STATISTICAL ANALYSIS PLAN

A Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Evaluate the Safety and Efficacy of IW-1973 in Patients with Type 2 Diabetes with Albuminuria Treated with Renin-Angiotensin System Inhibitors

Statistical Analysis Plan Status: Final V2
Statistical Analysis Plan Date: 24 September 2019

Study Drug: Praliciguat (IW-1973) Tablet

Cyclerion Study Number: C1973-203
Covance Study Number: 8362330

Clinical Phase: 2

Sponsor:
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(formerly part of Ironwood Pharmaceuticals, Inc.)

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Multiple Sites

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical efficacy and pharmacokinetic (PK) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

[redacted]

[redacted]
Date

Sponsor approval:

[redacted]

[redacted]

[redacted]

[redacted]
Date

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3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ABPM	ambulatory blood pressure monitoring
ADaM	analysis data model
ADMA	asymmetric dimethylarginine
ALQ	above the limit of quantitation
ANCOVA	Analysis of covariance
AOBP	automated office blood pressure
AE	adverse event
AECI	Adverse event of clinical interest
ARU	aspirin reaction units
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
BID	Twice daily
BP	Blood pressure
BLQ	Below the limit of quantification
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
[redacted]	[redacted]
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CV%	coefficient of variation
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
EC	Early Clinical
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
[redacted]	[redacted]
FGF-23	fibroblast growth factor
FPG	fasting plasma glucose
FPI	fasting plasma insulin
HOMA-IR	Homeostatic model assessment of insulin resistance
ICAM-1	intercellular adhesion molecule 1
ICF	Informed consent form
ICH	International Conference on Harmonisation
IL-6	interleukin-6
ITT	Intent-to-Treat
[redacted]	[redacted]
KIM-1	kidney injury molecule 1
L-Arg	L- arginine
LLN	Lower limit of normal
LLOQ	Lower limit of quantification

LOCF	last-observation-carried-forward
LS	Least square
MAP	mean arterial pressure
MCP-1	monocyte chemoattractant protein 1
MCS	Mental component score
MedDRA	Medical Dictionary for Regulatory Activities
MEMS	Medication Event Monitoring System
MMRM	mixed-effect model repeated measures
NGAL	neutrophil gelatinase-associated lipocalin
PCS	potentially clinically significant
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic
PP	per protocol
PRU	$P2Y_{12}$ reaction units
PT	Preferred term
QD	Once daily
QTc	QT correction; QT interval corrected for heart rate
QTcF	QTc calculated using the Fridericia correction
SAA	serum amyloid A
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
sCr	serum creatinine
SD	standard deviation
SDMA	symmetric dimethylarginine
[redacted]	[redacted]
[redacted]	[redacted]
SI	International System of Units
SOC	System organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TGF-β	transforming growth factor beta
TNF-α	tumor necrosis factor alpha
TNFR-1	tumor necrosis factor receptor 1
UACR	urine albumin creatinine ratio
ULN	Upper limit of normal
ULOQ	upper limit of quantitation
VCAM-1	vascular cell adhesion molecule 1
WHO	World Health Organization

4 INTRODUCTION

Note: This study was initiated by/on behalf of Ironwood Pharmaceuticals, Inc. As of 01 April 2019, Cyclerion Therapeutics was established as an independent spin-off of Ironwood and has assumed the sponsorship of praliciguat (IW-1973).

This SAP has been developed after review of the clinical study protocol (protocol amendment No. 4 [dated 20 December 2017]).

This SAP describes the planned analysis of the safety, tolerability, efficacy and PK data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of efficacy and PK concentration data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Cyclerion and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR, along with the final version of the protocol, as applicable.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Cyclerion and Covance EC Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

Primary Objectives

1. To assess the safety and tolerability of oral praliciguat when administered daily for approximately 12 weeks to adult patients with type 2 diabetes mellitus with albuminuria who are on a stable regimen of renin-angiotensin system inhibitors

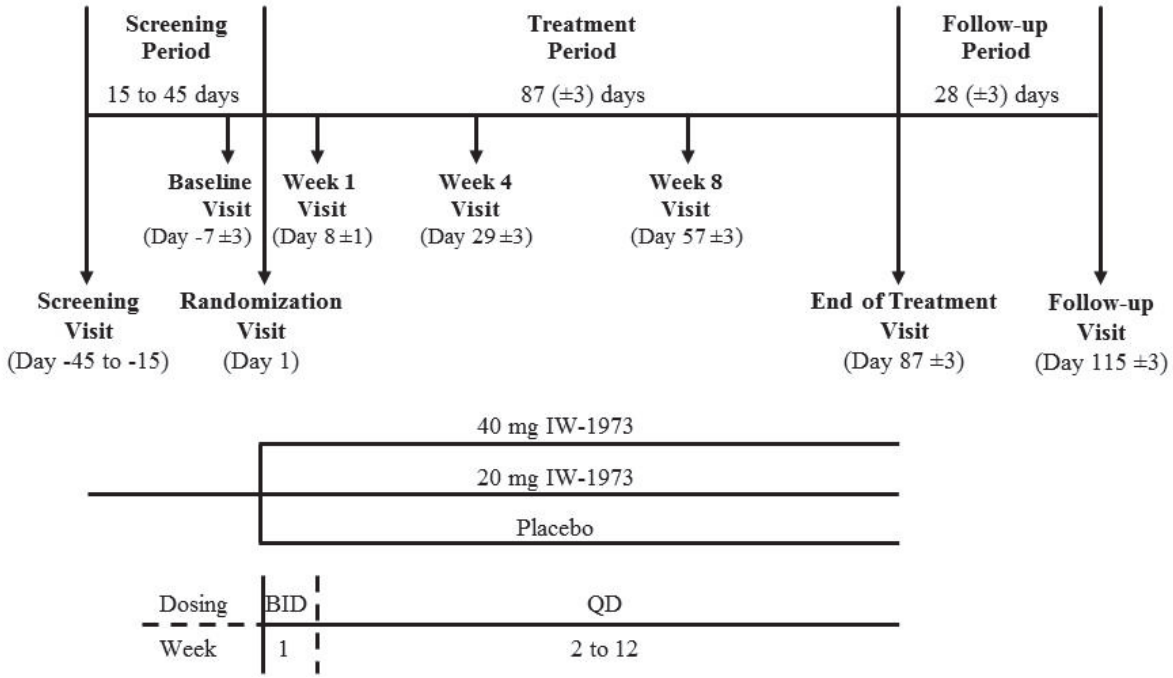
2. To evaluate the effect of oral praliciguat on renal function when administered daily for approximately 12 weeks to adult patients with type 2 diabetes mellitus with albuminuria who are on a stable regimen of renin-angiotensin system inhibitors

Exploratory Objectives

6 STUDY DESIGN

Study C1973-203 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group 12-week study to evaluate 2 dose levels of praliciguat compared with placebo. The study will enroll approximately 150 adult patients with type 2 diabetes mellitus, albuminuria, and impaired renal function. Patients will be stratified by baseline estimated glomerular filtration rate (eGFR) (ie, eGFR 30 to 45, >45 to 60, and >60 to 75 mL/min/1.73 m^2) and randomized in a 1:1:1 ratio to receive 20 mg praliciguat, 40 mg praliciguat, or placebo daily for approximately 12 weeks. Patients will receive daily oral study drug for up to 90 days. Total patient participation will be 131 to 163 days.

Figure 1: Overview of Study Design



7 TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs.

Study Treatment Name	Treatment Order on TFLs
Placebo	1
20 mg Praliciguat	2
40 mg Praliciguat	3
Overall Praliciguat	4

Table 2 summarizes the dosage and dosing regimen that will be administered during the 12-week double-blind treatment period.

Table 2. Dosage by Week

Dose	Week 1, BID Dosing	Weeks 2 through 12, QD Dosing
20 mg	one 10-mg praliciguat tablet, orally twice daily	two 10-mg praliciguat tablets, orally once daily
40 mg	one 20-mg praliciguat tablet, orally twice daily	two 20-mg praliciguat tablets, orally once daily
Placebo	one matching placebo tablet, orally twice daily	two matching placebo tablets, orally once daily

BID=twice daily; QD=once daily

Per Investigator discretion, on a per-patient basis, patients will be allowed to reduce his or her daily dose by half, ie, from 2 tablets daily to 1 tablet daily. Each patient's dose may only be reduced once and will not be increased after reduction.

8 RANDOMIZATION AND BLINDING

Patients who meet all the inclusion criteria and none of the exclusion criteria will be stratified by baseline eGFR and randomized 1:1:1 to 20 mg praliciguat, 40 mg praliciguat or placebo at the Randomization Visit on Day 1 through central randomization. The randomization schedule was prepared by an independent statistician using SAS® PLAN procedure (PC SAS® Version 9.3) using a block size of 3. The lowest randomization number within a stratum will be assigned to the first patient that qualifies for randomization, and subsequent assignments will proceed in increasing sequential order within a block as patients qualify for the study. The randomization schedule also includes separate blocks for patients at sites that have the capability to perform VerifyNow assessments to facilitate approximately equal proportions of patients with VerifyNow assessments in each treatment group.

This is a double-blind, placebo-controlled study in which the patients, investigators, study staff and the sponsor study team will remain blinded to the randomization scheme until the blind is formally broken for all subjects after all subjects have completed the study and the study database is locked.

Please refer to Section 13 for details on the external Data Monitoring Committee's (DMC) review of masked and potentially unblinded safety data to monitor trial safety.

Prior to database lock, a treatment assignment may be unblinded by the site only in emergency situations and/or by the Sponsor's Global Patient Safety group if the knowledge of the treatment received is essential for managing a serious adverse event (SAE).

9 STUDY SCHEMATIC AND SCHEDULE OF ASSESSMENTS

The schedule of evaluations for Study C1973-203 is presented in Table 3.

Table 3. Schedule of Events

Visit Days → Study Procedure ↓	Screening Period		Treatment Period					Follow-up Period
	Screening Visit (Day -45 to -15)	Baseline Visit (Day -7 ±3)	Randomization Visit (Day 1)	Week 1 Visit (Day 8 ±1)	Week 4 Visit (Day 29 ±3)	Week 8 Visit (Day 57 ±3)	End of Treatment Visit (Day 87 ±3)	Follow-up Visit (Day 115 ±3)
ICF signed	X							
Demographics	X							
Medical history	X							
Prior & concomitant meds	X	X	X	X	X	X	X	X
Inclusion/exclusion evaluation/review	X	X	X					
Physical exam	X						X	
Hepatitis (HBsAg, HCV) & HIV screen	X							
Drug screen (a)	X							
Urine pregnancy test (b)	X	X	predose	predose	predose	predose	predose	X
Weight (W) & height (H)	W, H	W	W	W	W	W	W	W
12-lead ECG (c)	X	X					predose	
Respiratory rate and oral temperature	X		pre: 0 (≤30m) pd: 1h (±15m)	pre: 0 (≤30m) pd: 1h (±15m)			X	X
Seated pulse and BP (d)	X	X						
First-void urine for UACR (e)	X	preVisit	preVisit	preVisit	preVisit	preVisit	preVisit	preVisit

Visit Days → Study Procedure ↓	Screening Period		Treatment Period					Follow-up Period
	Screening Visit (Day -45 to -15)	Baseline Visit (Day -7 ±3)	Randomization Visit (Day 1)	Week 1 Visit (Day 8 ±1)	Week 4 Visit (Day 29 ±3)	Week 8 Visit (Day 57 ±3)	End of Treatment Visit (Day 87 ±3)	Follow-up Visit (Day 115 ±3)
Issue UACR sample supplies	X	X	X	X	X	X	X	
Urinalysis sample (f)	X	X					predose	X
Serum chemistry, coagulation, hematology (f)	X	X	serum creatinine & glucose only pre: 0 (≤30m)	serum creatinine & glucose only pre: 0 (≤30m)	pre: 0 (≤30m)	serum creatinine & glucose only pre: 0 (≤30m)	pre: 0 (≤30m)	X
Hemoglobin A1c (f)	X	X		pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	X
Adverse event evaluations	X	X	X	X	X	X	X	X
Fasting plasma glucose & insulin (f)		X		pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	
Urine cotinine			predose					
24- or 12-h ABPM (h)		X (24h)			X (12h)	X (12h)	X (24h)	
Return of ABPM monitor			X			X	X	X
Orthostatic (seated to standing) pulse and BP (i)			pre: 0 (≤30m) pd: 1,2,4,6h (±15m)	pre: 0 (≤30m) pd: 1,2,4,6h (±15m)	pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	X
Randomization			X					

Visit Days → Study Procedure ↓	Screening Period		Treatment Period					Follow-up Period
	Screening Visit (Day -45 to -15)	Baseline Visit (Day -7 ±3)	Randomization Visit (Day 1)	Week 1 Visit (Day 8 ±1)	Week 4 Visit (Day 29 ±3)	Week 8 Visit (Day 57 ±3)	End of Treatment Visit (Day 87 ±3)	Follow-up Visit (Day 115 ±3)
MEMS instruction/review			X	X	X	X		
Study drug dispensed			X		X	X		
In-clinic study drug administration (j)			X	X	X	X	X	
Study drug return (k)				X	X	X	X	
Pharmacokinetic blood samples			pre: 0 (≤30m) pd: 1,3,6h (±15m)	pre: 0 (≤30m) pd: 1,3,6h (±15m)	pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m) pd: 3h (±15m)	X
[redacted]								
Study completion								X

ABPM=ambulatory blood pressure monitoring; automated office blood pressure (AOBP); BP=blood pressure; cGMP=cyclic guanosine monophosphate; ECG=electrocardiogram; [redacted] h=hour(s); H=height; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; KDQOL-SF=Kidney Disease Quality of Life–Short Form; m=minute(s); MEMS=Medication Event Monitoring System; pd=postdose; [redacted] pre=predose; [redacted] UACR=urine albumin creatinine ratio; W=weight

a. Urine drug screen for selected drugs of abuse

b. For female patients, a negative pregnancy test (by urine dipstick) must be documented at all study visits and confirmed negative before dosing, when applicable. Female patients who are postmenopausal (no menses for ≥12 consecutive months) or surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]) do not have to have a urine pregnancy test. Patients should be reminded of birth control requirements.

c. Patients must be supine for ≥5 m before the ECG recording (Note: If on initial ECG, QTcF is ≥450 msec for male patients or is ≥470 msec for female patients, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the patient's eligibility).

d. Seated BP will be the average of 3 measurements obtained by AOBP at 2-m intervals after the patient has been sitting quietly for ≥5 m.

e. At the Screening Visit, single urine sample, which may not be first void; thereafter, 2 first-void urine samples collected on the 2 consecutive mornings before each scheduled visit. Patients will be supplied with specimen collection supplies at the preceding study visit.

f. Except for the Screening Visit, patients must fast for ≥8 h before predose sample collection. Excess [redacted]

g. [redacted]

h. Patients will begin using the ABPM monitor at the clinic visit before dosing, where applicable, will wear it for ≥12 or 24 h, and return the monitor to the clinic.

i. Patient must sit quietly for ≥5 m before seated BP and pulse measurements are taken by AOBP, and then assume standing position for 30 to 60 seconds before standing BP and pulse measurements are taken. At End of Treatment visit, seated predose BP will be the average of 3 measurements. When applicable, BP and pulse measurements will be obtained before blood draws and before study drug administration.

j. Study drug will be administered in the clinic on study visit days after predose assessments (Day 1, morning dose only). Patients should take study drug with water, may take with or without food, and for QD dosing (Week 1 Visit onward), may swallow 2 tablets together.

k. At the Week 1 Visit, patients will bring the study drug bottles dispensed on Day 1 to the clinic. MEMS Caps will be read, and the subject will be administered their Day 8 (±1) study drug dose in the clinic from the Day 1 bottles. The subject will continue to dose from the Day 1 bottles until they return for the Week 4 Visit.

10 SAMPLE SIZE JUSTIFICATION

Using an estimate of standard deviation of 0.67[3], a sample size of 40 patients per treatment group would provide approximately 80% power to detect a mean between-group difference of -0.376 units in change from baseline in log-transformed UACR over 12 weeks, with a one-sided significance level of 0.05 for at least 1 dose versus placebo comparison. This difference corresponds to a 31% between-group reduction of geometric mean change from baseline in UACR. Assuming a drop-out rate of 20%, approximately 150 patients will be randomly assigned in a 1:1:1 ratio (approximately 50 patients per treatment group) to 20 mg praliciguat, 40 mg praliciguat, or placebo.

11 DEFINITION OF ANALYSIS POPULATIONS

The following populations will be defined for this study:

- **Screened:** All screened patients who have signed the informed consent form for the study and received a patient identification number.
- **Safety:** All randomized patients who receive at least 1 dose of study drug. Data from patients in this population will be summarized according to the treatment they actually received. If a patient received more than 1 treatment, then the patient's data will be summarized according to the treatment they received for the longest duration.
- **Intent-to-Treat (ITT):** All randomized patients who receive at least 1 dose of study drug. Patients in this population will be evaluated according to the treatment group they were assigned to at Randomization.
- **Per Protocol (PP) Population**: Subset of ITT patients who did not have any major protocol deviations that might have a potential impact on efficacy evaluations and did not have a dose reduction.
- **PK Population:** All randomized patients who receive at least 1 dose of study drug and have at least 1 postdose assessment with measurable PK concentration levels.

[redacted]

12 STATISTICAL METHODOLOGY

12.1 General

For descriptive summaries, the number of patients with non-missing values (n) for the summarized endpoint, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum will be calculated for continuous variables. For clinical laboratory data, vital signs and ECG data the 95% CI for the mean will also be presented. For summaries of continuous PK data, the geometric mean and the coefficient of variation (CV) will also be presented. For categorical variables, number and percentage of patients in each category will be presented. Percentages will be based on the total number of patients with non-missing values. If there are missing values, the number missing will be presented, but without a percentage.

All summary statistics will be presented by treatment group (Placebo, 20 mg Praliciguat, 40 mg Praliciguat, and Overall Praliciguat), unless otherwise specified.

Data from screen-failure subjects will be presented in by-patient listings.

All hypothesis tests will be one-sided with a 5% significance level (two-sided significance level of 10%), and two-sided 90% confidence intervals (one-sided 95% confidence intervals) will be used, unless otherwise specified.

All statistical analyses will be performed using SAS® Version 9.4 or later. SF-12 scoring for the component scores will be performed using QualityMetric Health Outcomes™ Scoring Software 5.0

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilized to ensure compliance with CDISC standards.

