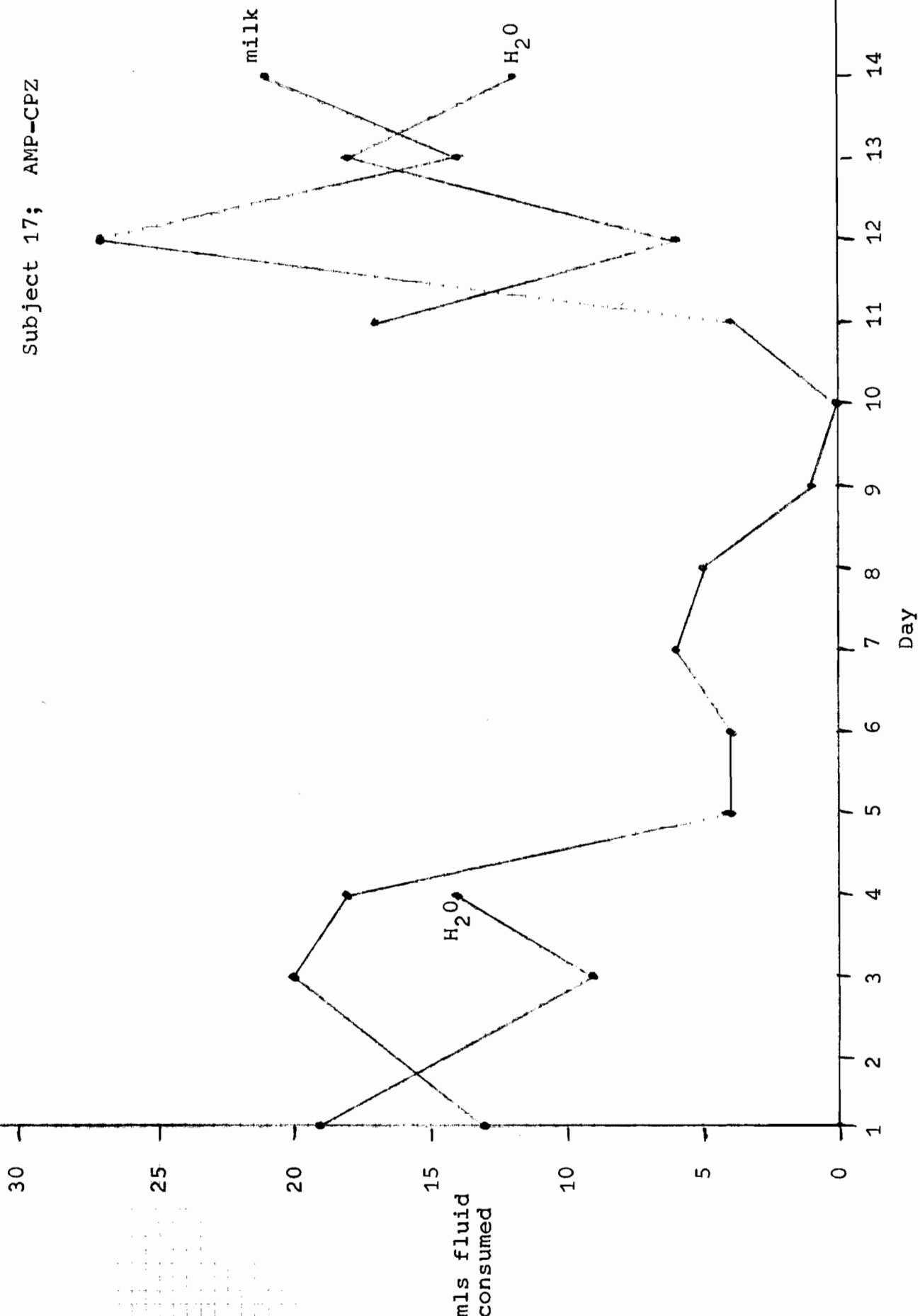
Subject 15; AMP-CPZ



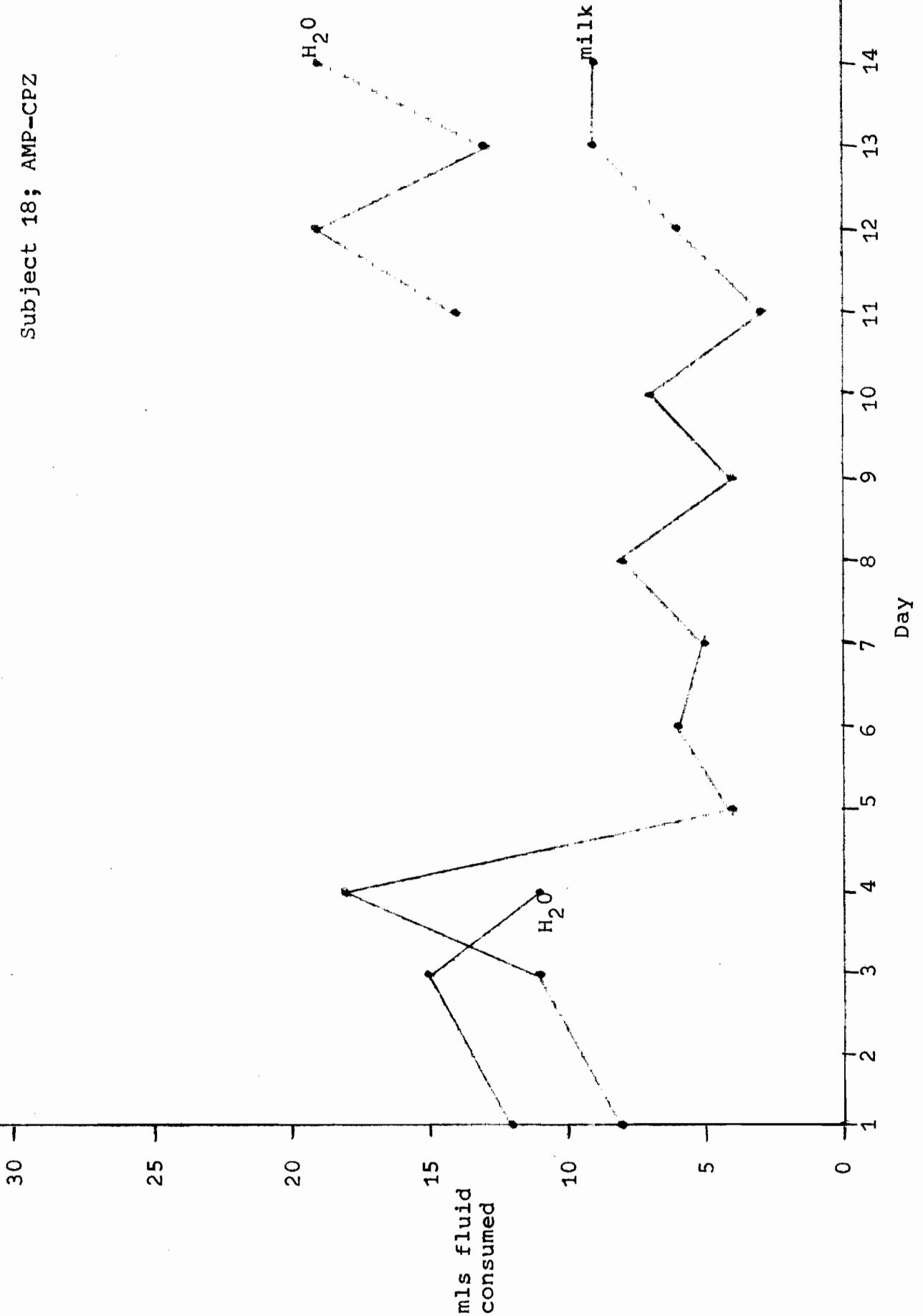