12.1.1 Study Periods

Table 4. Study Periods

Period	Start Date	End Date
Screening/Baseline	Date of Signed ICF	Up to Date/Time of First Dose
Treatment	Date/Time of First Dose	Date of Last Dose
Follow-up	Date of Last Dose +1	Follow-up Visit Date

12.1.2 Definition of Baseline and Change from Baseline

The following definitions of baseline will be used to calculate change from baseline endpoints, unless specified otherwise:

Baseline for UACR will be defined as the average of the assessments from the samples collected on the 2 consecutive mornings before the scheduled Randomization Visit (Day 1). Log Baseline will be calculated as the average of the log-transformed values from the individual assessments. If only one sample was collected, then the single assessment will be used.

For endpoints evaluated from ABPM monitoring, baseline will be calculated using the predose assessments at the Baseline Visit that correspond to the respective postdose assessments.

For all other endpoints, study baseline will be defined as the last non-missing assessment before first administration of study drug, usually the predose assessment on Day 1

12.1.3 Handling of Dropouts or Missing Data

All available data will be included.

For mixed-effect model repeated measures (MMRM) analyses, patients with missing baseline and all treatment period values will be excluded. The missing at random assumption of MMRM will be utilized, and no imputation will be performed for missing observations.

For responder analyses, all patients will be included. Patients with missing postdose data will be treated as non-responders.

All safety and tolerability data will be summarized and analyzed when data values are available for a patient. Data handling for missing dates and other key safety data are described in Section 16.

12.1.4 Multiple Comparisons/Multiplicity

No multiple comparison adjustments are planned for this study, as the focus is more on estimation rather than inferential testing. All reported p-values will be considered nominal.

12.1.5 Repeat and Unscheduled Readings

If a patient has repeated safety assessments (eg, for a lab endpoint) prior to initial dosing of study drug, then the results from the final non-missing assessment made prior to the start of study drug will be used as baseline. If there is more than 1 safety measurement (eg, for a lab endpoint) at a postbaseline timepoint, only the last measurement will be used. All postbaseline assessments, including unscheduled assessments, if any, will be used for PCS value determination, and all assessments will be presented in by-patient listings.

12.1.6 Protocol Deviations

Major protocol deviations will be identified and documented for all randomized patients prior to unblinding through data reviews and programmatic checks of the study data and used to define the PP population, unless specified otherwise. Major protocol deviations will be determined based on review of all protocol deviations performed by members of the study team, including but not limited to the Sponsor Medical Monitor and study Biostatistician. The categories of major protocol deviations to be reviewed will include, but are not limited to, patients who:

Did not meet any of the following key inclusion/exclusion criteria (Inclusion criteria # 3, 4, 6a, 6b or Exclusion criteria # 1, 8, 10, 11, 12, 18 - use of PDE 5 inhibitors, nitrates, or nitric oxide donors)

Had overall study drug compliance rate ≤60% in the last 8 weeks of the treatment period or did not have measurable (non-BLQ) plasma concentration levels at predose assessments at Week 8 and Week 12, despite being randomized to one of the Praliciguat arms. The unblinded review of plasma concentration levels to identify such cases will be performed after database lock and study unblinding.

Received the wrong treatment or incorrect dose.

Received disallowed concomitant medication that could meaningfully impact results, such as PDE5 inhibitors (sildenafil, tadalafil, vardenafil, etc.) or nitrates (nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, sodium nitroprusside, amyl nitrate, etc.), if used > 2× a week for all 12 weeks of the Treatment Period or for the last 6 weeks, or other sGC stimulators, including riociguat.

The number and percentage of subjects with major protocol deviations will be summarized by type of deviation and by treatment group for the ITT Population. All protocol deviations will be presented in a by-patient listing.

12.2 Demographics and Patient Disposition

The number of patients screened and screen-failed, along with the reason for screen failure will be presented for the Screened Population. Categorical summaries of patients who are included in

each of the analysis populations, who completed the study, or who discontinued early (along with the reasons for discontinuation) will be presented. Patient disposition will also be summarized by investigational site. In addition, by-patient listings of patient disposition, including all patients who failed screening or terminated early, will be presented.

Patient demographics (age, age category, sex, race, ethnicity, weight, height, and body mass index [BMI, defined as weight in kg divided by height in meters squared]) and baseline eGFR strata will be summarized by treatment group for the ITT and if different, for the Safety and Per Protocol Populations.

12.3 Medical History

Medical history, abnormalities and surgeries, reported and occurring prior to screening will be coded using MedDRA version 20.0 or newer. Categorical summaries will be presented by MedDRA system organ class (SOC) and preferred term by treatment arm and overall for the Safety Population. Patients will be counted once per SOC and PT.

12.4 Prior and Concomitant Medication

Prior medications will be defined as medicines taken or procedures performed on the patient prior to the date of first dose of study drug. Concomitant medications and procedures will be defined as medications taken or procedures performed on or after the date of first dose of study drug. Any medication taken or procedure performed after the date of last dose of study drug will not be considered concomitant for the purposes of analysis.

Reported medication will be coded using the World Health Organization (WHO) Drug Dictionary, Version March 2017 Enhanced Dictionary Version B2 or newer to their Anatomical Therapeutic Chemical (ATC) class and PT. Categorical summaries for both prior and concomitant medications will be presented by ATC and PT for the ITT Population. Patients will be counted once per ATC and PT.

12.5 Exposure and Drug Compliance

Exposure to study drug, calculated as the number of days from the first dose taken to the date of the last dose taken, inclusive, will be summarized by treatment group for the ITT Population. The total number of doses taken between each scheduled visit and overall for the entire study will be calculated for each patient. Patient-years, defined as exposure to the study drug in years, will be summarized by treatment for the ITT Population.

Dosing compliance for the treatment period will be defined as the number of doses actually taken by a patient divided by the number of doses that were expected to be taken, multiplied by 100. The total number of doses actually taken will be calculated by subtracting the total number of tablets returned from the total number of tablets dispensed, divided by 2. For patients who had a dose reduction, the total number of actual doses taken from the date of dose reduction will be the difference between the total number of tablets dispensed and returned. The total number of doses expected to be taken is the number of days between the date of first dose taken and the date of the end of treatment visit, inclusive. In addition, drug compliance for the intervals Randomization Visit up to Week 4 Visit, Week 4 Visit up to Week 8 Visit, Week 8 Visit to Week 12 Visit, and Randomization Visit to Week 12 Visit will be presented. Patients will only be included in the intervals that they were on study (that is, the intervals that are prior to or

contain the last dose date). Summaries will be presented by treatment arm and overall for the ITT Population.

Compliance rates will also be categorized as missing, <60%, ≥60% and < 80%, ≥80% and <120%, and ≥120% and summarized by treatment group.

Study drug is dispensed to patients in bottles equipped with a Medication Event Monitor System (MEMS) cap, which records the dates and times the bottle is opened and closed. Data obtained from MEMS caps will be presented in by-patient listings.

12.6 Efficacy Analyses

12.6.1 Baseline Summaries for Efficacy Endpoints

Baseline efficacy parameters including UACR, eGFR, eGFR strata (30 - 45, >45 - 60, >60 - 75), 24-hour MAP, SBP, DBP, and pulse rate, hemoglobin A1c, HOMA-IR, fasting plasma glucose, fasting plasma insulin, total cholesterol, LDL cholesterol, and triglycerides will be summarized descriptively by treatment group for the ITT population.

12.6.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in UACR over Weeks 8 and 12.

12.6.2.1 Definition of Endpoint

UACR will be calculated using the following equation:

$$UACR(mg/g) = \frac{urine\ albumin\ (mg/dL)}{urine\ creatinine\ (g/dL)}$$

UACR value for a visit will be defined as the average of UACR values obtained from the individual samples collected on the mornings prior to the visit. These individual values will be log-transformed prior to calculating averages or change from baseline. If only one sample was collected, then the single assessment will be used. If UACR values of 0 are present, a small constant (0.1) will be added to all data prior to performing the log transformation.

12.6.2.2 Main Analytical Approach

Corresponding with the primary efficacy objective of the trial, the primary inference for hypothesis testing is the treatment difference between the placebo group and the pooled praliciguat groups on the change from baseline in log UACR over Weeks 8 and 12. The primary efficacy analysis will be conducted using the ITT population using a mixed-effects model repeated measures (MMRM) analysis with change from baseline in log-transformed UACR as the response variable, treatment, visit, treatment-by-visit interaction, and baseline eGFR stratum **(using the actual stratum based on the eGFR lab values rather than the information from IRT)** as fixed effects; and baseline log UACR and baseline MAP as covariates with unstructured as the variance-covariance structure. All available data will be included in the analyses and appropriate contrasts will be specified to obtain parameter estimates for the specified timepoints.

Treatment differences between the pooled praliciguat dose groups and the placebo group will be estimated overall. The null hypothesis of the test will be interpreted as equality between the

placebo and pooled treatment groups, and rejection of the null hypothesis as evidence that the pooled praliciguat groups have a greater effect on lowering UACR than the placebo group.

The nature of these differences will be explored further by estimating the treatment differences between each praliciguat dose group and the placebo group, overall and at each assessment timepoint. Least square (LS) means, and LS mean differences between each praliciguat group and placebo, and their associated two-sided 90% confidence intervals (CIs) will be calculated overall and for each assessment timepoint. The contrasts between each praliciguat dose group and the placebo group at each assessment timepoint will be compared using a one-sided significance level of 0.05.

If the treatment-by-visit interaction is significant at the 0.1 significance level, LS mean treatment differences relative to the previous visit will also be presented. Please see example SAS code in Appendix 5.

Continuous summaries for baseline, each week, and change from baseline on the original scale will be presented by treatment group. LS means, LS mean differences and 90% CIs will be exponentiated back to original scale, and the geometric mean change (%) and the associated confidence intervals will be derived as 100 * [exp (LS mean change)-1].

12.6.2.3 Sensitivity/Supportive Analyses

Table 5. Sensitivity Analyses of Primary Efficacy Endpoint

Endpoint/Method	Description	Summary Method
Weeks 8 and 12 Per Protocol Population	Primary efficacy analysis will be repeated using the Per Protocol Population	Continuous Summary MMRM overall MMRM by visit
Weeks 8 and 12 Subset of ITT Population	Primary efficacy analysis will be repeated on subset of patients who completed the 12-week treatment period	Continuous Summary MMRM MMRM by visit
Week 12 – LOCF ITT Population	A last-observation-carried-forward (LOCF) approach will be used to impute missing postbaseline for change from baseline in UACR. Under the LOCF approach, the patient's previous value during the Treatment Period will be used in case of missing postdose assessments. In the case of premature discontinuation from the trial, the patient's last available value during the Treatment Period will be used. If no previous postdose value exists, a log change-from-baseline value of "0" will be imputed. Analysis of change from baseline in UACR at Week 12 will be performed using an ANCOVA model with change from baseline in log-transformed UACR as response variable; treatment, baseline eGFR stratum as fixed effects, and log baseline UACR and baseline MAP as covariates.	Continuous Summary ANCOVA

Table 5. Sensitivity Analyses of Primary Efficacy Endpoint

Endpoint/Method	Description	Summary Method
Weeks 8 and 12 By eGFR strata ITT Population	Primary efficacy analysis (with the exception of including the eGFR stratum as a fixed effect) will be repeated for the eGFR strata using the ITT population	Continuous Summary MMRM overall MMRM by visit
Weeks 8 and 12 By eGFR strata PP Population	Primary efficacy analysis (with the exception of including the eGFR stratum as a fixed effect) will be repeated for the eGFR strata using the PP population	Continuous Summary MMRM overall MMRM by visit
Weeks 8 and 12 – include additional covariates ITT Population	If baseline imbalances are apparent across treatment groups, then the primary efficacy analysis will be repeated including these baseline parameters as covariates in the MMRM model.	Continuous Summary MMRM MMRM by visit
Weeks 8 and 12 – by geographic region ITT Population	Primary efficacy analysis will be repeated by geographic region subgroup, as defined in Appendix 3- Table 11.	Continuous Summary MMRM overall MMRM by visit
Weeks 8 and 12 Rank Transform ITT Population	Change from baseline and baseline values will be ranked based on the normalization method of Blom with ties set to the mean. If the results of the sensitivity analysis show consistency with those obtained from the original analysis, only results from the original analysis will be reported.	

12.6.2.4 Graphical Presentation of Primary Efficacy Data

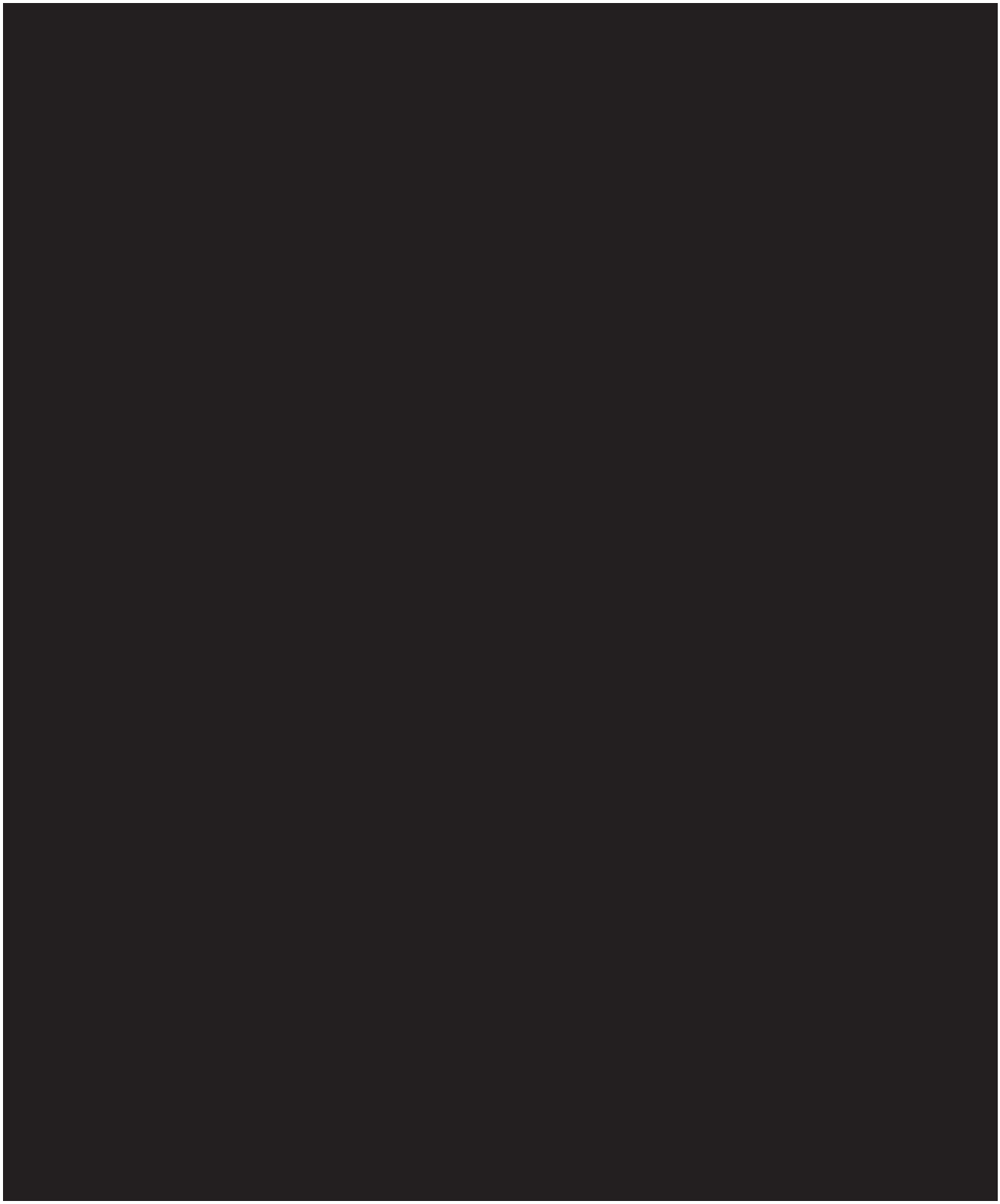
Geometric Change (%) to baseline in UACR assessments over time, along with the corresponding 90% confidence intervals will be presented by treatment group.

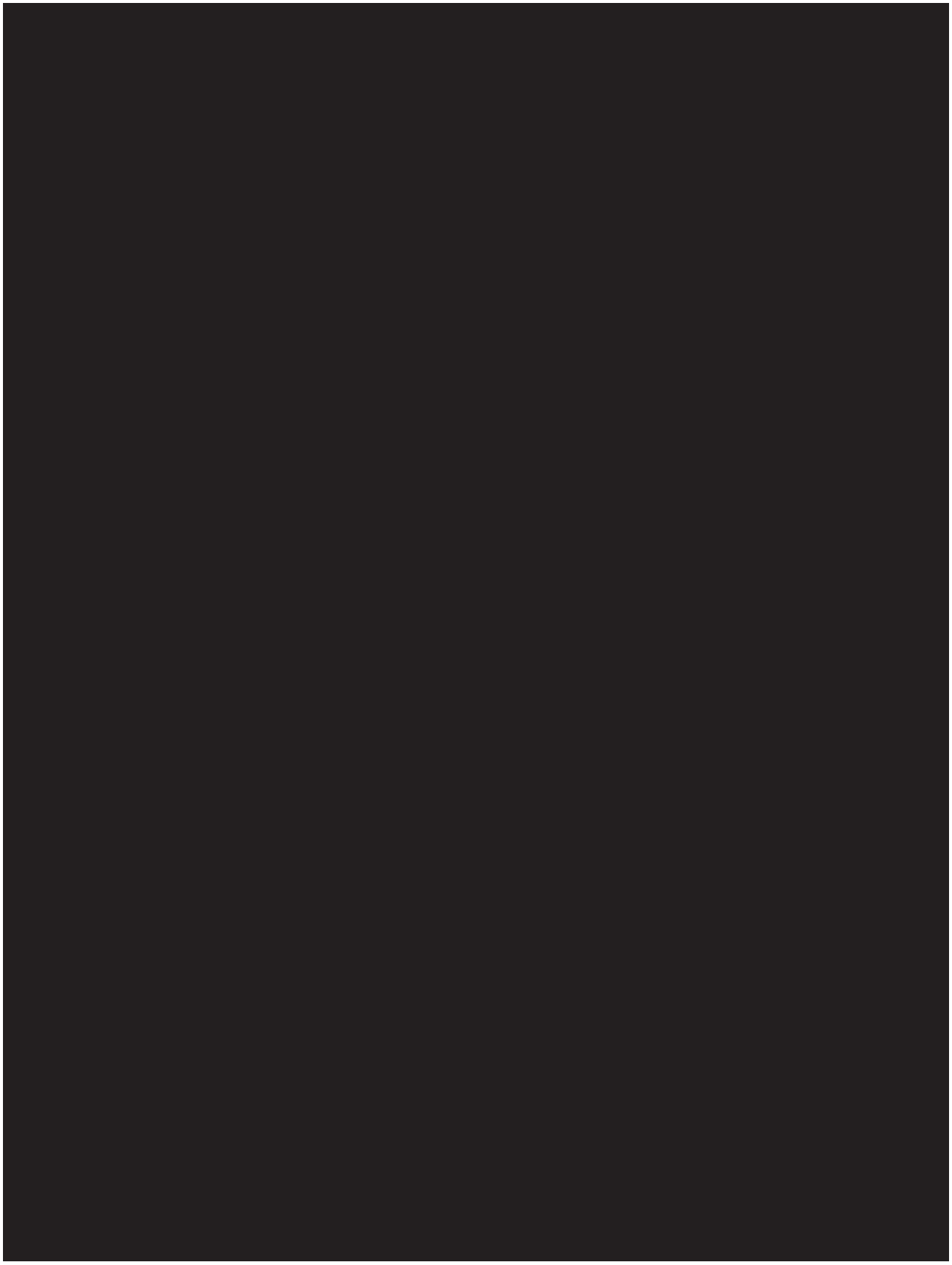
Boxplots of observed values of UACR will be presented by treatment group for all assessment weeks.

In addition, cumulative distribution function plots of the percent change from baseline values at Week 12 will be plotted by treatment group.

12.6.3 Exploratory Efficacy Endpoints

[redacted]





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12.6.4 Subgroup Analyses

Analysis for change from baseline in UACR will be performed for each of the following subgroups:

Sex (male/female)

Age categories (18 - 45, >45 - 65, >65)

Race (white/black)

Ethnicity (Hispanic/not Hispanic)

Actual Baseline eGFR strata (30 - 45, >45 - 60, >60)

Baseline UACR (≤ median, > median)

Baseline MAP (≤ median, > median)

Baseline BMI (≤30, >30)

Insulin use at baseline (yes/no)

Baseline hemoglobin A1c (≤ median, > median)

[redacted]

Subgroup analyses will be performed only if the total number of subjects in each treatment group within a subgroup category is ≥10. MMRM models will be used with change from baseline as the response variable, treatment, visit, treatment-by-visit interaction and eGFR stratum as fixed effects, and the respective baseline value as covariate with unstructured as the variance-covariance structure. Separate models will be used for each subgroup and appropriate contrasts will be specified to obtain parameter estimates for each subgroup.

12.7 Pharmacokinetic Assessment

12.7.1 Pharmacokinetic Analysis

Plasma concentration of Praliciguat will be summarized using the PK Population for each assessment timepoint by active treatment groups. Concentrations that are BLQ will be treated as zero on Day 1 and as missing on all other study days for the computation of descriptive statistics. Results where the actual sampling time deviated by greater than 25% from the nominal time will be excluded from the descriptive statistics. A by-subject listing of all concentration-time data for each treatment and scheduled sample collection time will be presented. A listing of PK blood sample collection times, and elapsed time relative to dose will be provided.

[redacted]

12.8 Safety and Tolerability Assessments

The following endpoints will be evaluated to explore the safety and tolerability of praliciguat.

12.8.1 Primary Safety Endpoints

The primary safety endpoints are the incidence of patients with treatment-emergent adverse events (TEAEs) and study drug-related TEAEs.

12.8.2 Adverse Events

A TEAE is defined as an adverse event (AE) that started or worsened in severity after the administration of study drug.

TEAEs will be summarized for each treatment group by SOC and PT; by relationship to study drug, and by severity for the Safety population. If a patient has more than 1 TEAE coded to the same preferred term, the patient will be counted only once for that preferred term by identifying those TEAEs with the highest severity and the strongest causality relationship to study drug per investigator.

TEAEs will also be summarized by study period, where AEs that started during the Screening Period, Treatment Period, or Follow-up Period will be presented by treatment group for the respective period of onset. In addition, the incidence of AEs leading to premature discontinuation of study drug will be summarized by treatment group.

For presentation of AE incidence, AEs will be sorted alphabetically by SOC, and within each SOC, by decreasing incidence of PT in the overall praliciguat group. An additional presentation will include a summary of TEAEs for each treatment group by PTs only, sorted by decreasing incidence of PT in the overall praliciguat group.

Listings of AEs in screen-failure patients, pretreatment AEs in randomized patients, TEAEs, severe TEAEs, study drug-related TEAEs, SAEs, TEAEs leading to study discontinuation, and AEs leading to death (if any) will be provided.

12.8.3 Subgroup Analyses

Subgroup analyses of TEAEs will be performed by sex, race, ethnicity, baseline eGFR strata, baseline UACR, baseline hemoglobin A1c levels and insulin use at baseline. See Section 12.6.4 for definitions of the subgroups. Subgroup analyses will be performed only if the total number of subjects in each treatment group within a subgroup category is ≥10

12.8.4 TEAEs of Clinical Interest (AECI)

Although not collected as such in the protocol, based on a possible class effect with sGC stimulators, TEAEs related to bleeding, hypotension, and elevated heart rate will be categorized as AECI. These will be summarized by treatment group, by severity and by PT and presented in a by-patient listing. See Appendix 1 for details on the determination of the events for each category of interest.

12.8.5 Clinical Laboratory Endpoints

For each quantitative clinical laboratory endpoint, descriptive statistics of the observed values (in standard units) as well as change from study baseline will be presented overall for each assessment timepoint for the Safety population.

Laboratory test values will also be categorized as low, normal, or high based on reference ranges provided by the lab. Shifts from study baseline to each later timepoint will be tabulated. If there is more than 1 measurement for a lab endpoint at a postbaseline timepoint, only the last measurement will be used. Listings of laboratory endpoints with reference ranges and the above categorizations will be provided.

Clinical laboratory test values will also be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 6. The number and percentage of patients who have PCS postbaseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 assessment in the corresponding postbaseline period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS value in the corresponding postbaseline period. A supportive listing of patients with PCS postbaseline values will be provided, including the baseline and all postbaseline (including non-PCS) values. A listing of all TEAEs for patients with postbaseline PCS laboratory values will also be provided.

Table 6. Criteria for Potentially Clinically Significant Laboratory Results

Parameter	*SI Unit*	*Lower Limit*	*Higher Limit*
CHEMISTRY			
Albumin	g/L	< 0.75 × LLN	> 1.1 × ULN
Alanine aminotransferase	U/L	—	≥ 3 × ULN
Alkaline phosphatase	U/L	—	≥ 3 × ULN
Aspartate aminotransferase	U/L	—	≥ 3 × ULN
Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Bilirubin, total	µmol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Cholesterol, total	mmol/L	—	> 1.6 × ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose	mmol/L	< 0.5 × LLN	> 2 × ULN
Phosphate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Protein, total	g/L	< 0.8 × LLN	> 1.1 × ULN
Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Uric acid	µmol/L	< 0.9 × LLN	> 1.1 × ULN
HEMATOLOGY			
Hematocrit	Ratio	< 0.8 × LLN	> 1.1 × ULN
Hemoglobin	g/L	< 0.8 × LLN	> 1.1 × ULN

Table 6. Criteria for Potentially Clinically Significant Laboratory Results

Parameter	*SI Unit*	*Lower Limit*	*Higher Limit*
Neutrophils, absolute cell count	10^9/L	< 0.8 × LLN	> 1.5 × ULN
Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
Red blood cell count	10^{12}/L	< 0.8 × LLN	> 1.1 × ULN
White blood cell count	10^9/L	< 0.7 × LLN	> 1.5 × ULN

LLN = lower limit of normal value provided by the laboratory; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal value provided by the laboratory.

12.8.6 Vital Signs

Descriptive statistics of the observed values as well as change from study baseline will be presented for seated BP and pulse at each assessment timepoint for the Safety population. All vital signs evaluations at each assessment timepoint will be presented in a by-patient listing. The number and percentage of patients who had a potentially clinically significant change from study baseline in BP and pulse (based on the criteria in Table 7), will be presented by treatment group for the Safety population. Percentages will be calculated relative to the number of patients who did not meet the observed value criteria in Table 7) and had at least 1 assessment in the corresponding postbaseline period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS value in the corresponding postbaseline period. Percentage of patients with a PCS change in weight will be calculated relative to the number of patients with non-missing baseline values.

Table 7. Criteria for Potentially Clinically Significant Vital Signs Results

Vital Sign Parameter	*Flag*	*Criteria**	
		Observed Value	*Change from Study Baseline*
Seated Systolic Blood Pressure (mmHg)	High	≥180	Increase of ≥30
	Low	≤90	Decrease of ≥30
Seated Diastolic Blood Pressure (mmHg)	High	≥105	Increase of ≥20
	Low	≤50	Decrease of ≥20
Seated Pulse Rate (bpm)	High	≥110	Increase of ≥20
	Low	≤50	Decrease of ≥20
Weight, kg	High	—	Increase of >5 kg and ≥5%
	Low	—	Decrease of >5 kg and ≥5%

*A postbaseline value is considered potentially clinically significant if it meets both the criteria for observed value and change from baseline.

Orthostatic changes in systolic BP, diastolic BP, and pulse will be summarized for each treatment group. An orthostatic measurement is obtained by subtracting the seated measurement from the standing measurement.

The number and percentage of patients who meet the following notable orthostatic criteria at any postdose timepoint during a visit, as well as over the overall treatment period will also be summarized by treatment group:

- Orthostatic decrease in systolic BP of >20 mmHg from seated to standing
- Orthostatic decrease in diastolic BP of >15 mmHg from seated to standing
- Orthostatic increase in pulse of >30 bpm from seated to standing

A supportive listing of patients with PCS postbaseline values or notable orthostatic values will be provided, including the baseline and all postbaseline (including non-PCS) values. A listing of all TEAEs for patients with postbaseline PCS vital signs values will also be provided.

12.8.7 Electrocardiogram

For each ECG endpoint, descriptive statistics of the observed values as well as change from study baseline will be presented overall for each assessment timepoint for the Safety population. Shift tables from study baseline to the end of treatment visit for the overall ECG interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) will be summarized for all subjects in the Safety population. The number and percentage of patients who had a potentially clinically significant change from study baseline in ECG values (based on the criteria in Table 8), will be presented by treatment group. Percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 assessment in the corresponding postbaseline period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS value in the corresponding postbaseline period.

Table 8. Criteria for Potentially Clinically Significant ECG Results

ECG Parameter (unit)	Higher Limit
QRS duration (msec)	≥150
PR interval (msec)	≥250
QTc interval (msec)	>480

ECG endpoints will also be presented in a by-patient listing.

12.8.8 [redacted]

[redacted]

[redacted]

12.9 [redacted]

13 INTERIM ANALYSES

Please refer to the study protocol and DMC charter for information on the DMC activities.

No interim analyses of efficacy (specified as optional in Section 5.14 of the Protocol) will be performed.

14 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

The following analyses will be performed in addition to those described in the study protocol.

- Assessment of TEAEs of clinical interest

The following changes will be made to the analyses as described in the study protocol.

- Due to the potential of many trial sites having a small number of patients, site will not be included as a fixed effect in the primary model, as noted in the protocol. The trial sites will instead be pooled into 5 geographical regions (defined in Appendix 3), and a sensitivity analysis of the primary analysis will be performed by geographical region.
- The conditionality requirement for exploring the nature of differences between each praliciguat dose group and the placebo group will be dropped. Contrasts will be specified to estimate these treatment differences, regardless of whether the primary null hypothesis is rejected. No multiplicity adjustments will be performed.

15 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

16 DATA HANDLING CONVENTIONS

16.1 End of Treatment Assessment

Assessments performed at the end of treatment visit will be included in Week 8 and Week 12 evaluations as follows:

If a patient has a missing Week 8 visit, but has a non-missing EOT assessment, then the EOT assessment will be used as the Week 8 assessment if the EOT assessment was conducted on or after study day 50 but before study day 77.

If a patient has a non-missing Week 8 visit and has a non-missing EOT assessment, then the EOT assessment will be used at the Week 12 assessment if the EOT assessment was performed on or after study day 77.

16.2 Repeated or unscheduled assessments of safety endpoints

If a patient has repeated safety assessments (eg, for a lab endpoint) prior to initial dosing of study drug, then the results from the final non-missing assessment made prior to the start of study drug will be used as baseline. If there is more than 1 safety measurement (eg, for a lab endpoint) at a postbaseline timepoint, only the last measurement will be used. All postbaseline assessments, including unscheduled assessments, if any, will be used for PCS value determination, and all assessments will be presented in by-patient listings.

16.3 Conventions for Summarizing Adverse Events

The following conventions will be followed in summarizing TEAEs within a treatment group:

- For patient incidence summaries, each patient will be counted only once per category within each SOC, PT, or the overall AE summary
- If a patient reported more than 1 AE within an SOC or PT, then the TEAE with the highest severity or strongest causality relationship to study drug per investigator within each SOC

and each PT will be included in the respective summaries by severity or relationship, respectively.

16.4 Missing Date Information for Adverse Events

If it is not possible to determine when an AE started due to incomplete start dates/times, it will be assumed to be treatment emergent.

16.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started prior to the initiation of study drug dosing, all efforts should be made to obtain the severity from the Investigator. If it is still missing after all efforts, then a severity of "Mild" will be assigned. If the severity is missing for a TEAE, then a severity of "Severe" will be assigned. The imputed values for the missing severity assessment will be used for the incidence summary, while the actual missing values will be presented in by-patient listings.

16.6 Missing Relationship to Study Drug for Adverse Events

If the relationship to study drug is missing for a TEAE, all efforts should be made to obtain the relationship from the Investigator. If it is still missing after all efforts, a study drug causality of "Related" will be assigned in the corresponding analysis-derived data set for non-serious adverse events. The imputed values for the missing relationship to study drug will be used only for incidence summary, while the actual missing values will be presented in by-patient listings. For SAEs and AECIs, if causality from investigators is missing after all efforts to obtain it, then the causality determination from the sponsor will apply.

16.7 Missing Date Information for Prior or Concomitant Medications

If the start date of a medication is missing or incomplete (ie, partially missing), then the medication will be assumed to be concomitant.

17 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.
3. de Zeeuw D., Coll B, Andress D, Brennan JJ, Tang H, Houser M, et al. The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. Journal of the American Society of Nephrology : JASN 2014;25(5):1083-93.

18 APPENDIX 1 – ADVERSE EVENTS OF CLINICAL INTEREST

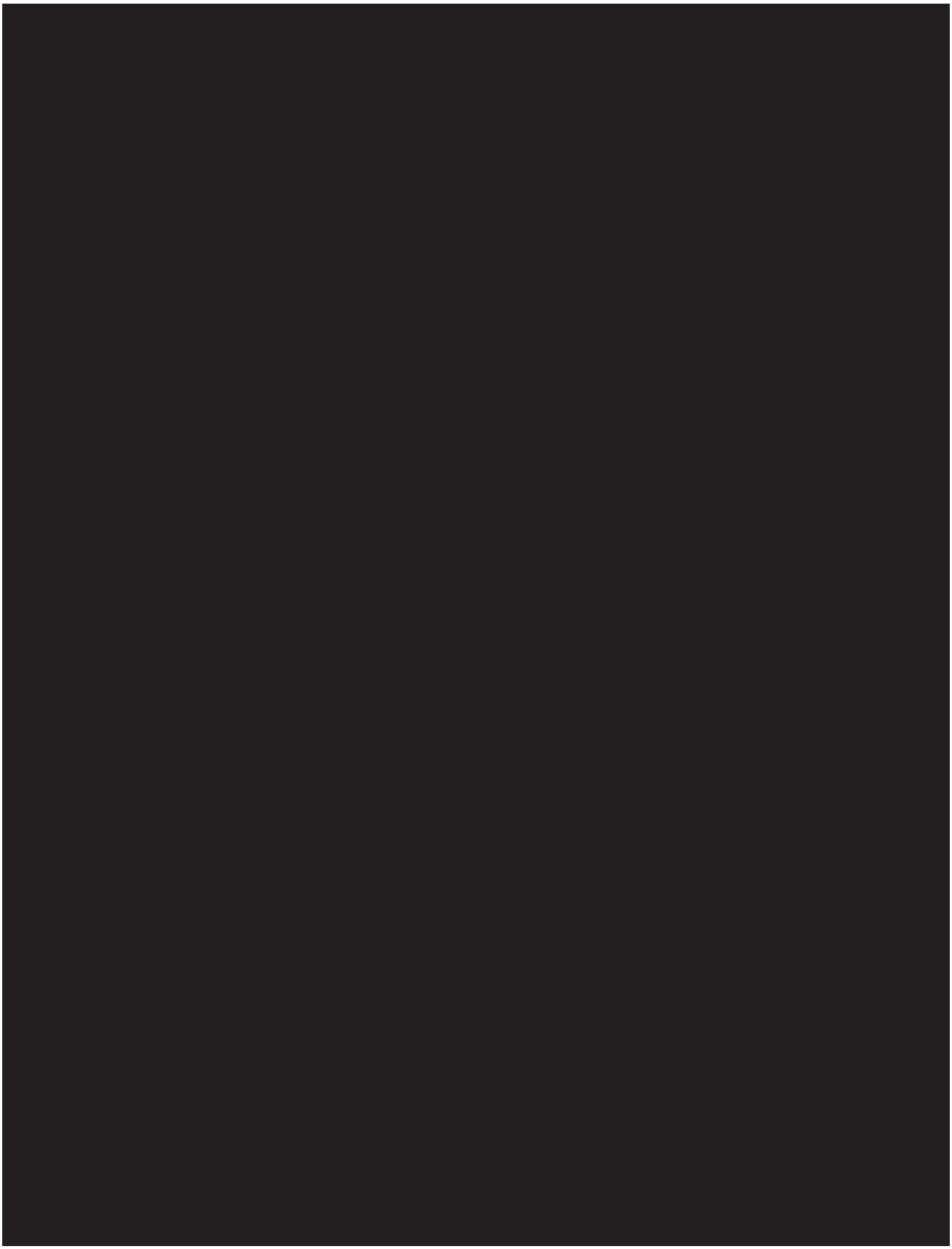
The table below provides the criteria for identifying adverse events within each category. Medical review of AEs prior to database lock will identify any additional adverse events.