Subject 16; AMP-CPZ



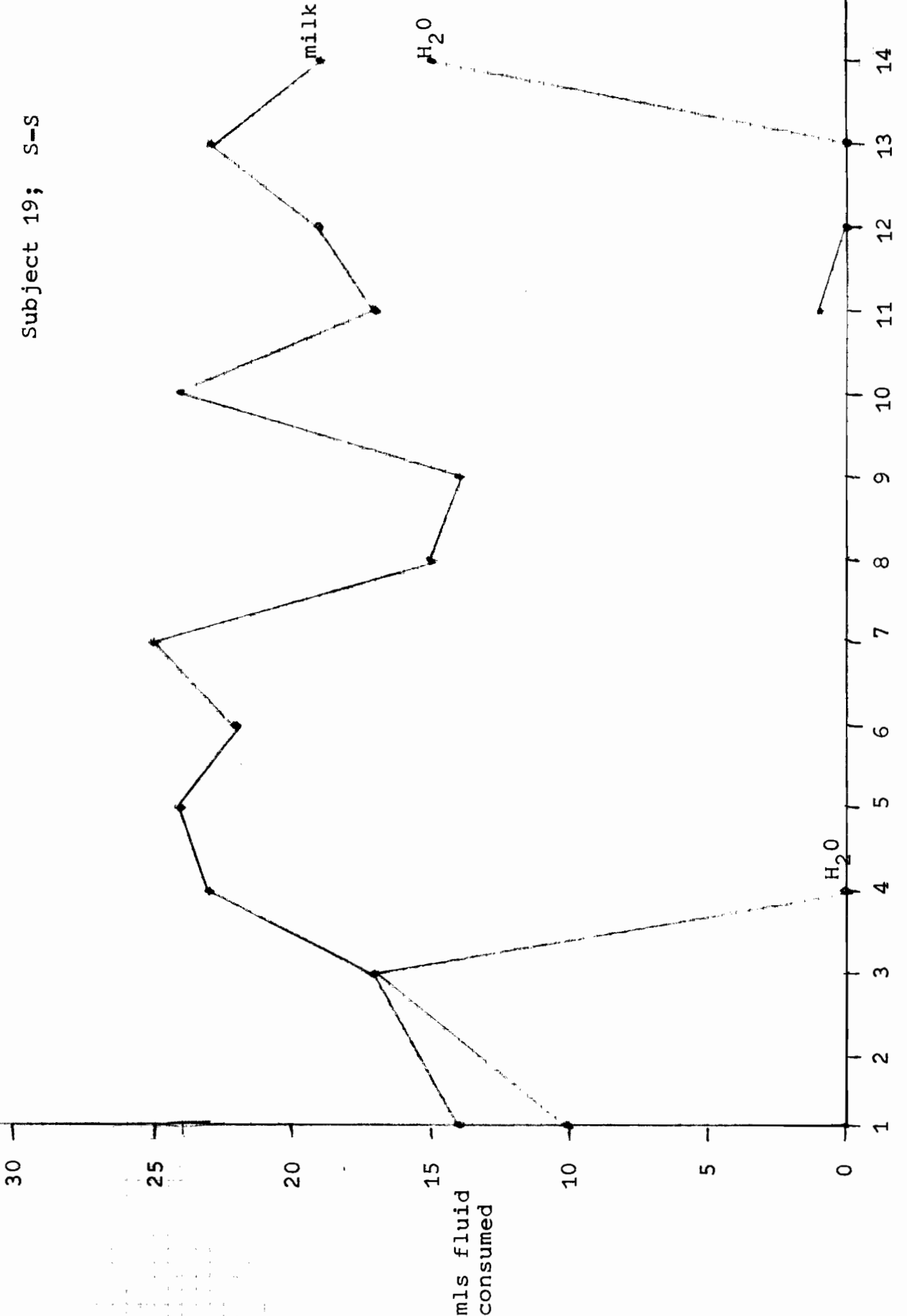