Event Category	AE Criteria
Bleeding Events	Identify using MedDRA SMQ of 'haemorrhage terms (excluding laboratory terms)'
Hypotensive Events	Identify using the following MedDRA preferred terms: Blood pressure ambulatory decreased Blood pressure decreased Blood pressure diastolic decreased Blood pressure systolic decreased Blood pressure orthostatic decreased Orthostatic hypotension Presyncope Syncope Dizziness Dizziness postural
Elevated Heart Rate	Identify using the following MedDRA preferred terms: Heart rate increased Orthostatic heart rate increased Tachycardia Palpitations
Headache	Identify using MedDRA HLGT Headache that include the word *headache* with the exception of 'Typical aura without headache'

SMQ=standardized MedDRA query.

19 APPENDIX 2 [redacted]

[redacted]



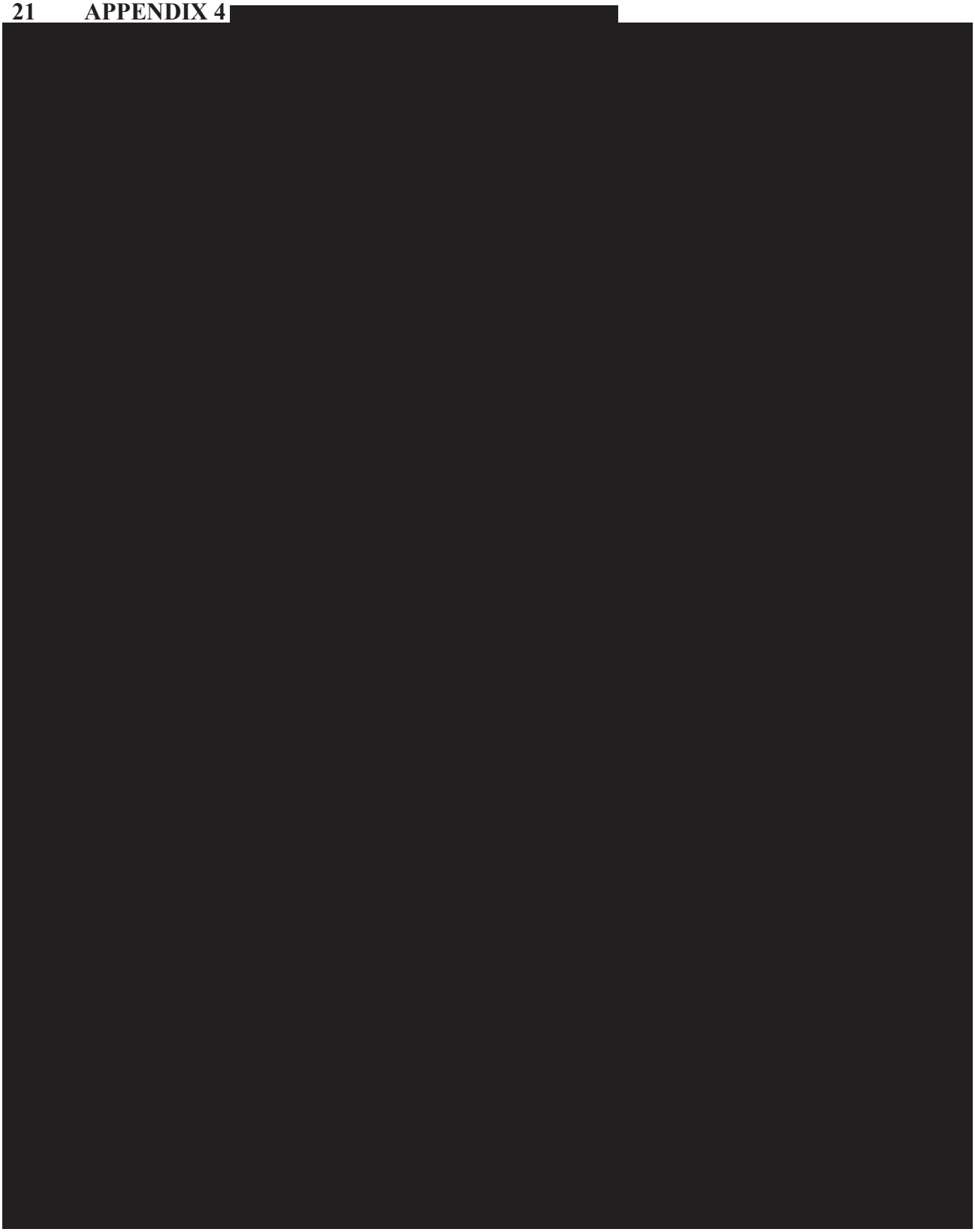
20 APPENDIX 3 – POOLING OF TRIAL CENTERS

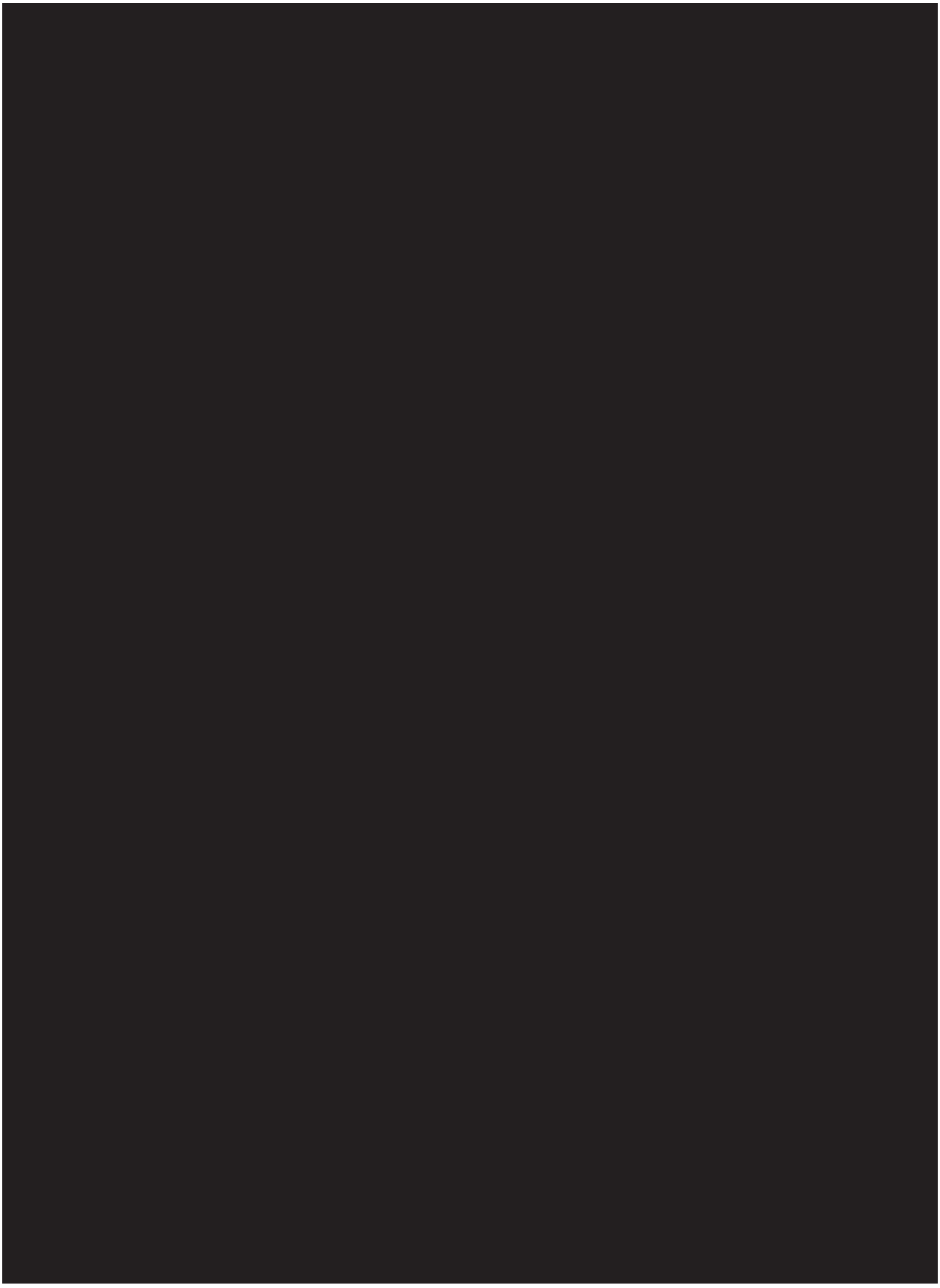
Because of the potential of many trial centers to have a small number of patients, the centers will be pooled by the following 5 geographic regions (as listed in Table 11): Northeast, Southeast, Midwest, Southwest, and West. Analyses using geographic region will use this 5-category geographic region variable.

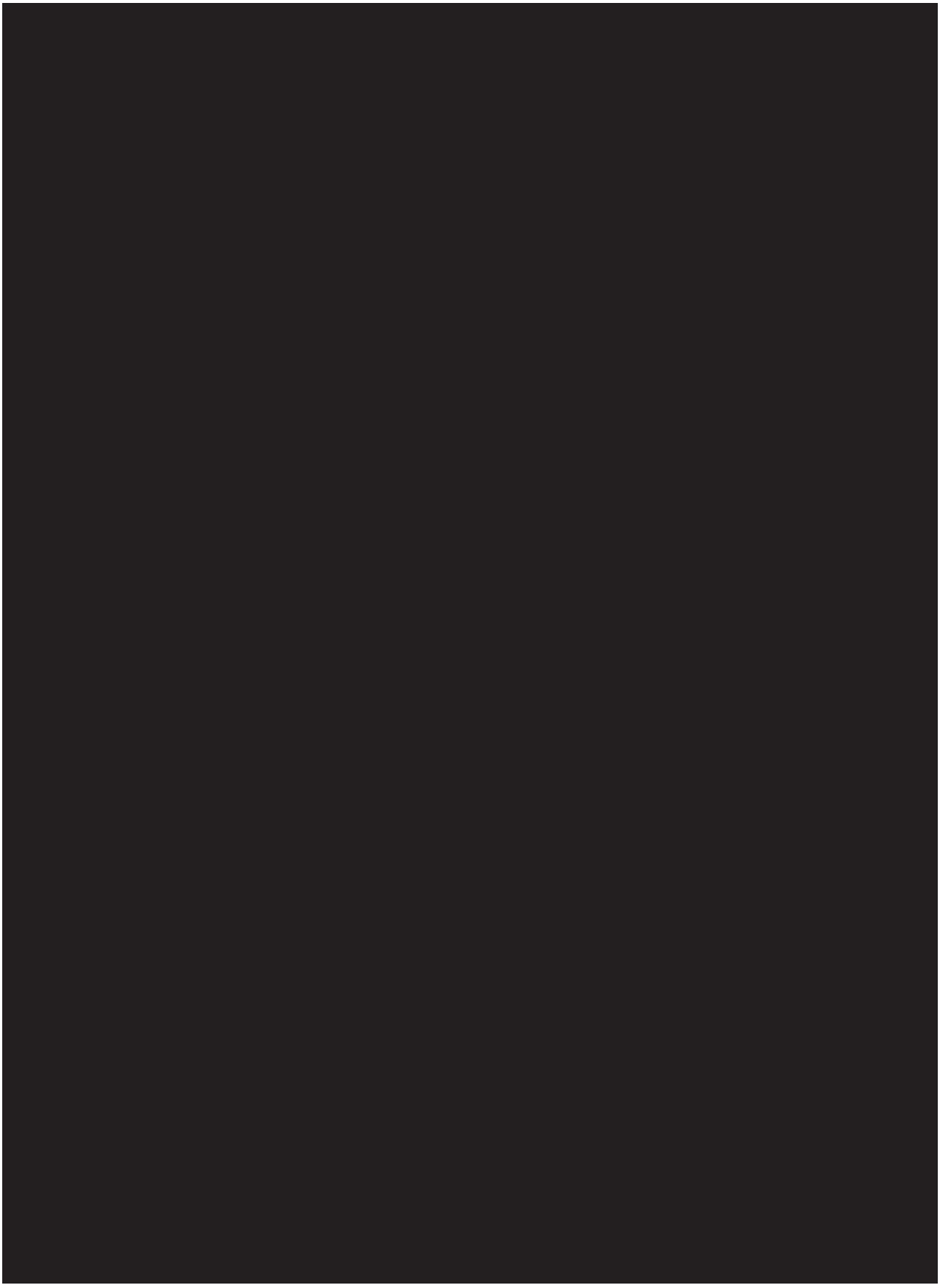
Table 11. Definition of Geographic Regions

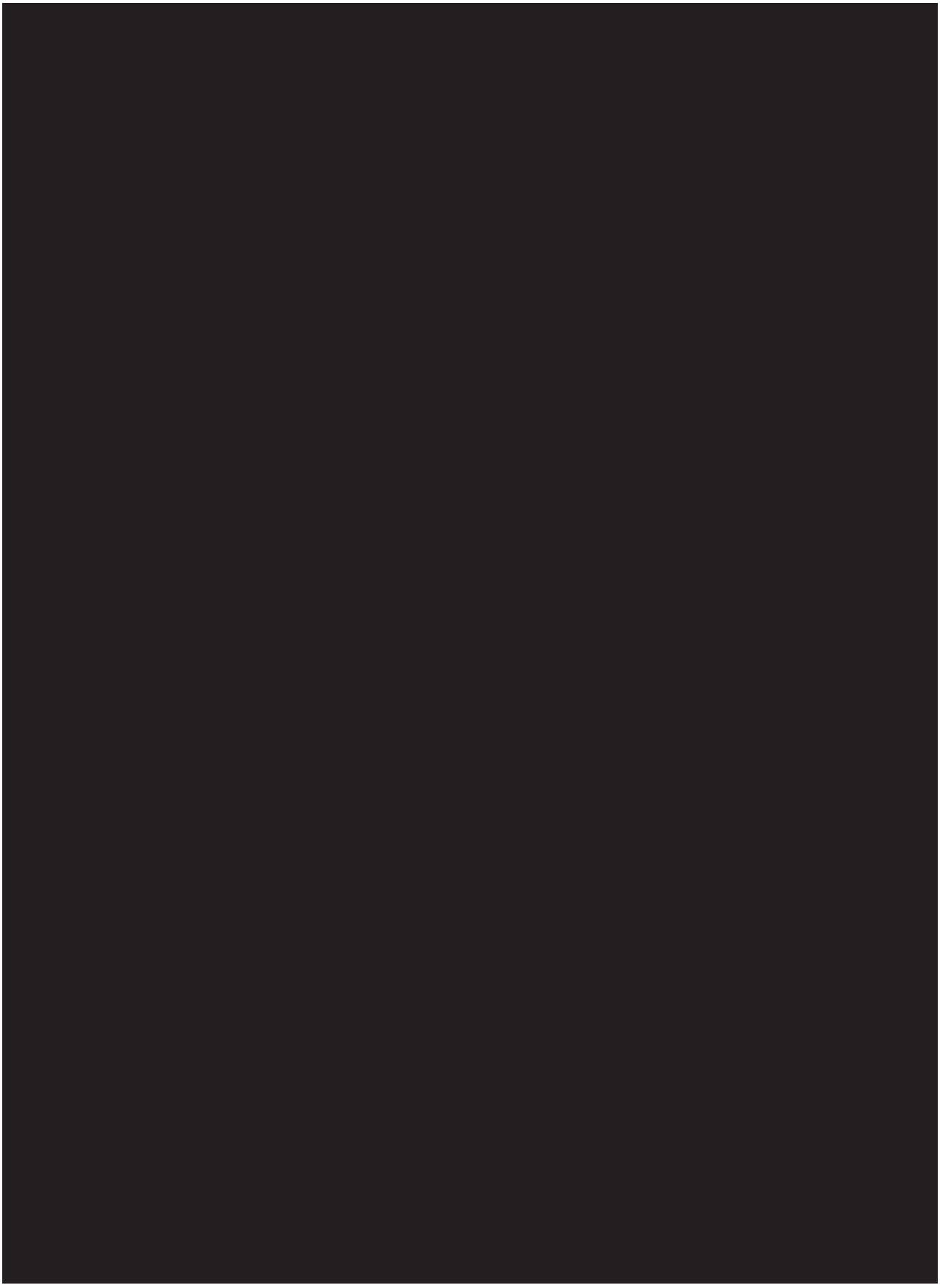
Northeast	***Southeast***	***Midwest***	***Southwest***	***West***
CT	AL	IA	AZ	CA
DC	AR	IL	NM	CO
DE	FL	IN	OK	ID
MA	GA	KS	TX	MT
MD	KY	MI		NV
ME	LA	MN		OR
NH	MS	MO		UT
NJ	NC	ND		WA
NY	SC	NE		WY
PA	TN	OH		
RI	VA	SD		
VT	WV	WI		

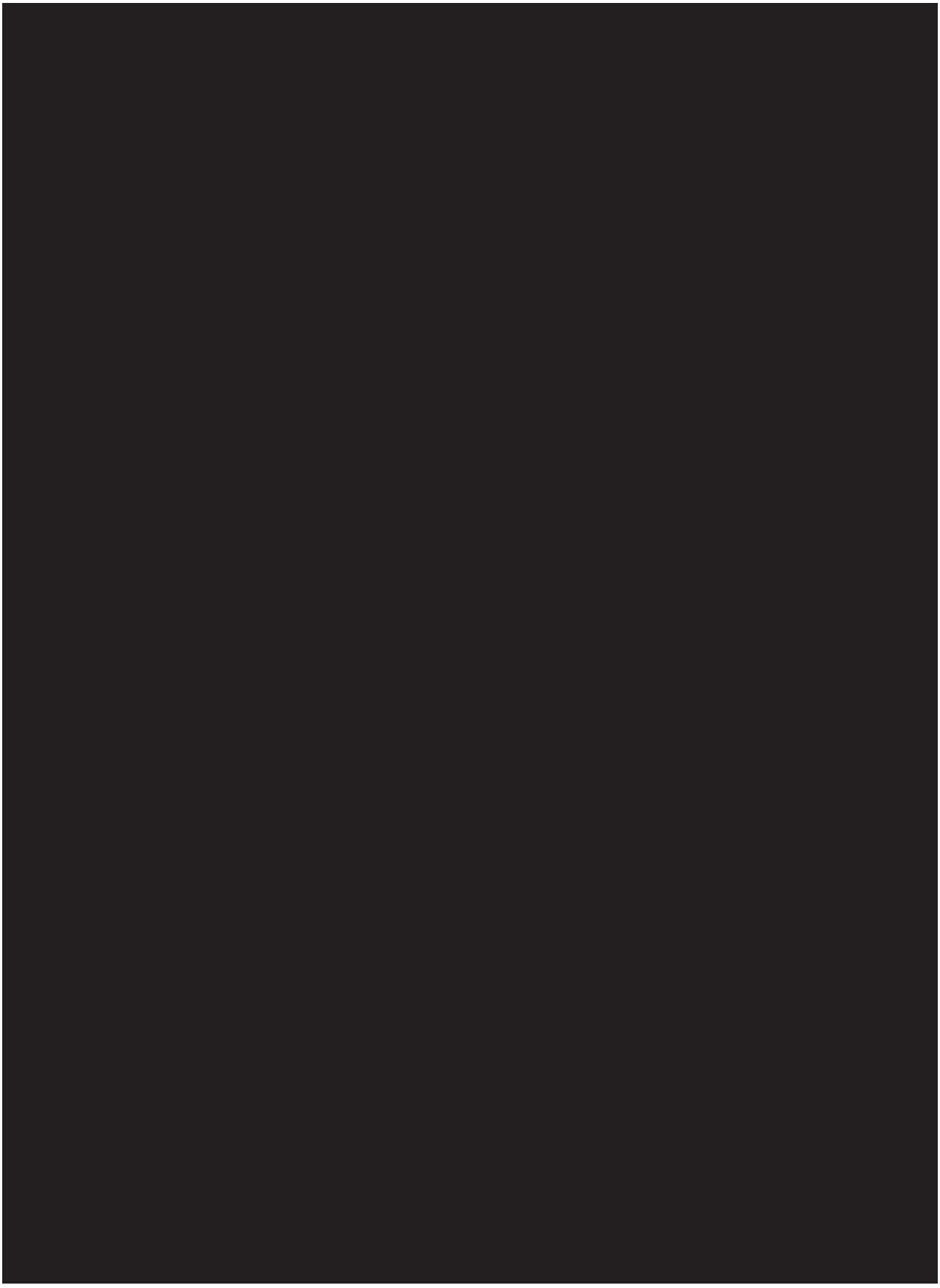
21 APPENDIX 4

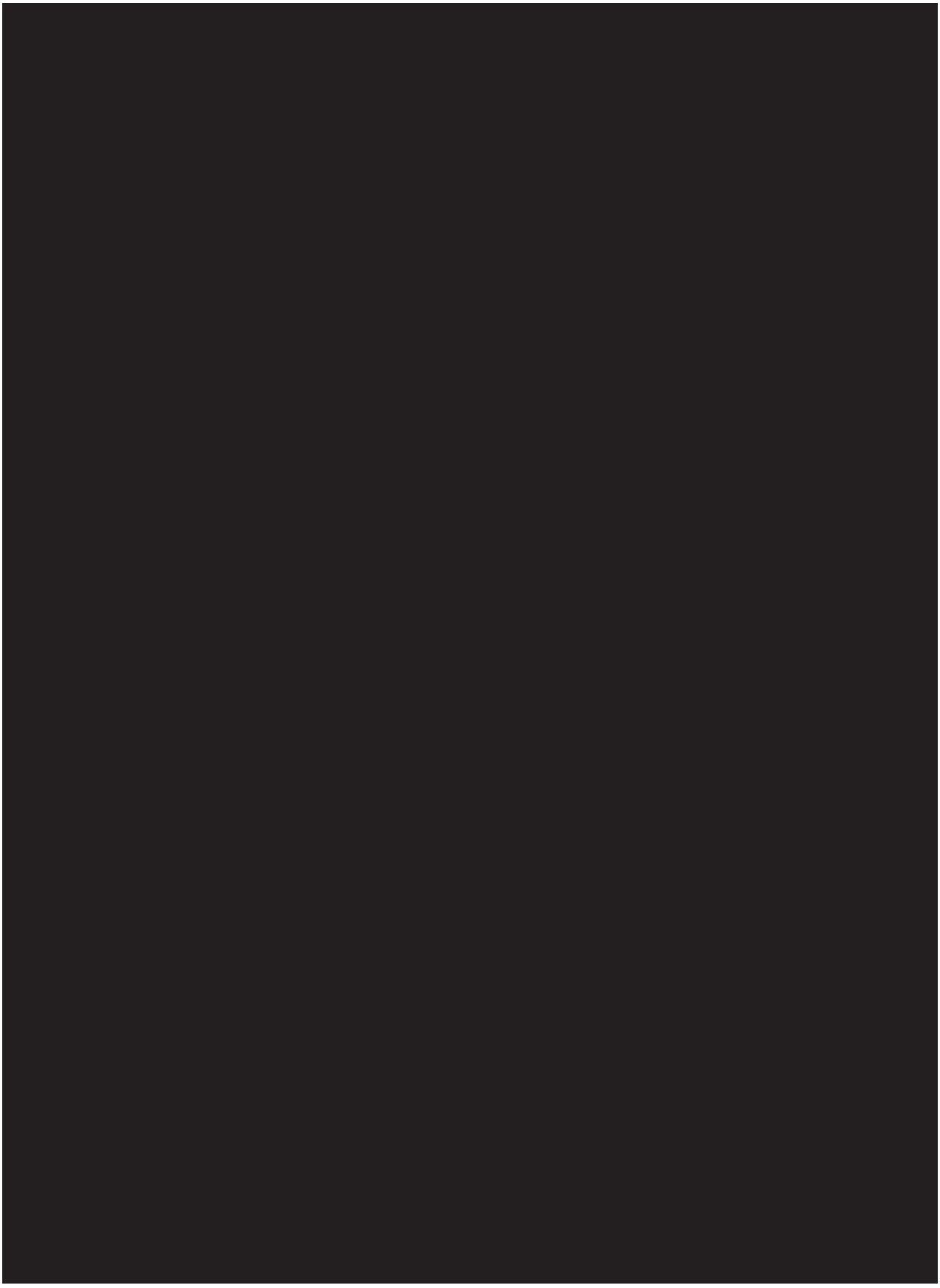


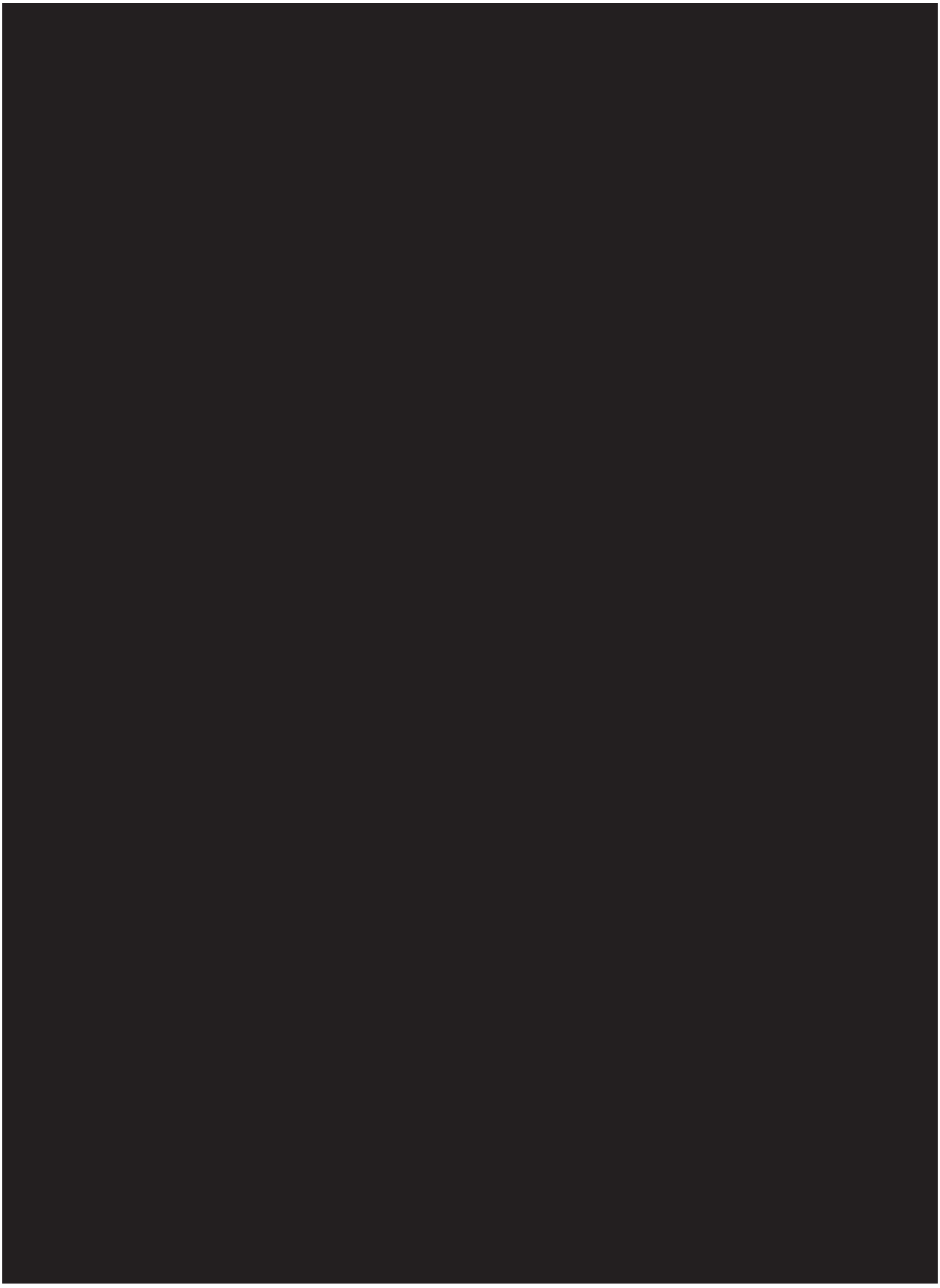


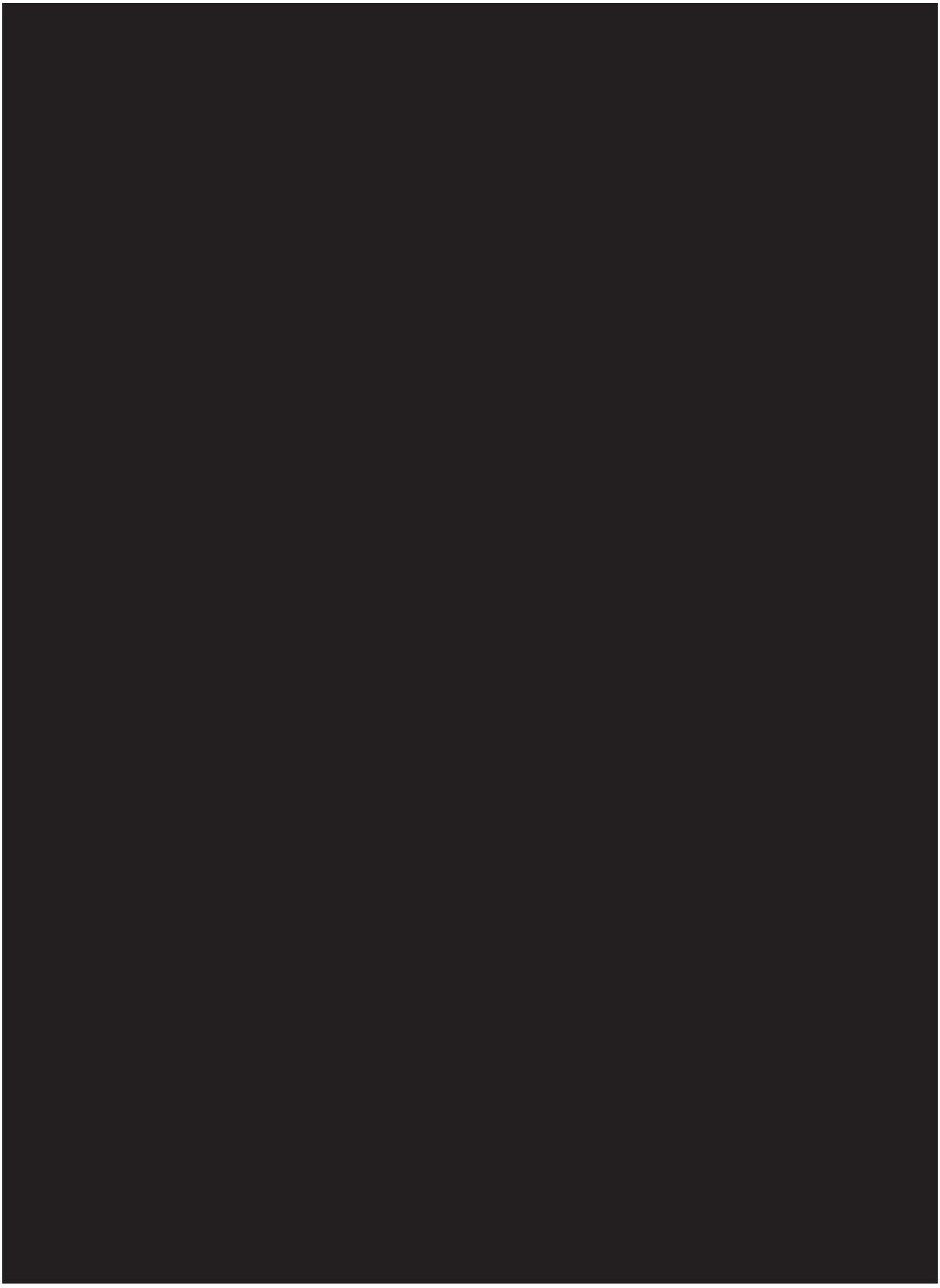


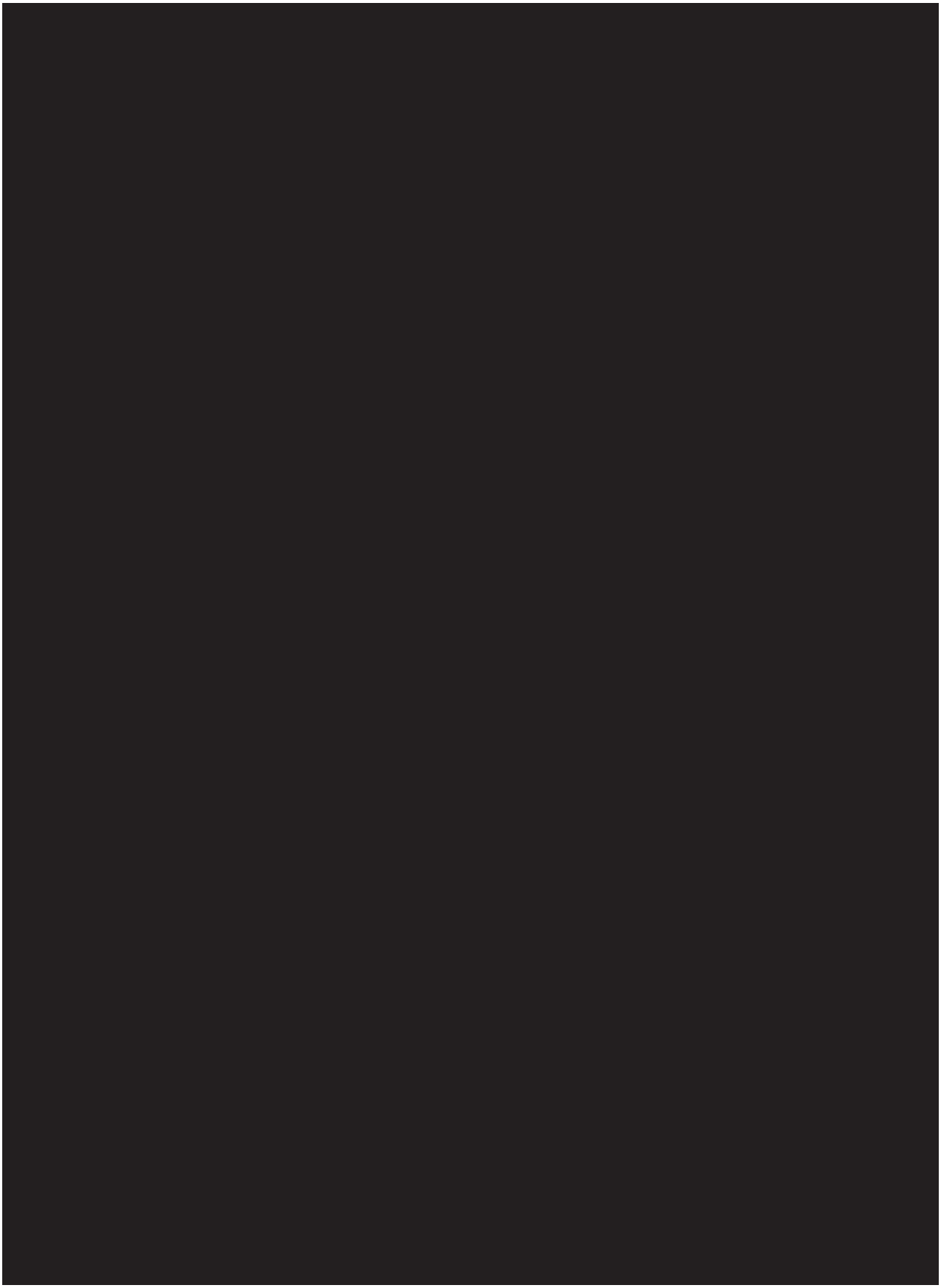