Subject 17; AMP-CPZ



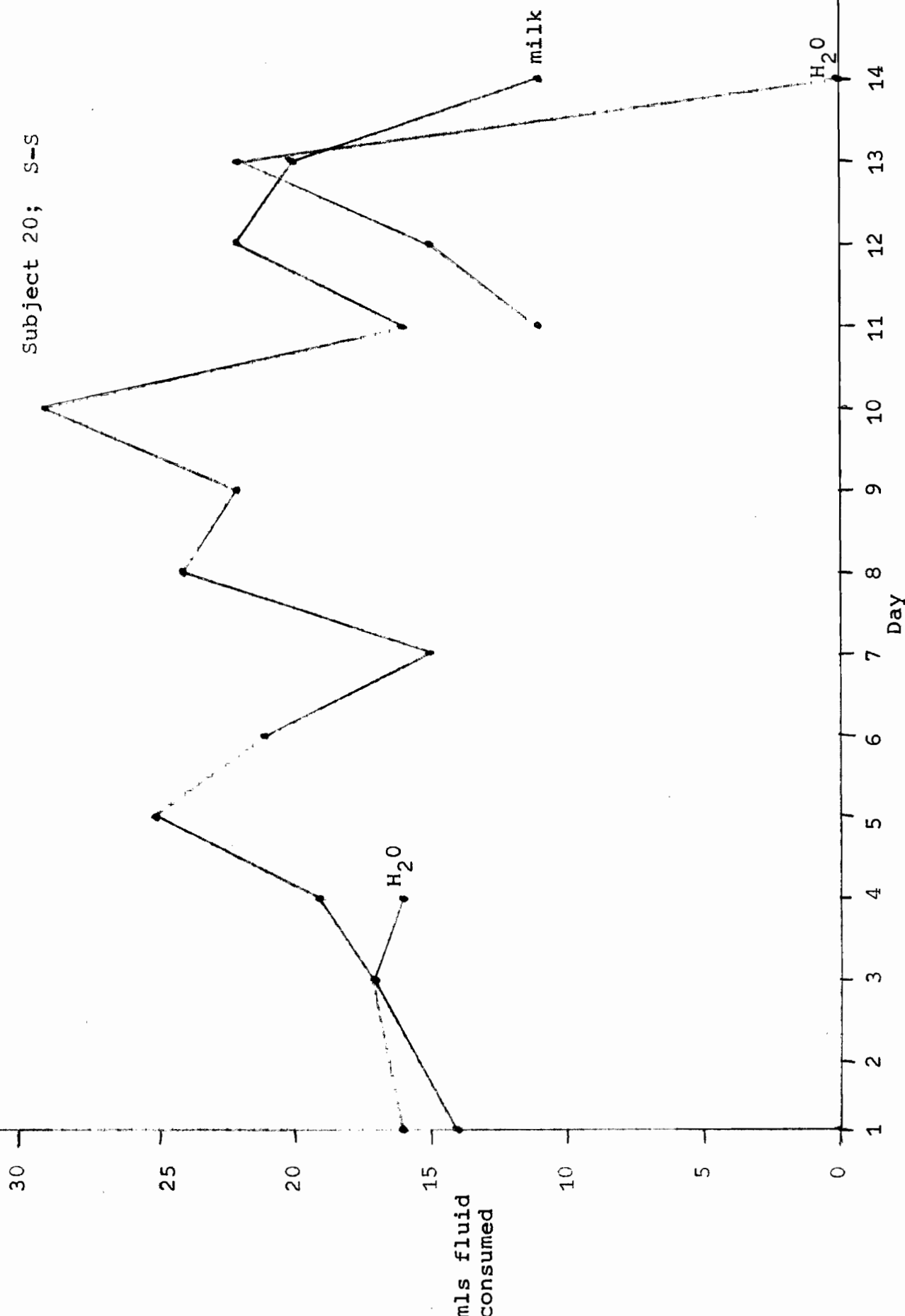
Subject 18; AMP-CPZ