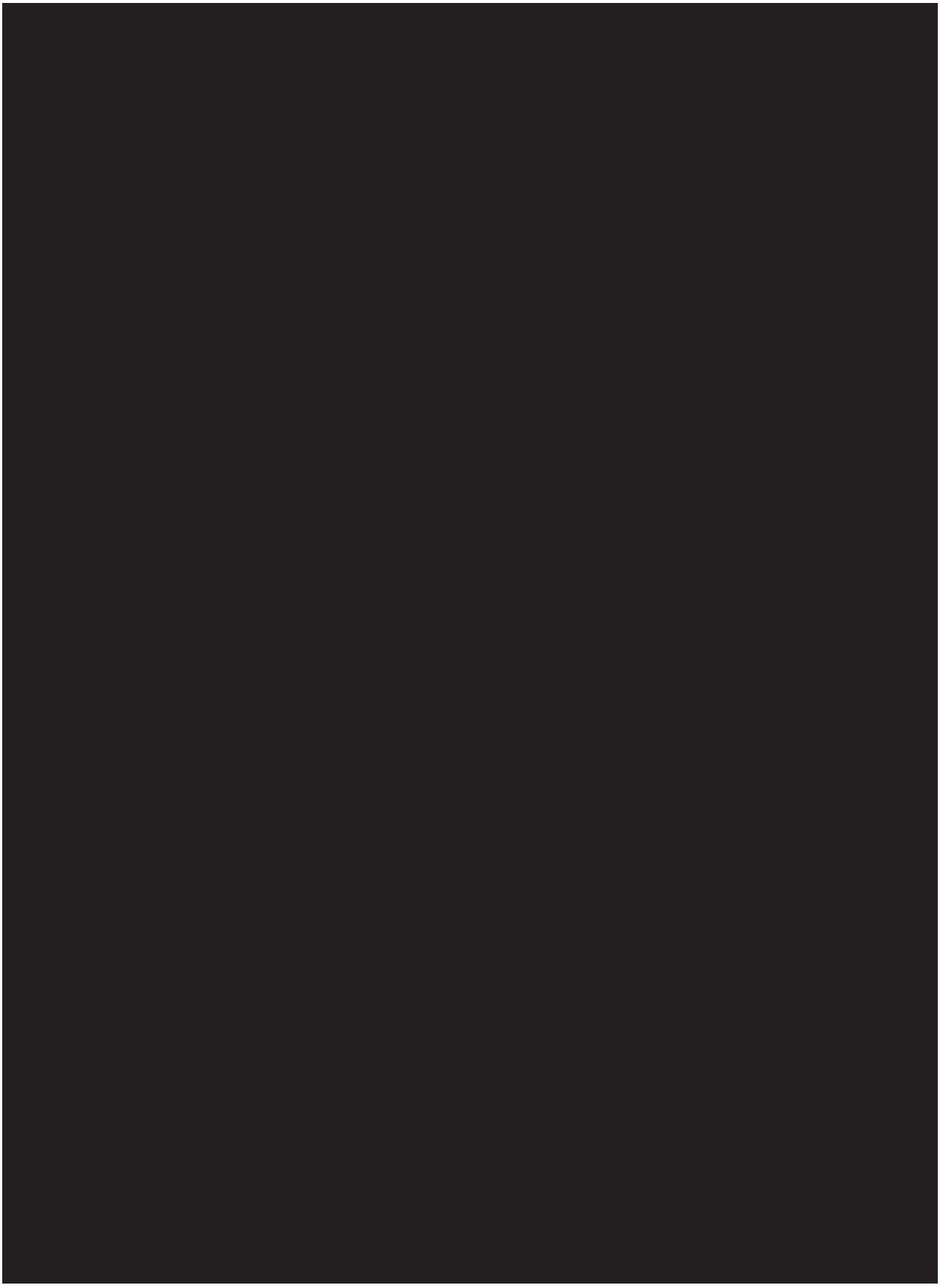


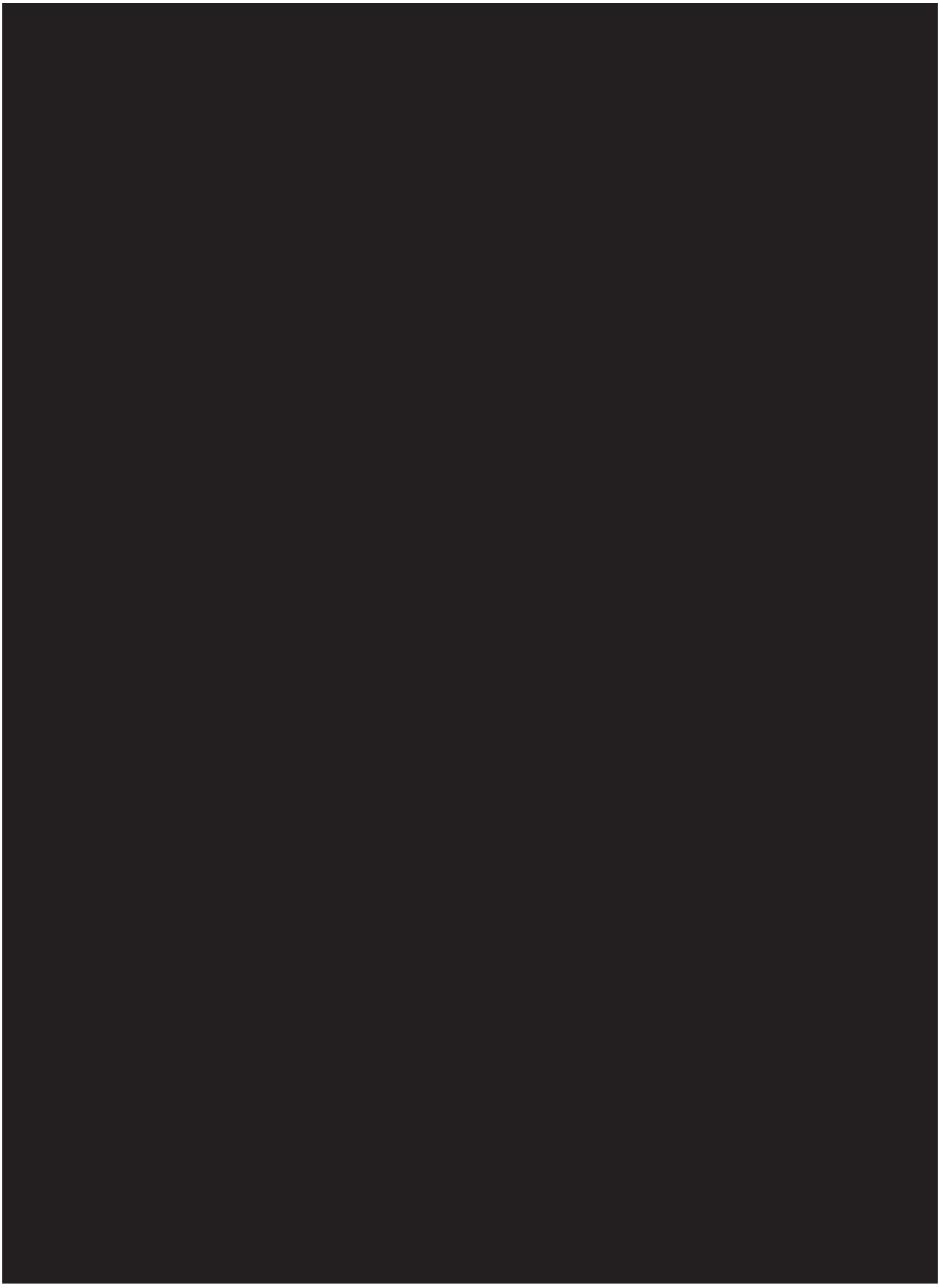


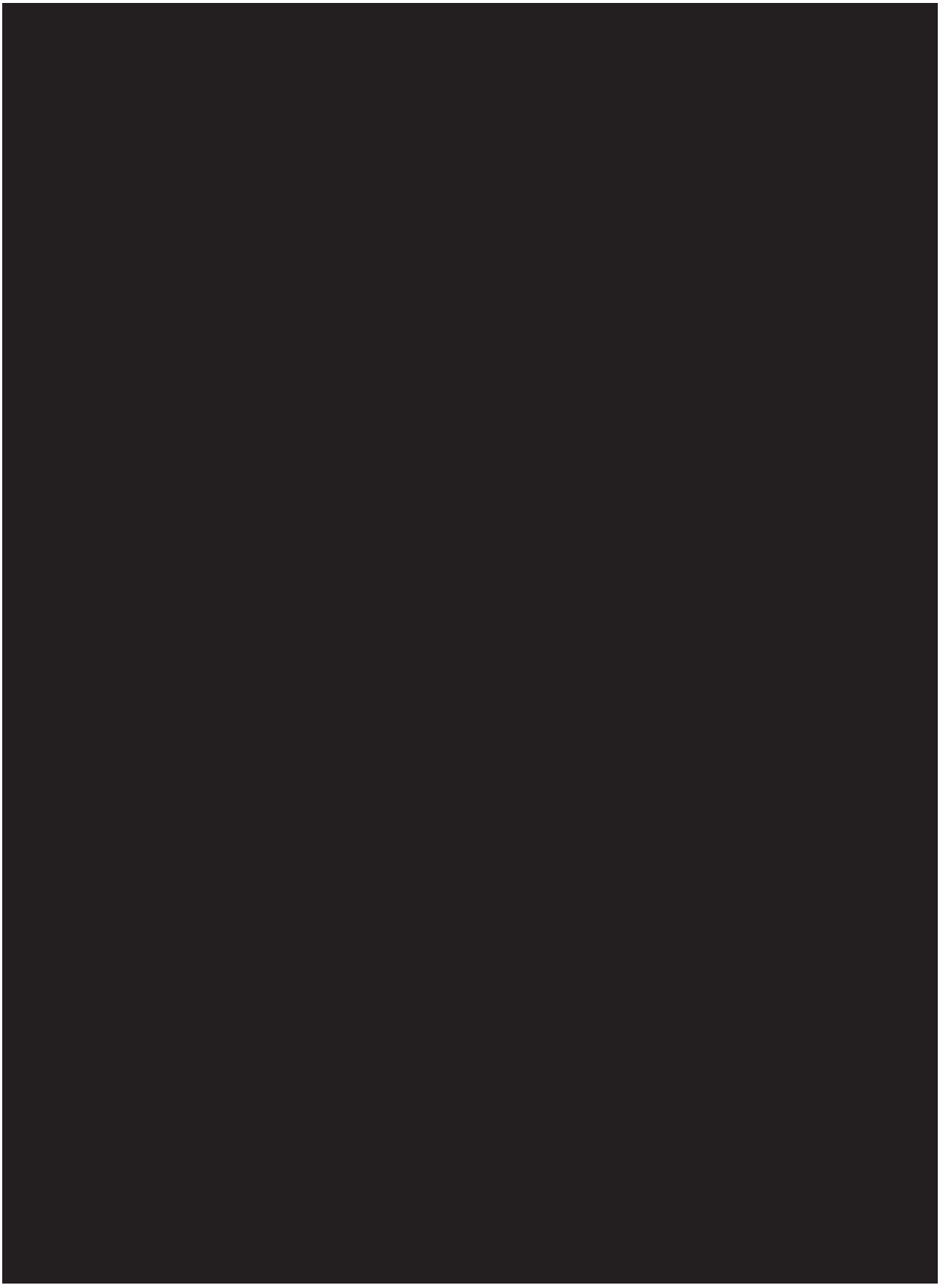


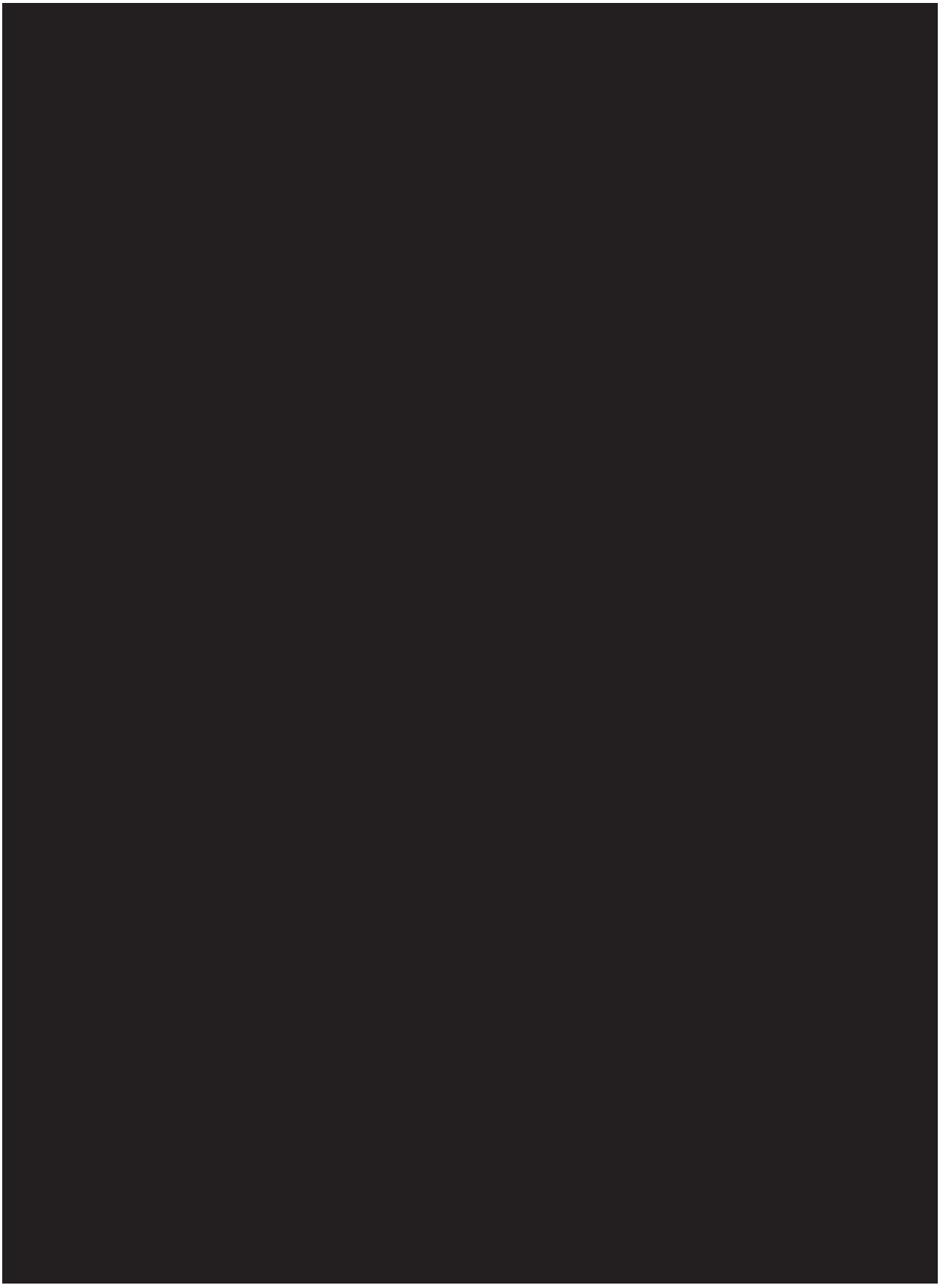


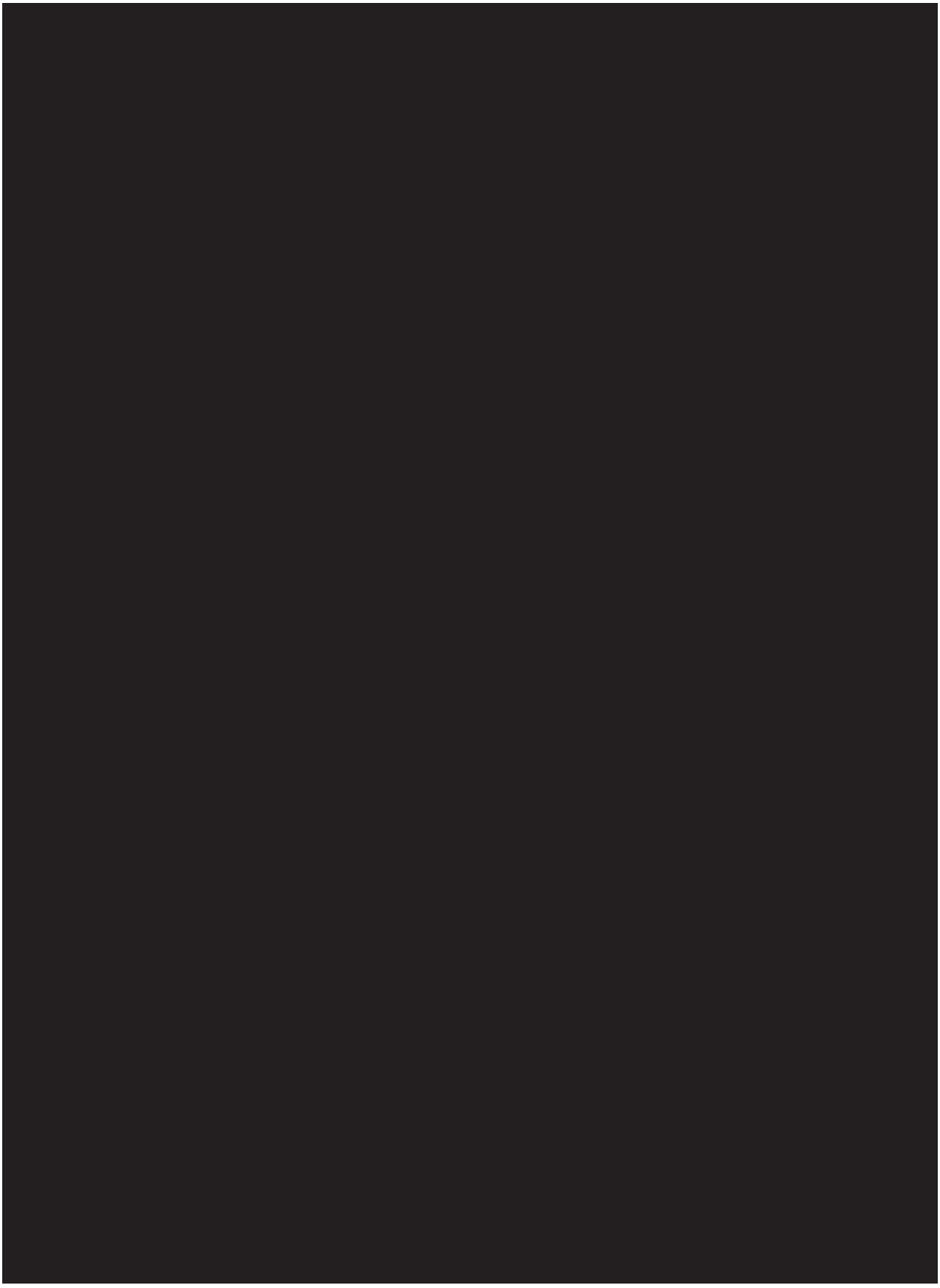


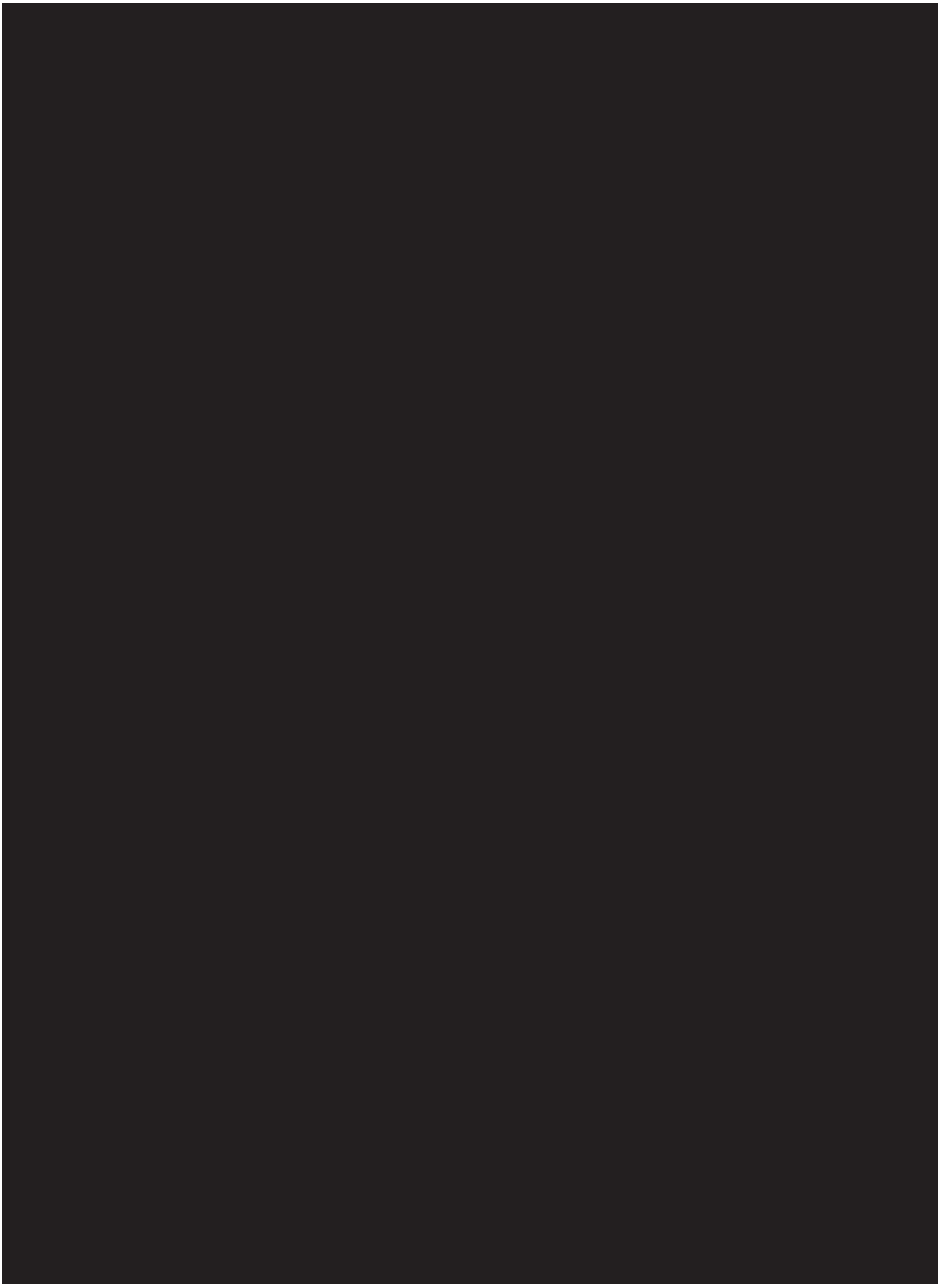


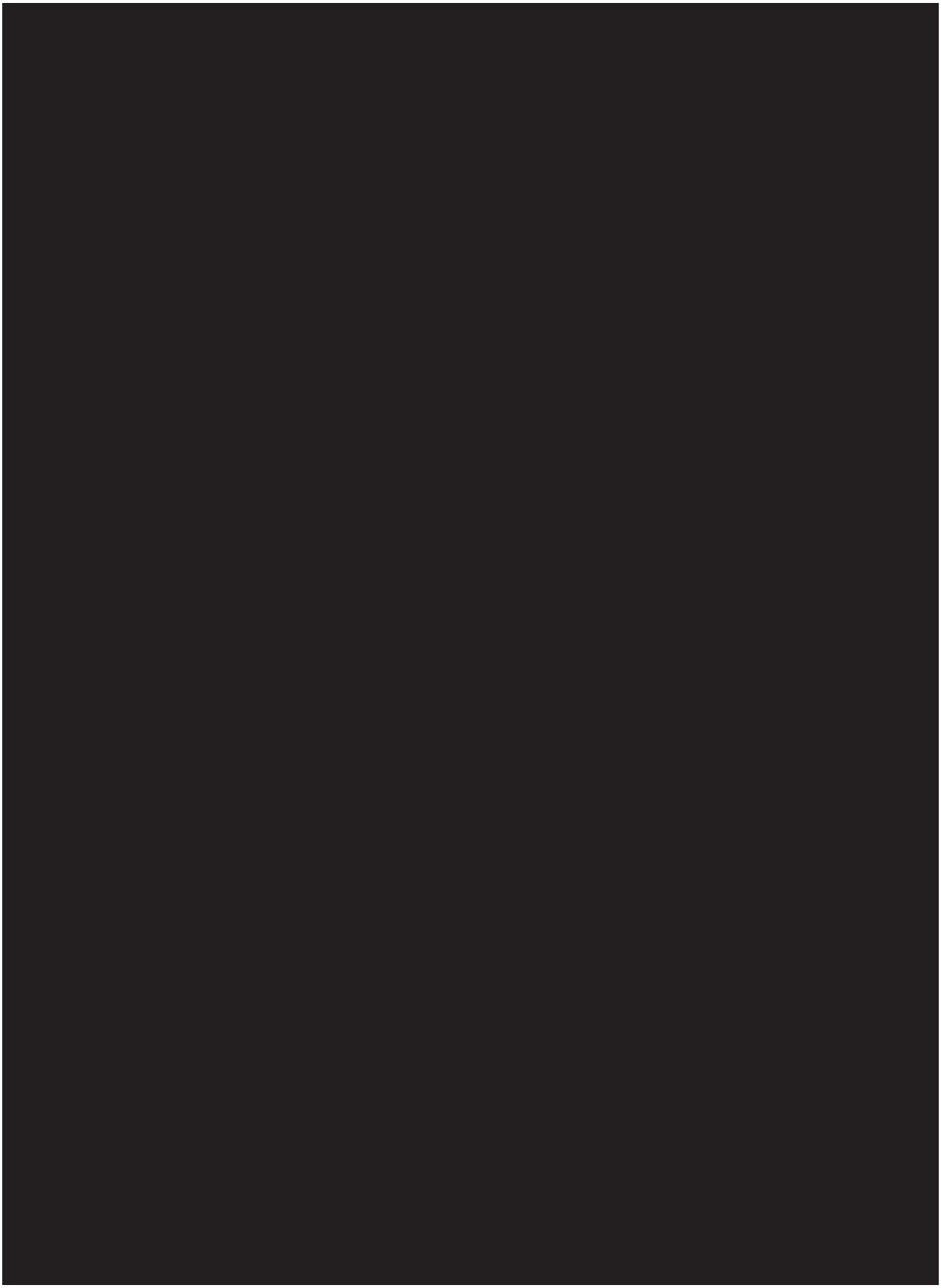


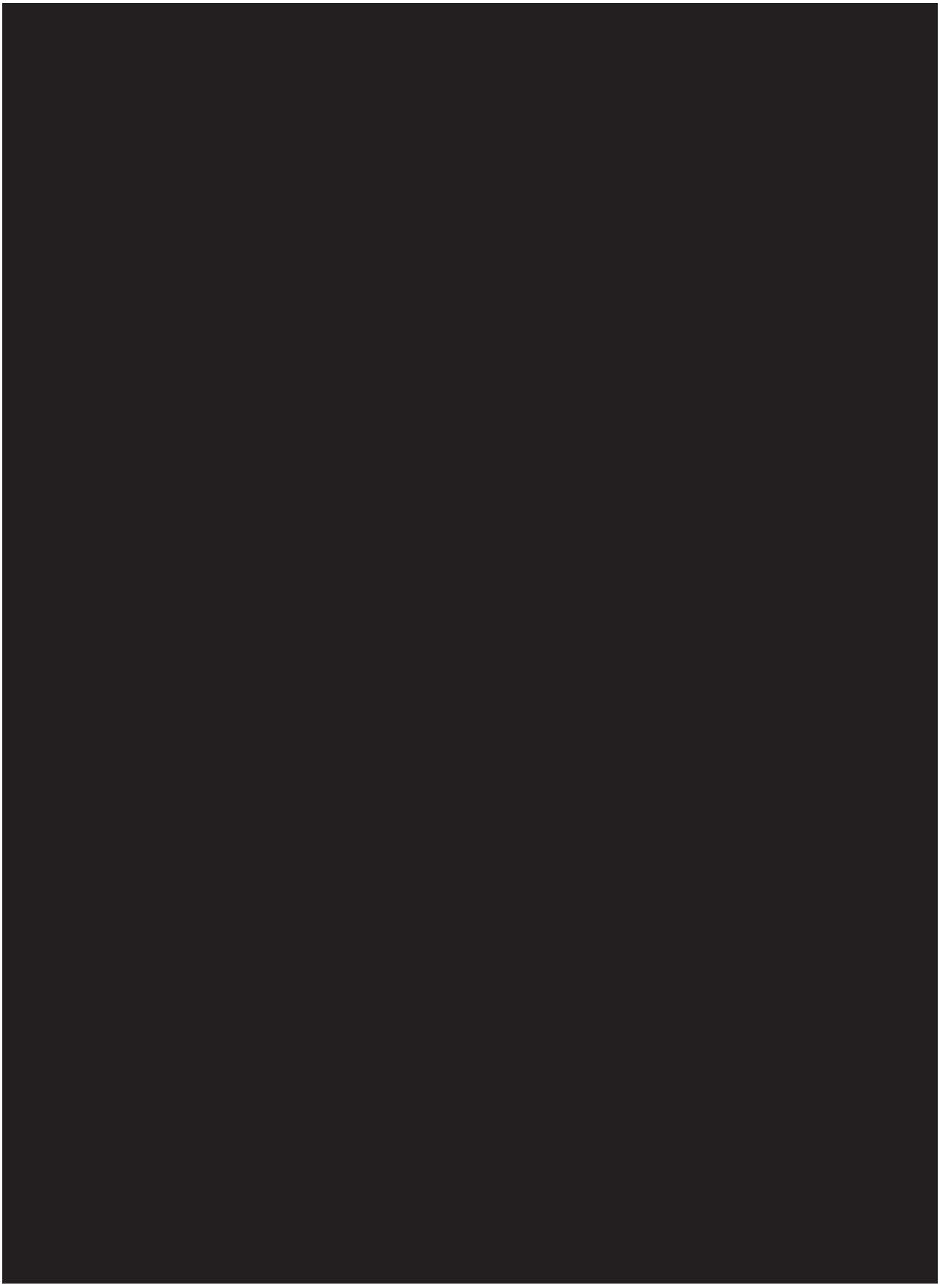


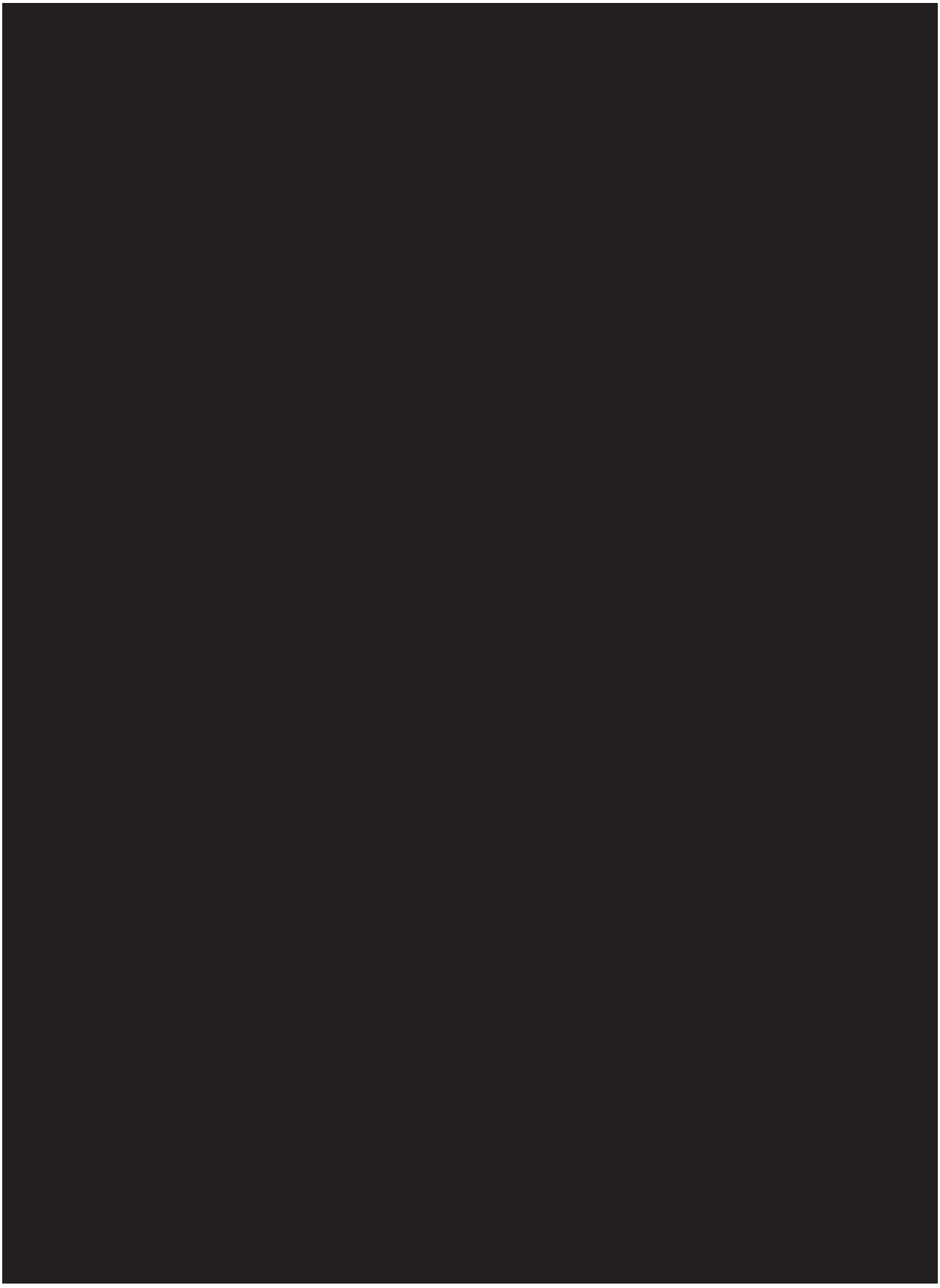


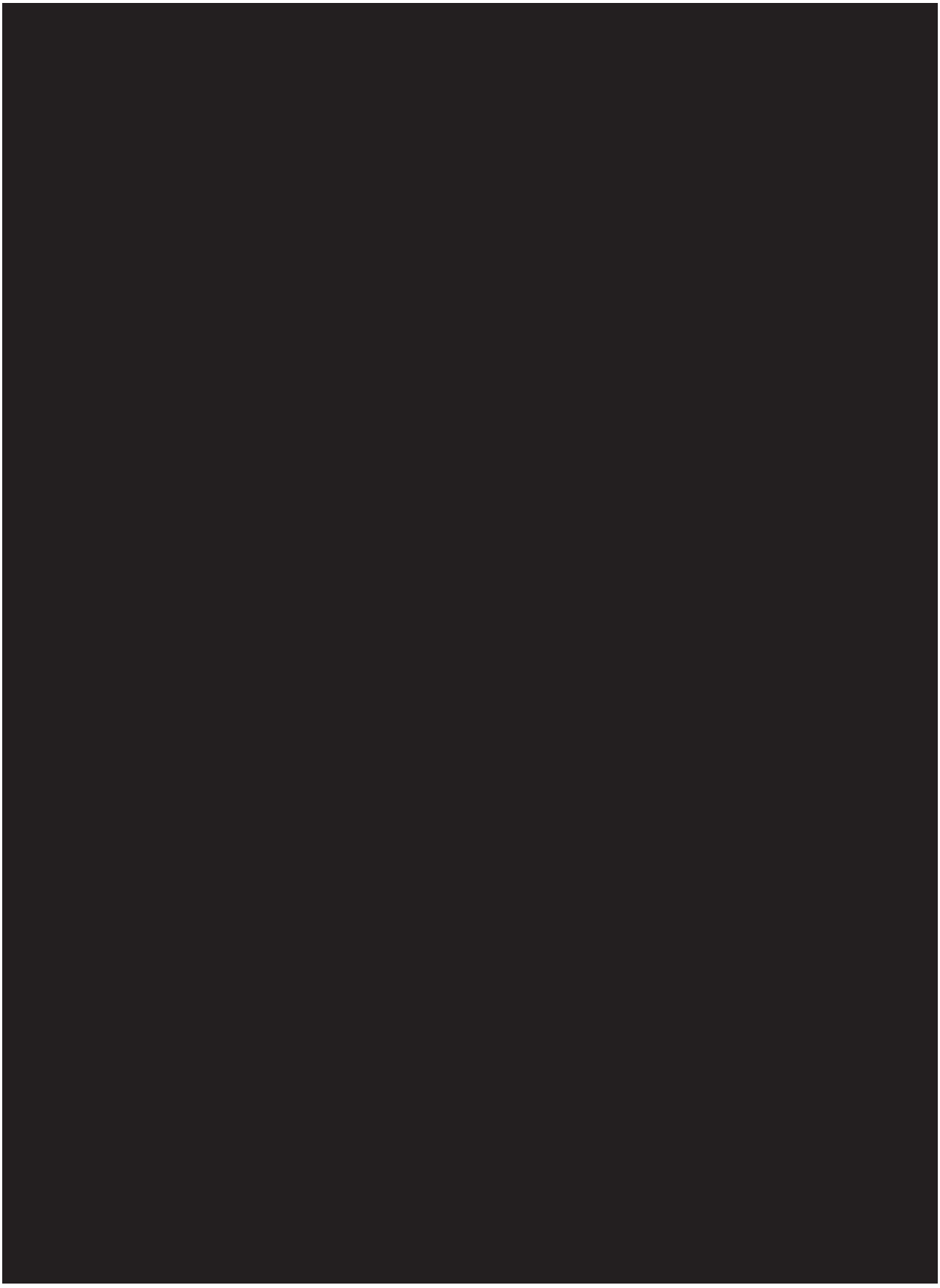