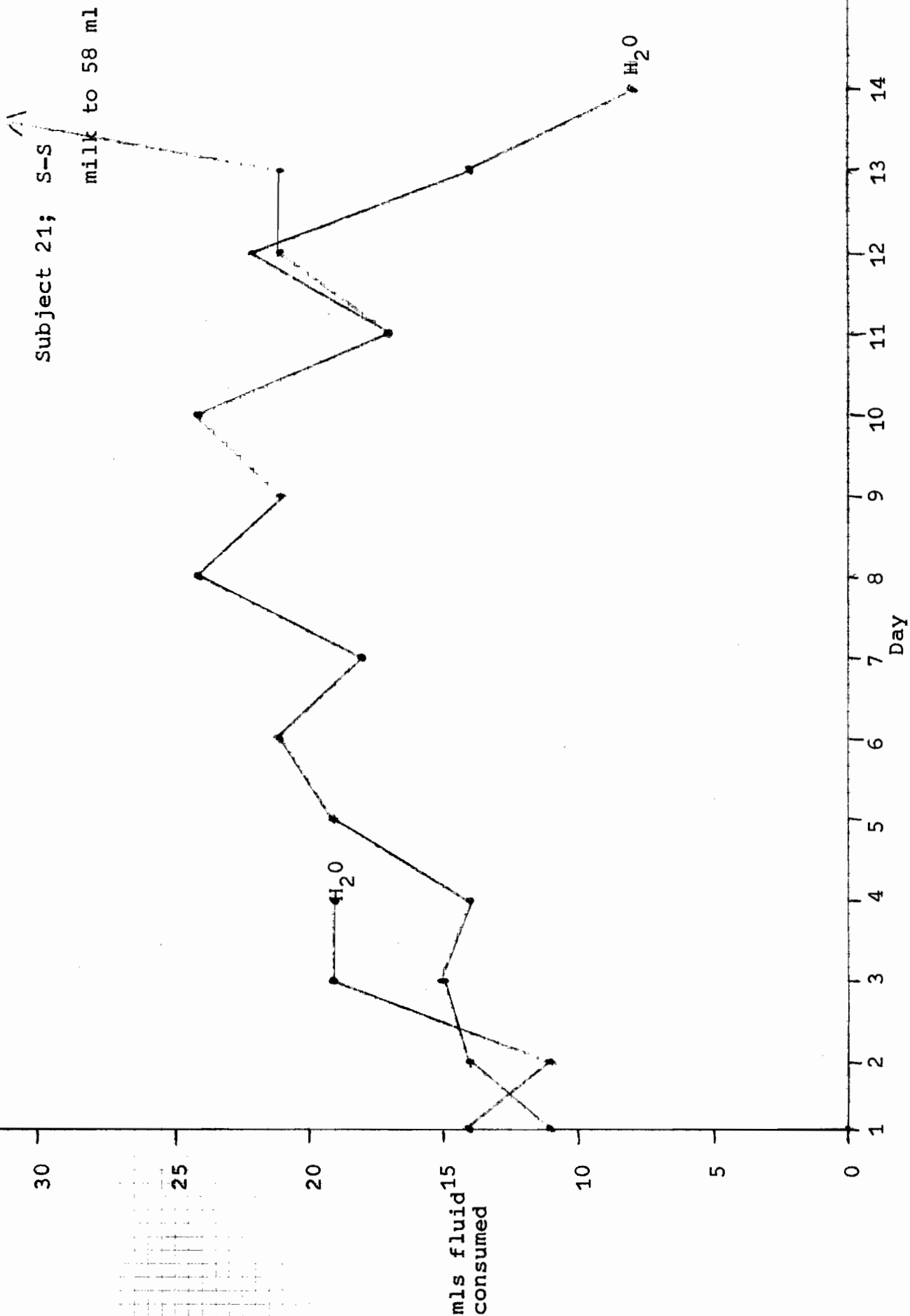


Subject 19; S-S



Subject 20; S-S





Subject 22; S-S

milk

H₂O

H₂O

30

25

20

15

10

5

0

mls fluid consumed

Day

1

2

3

4

5

6

7

8

9

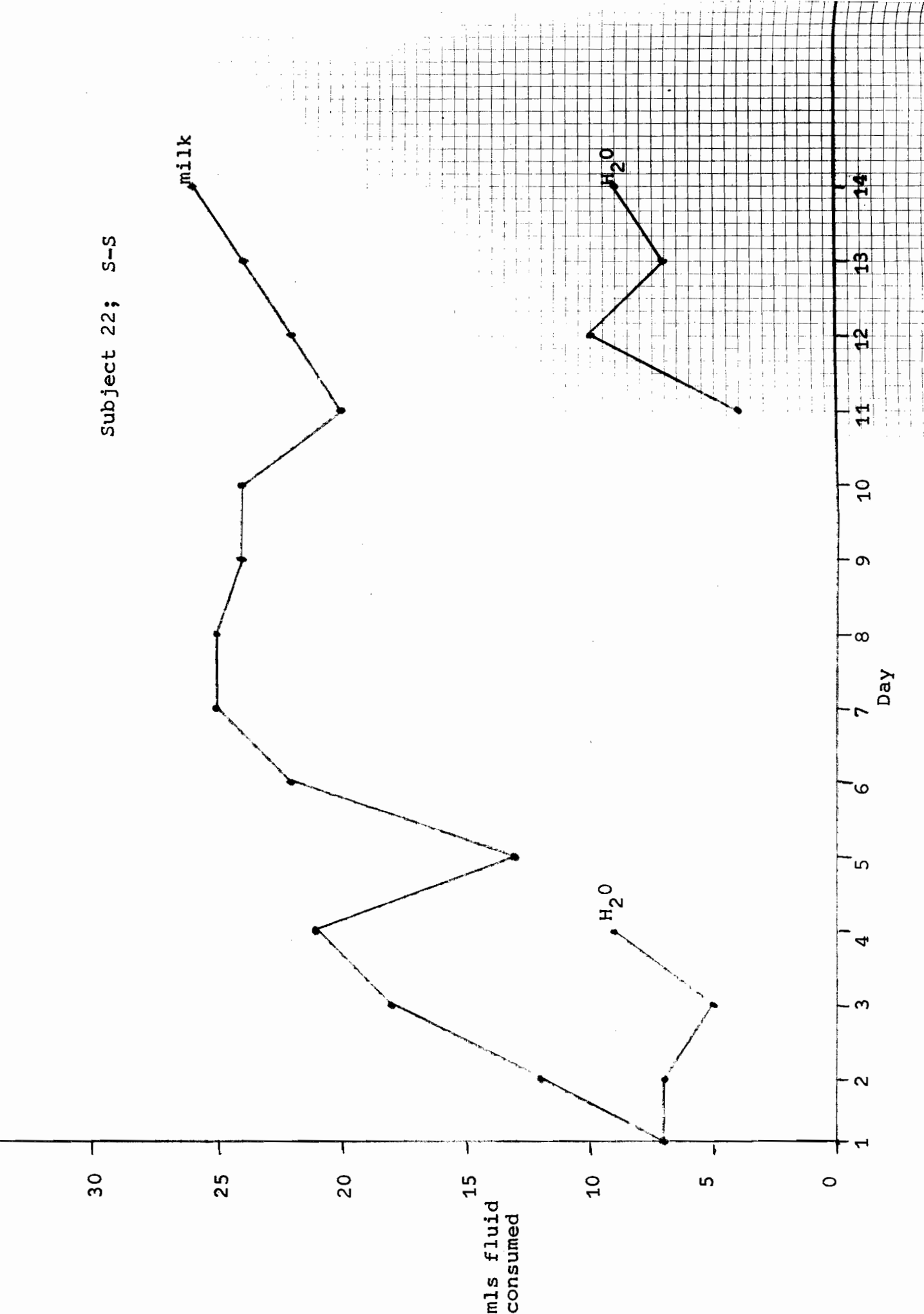
10

11

12

13

14



Subject 23; S-S