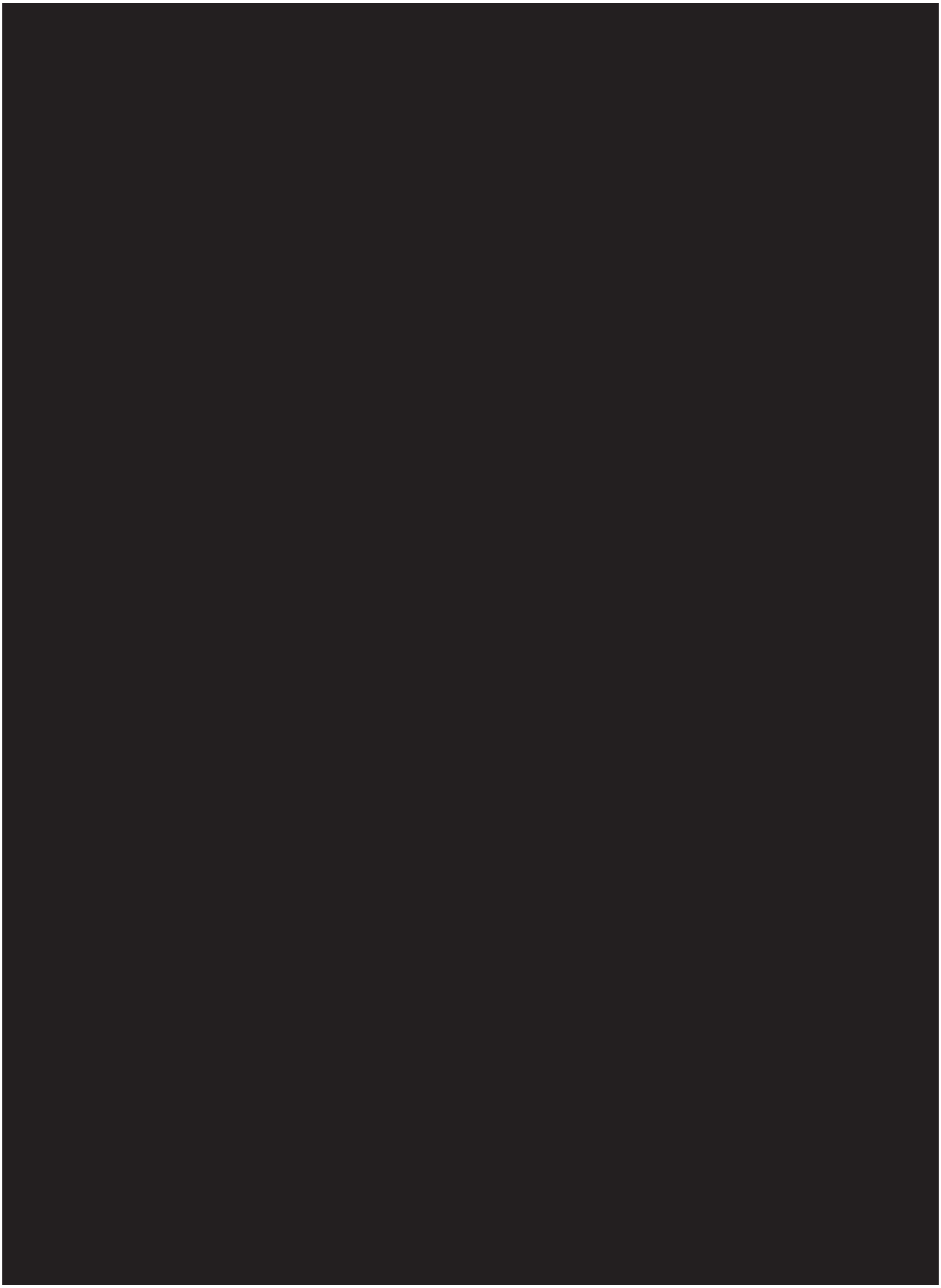


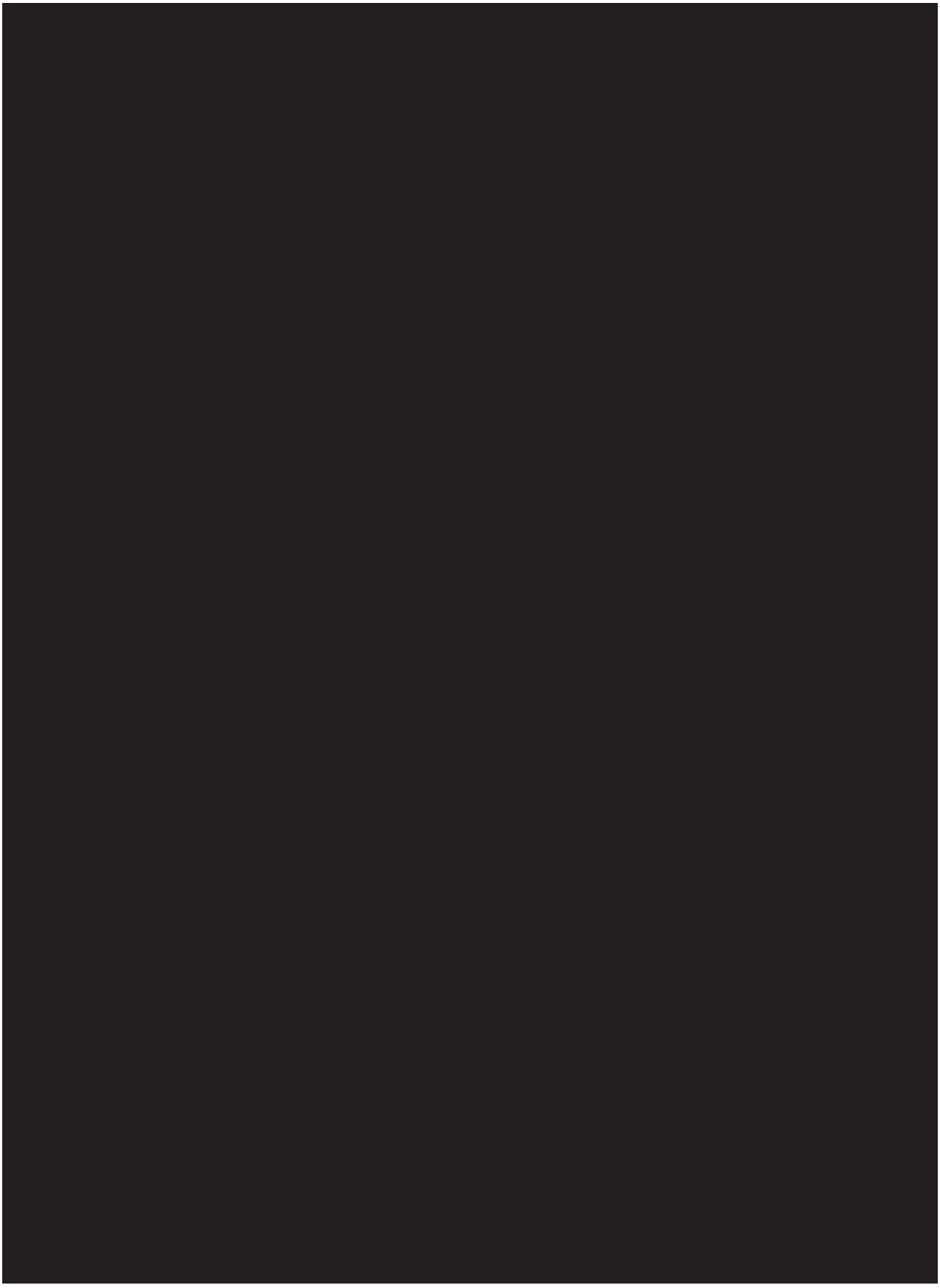


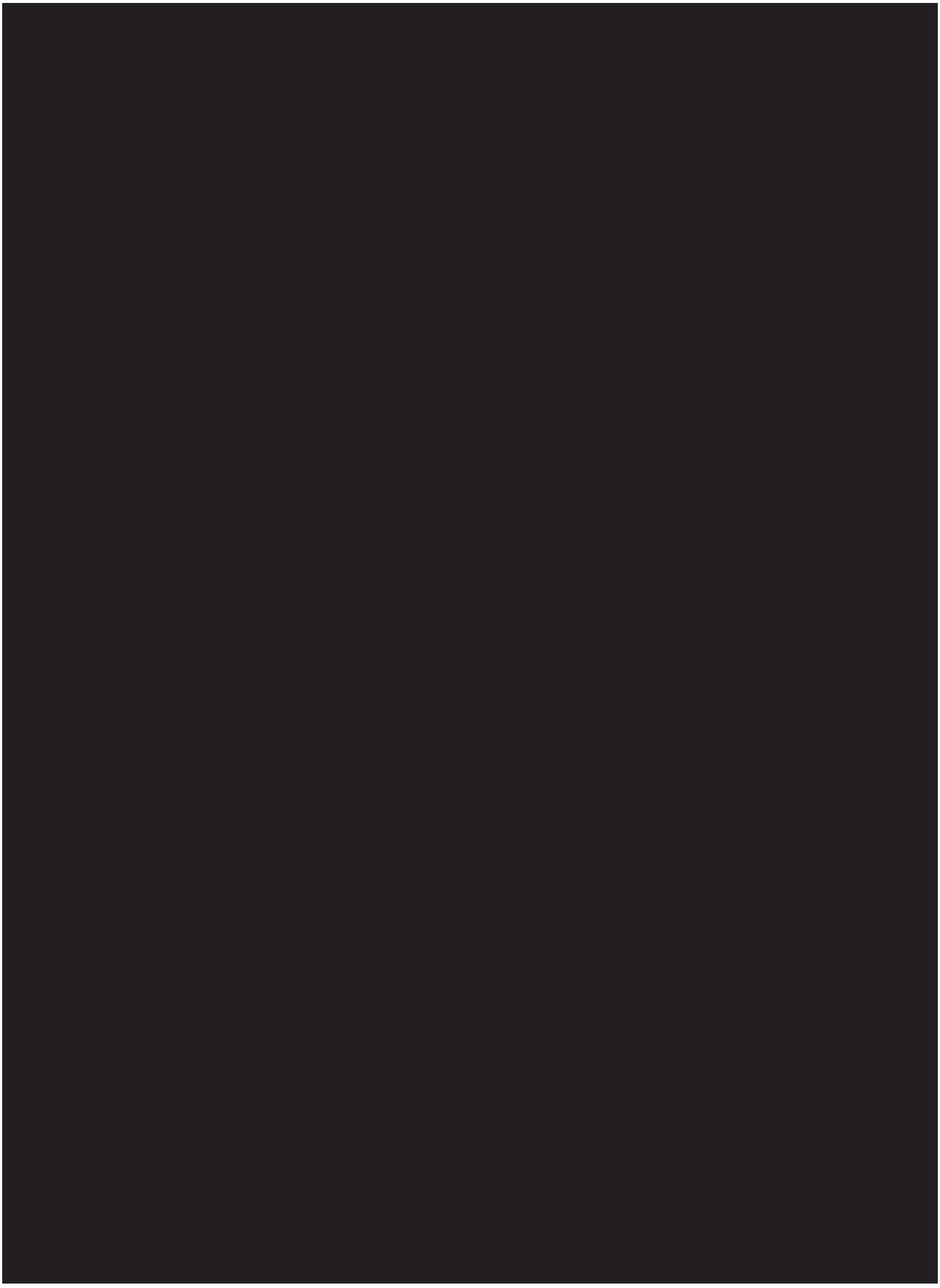


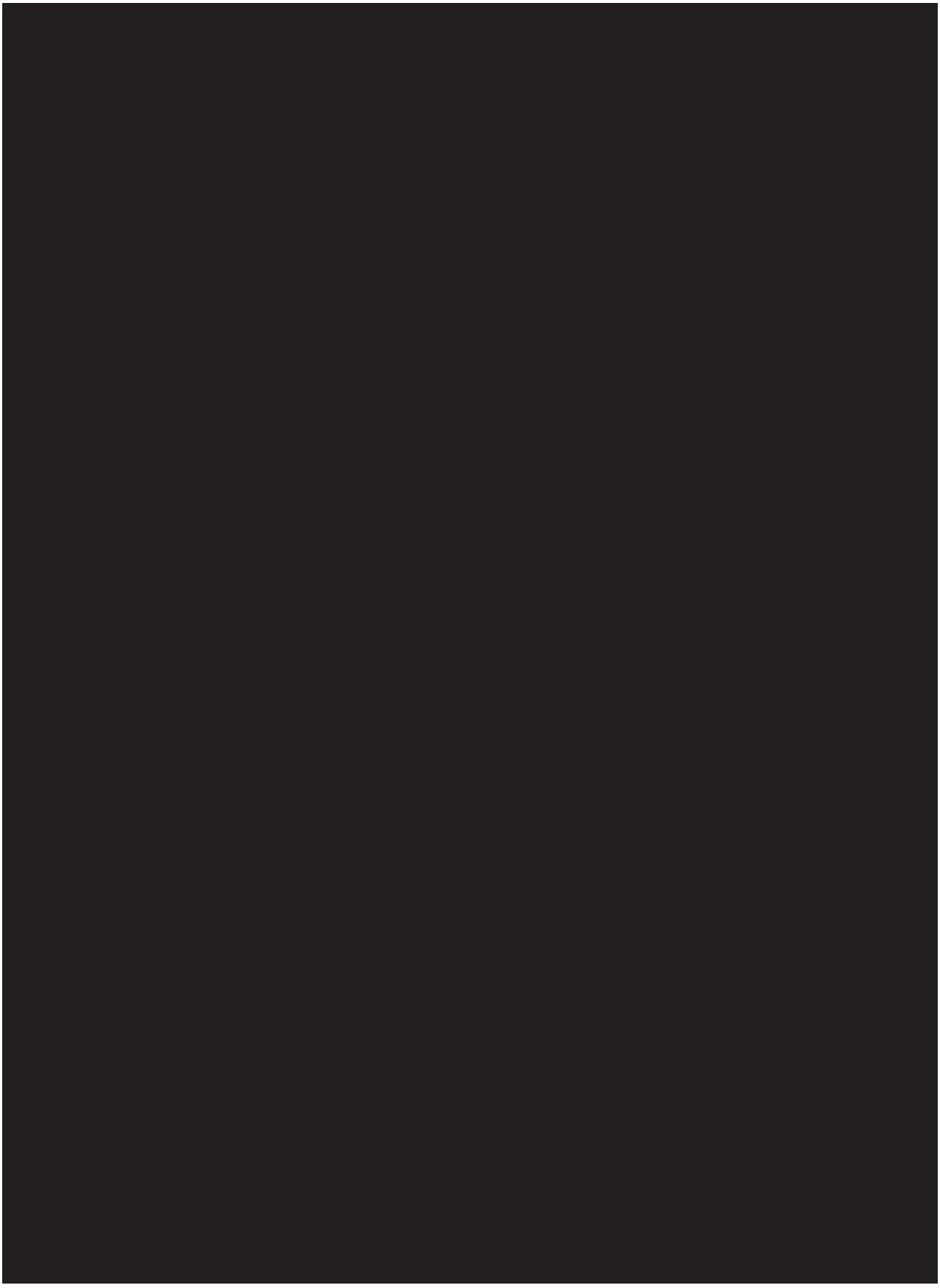


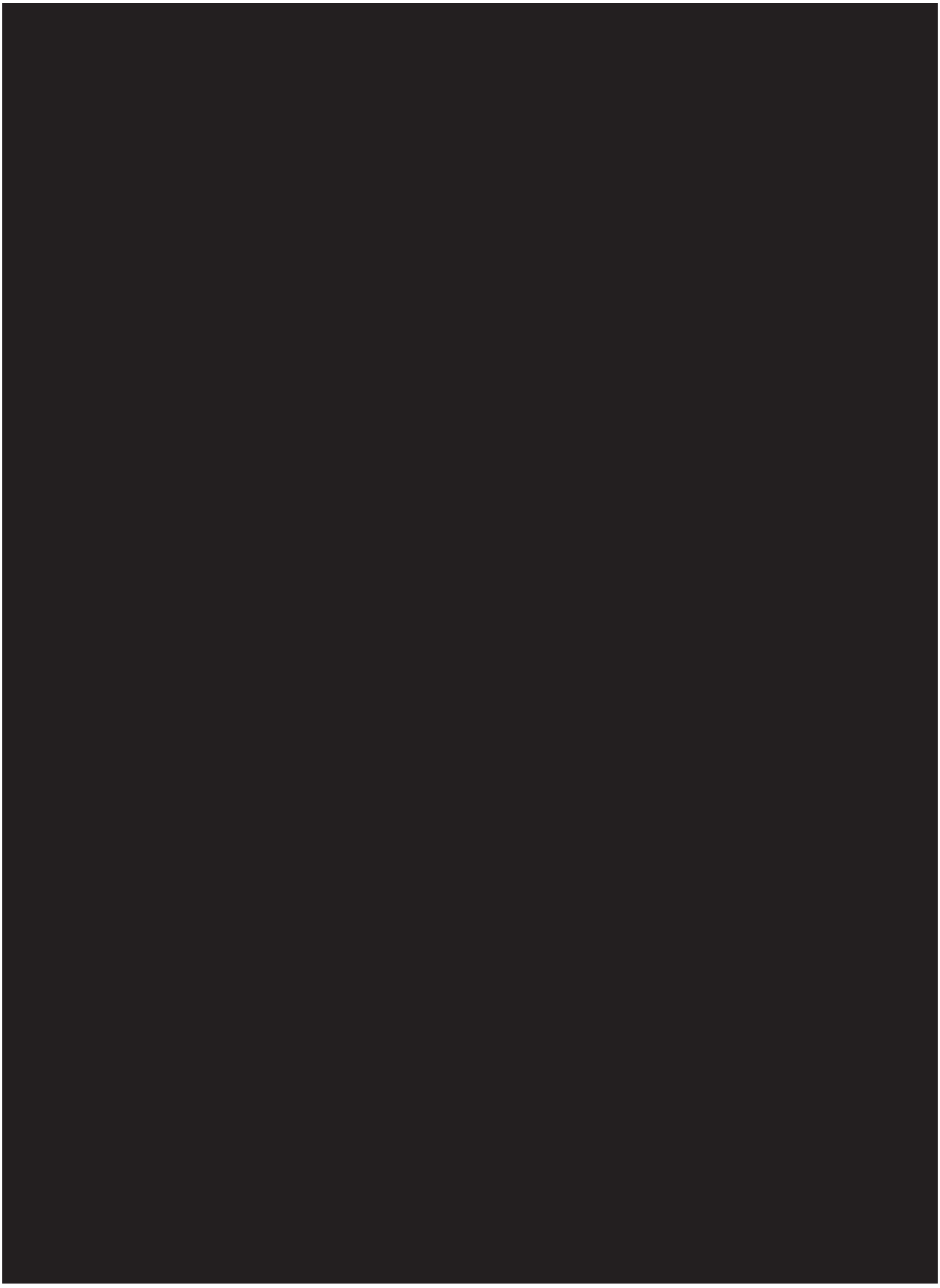


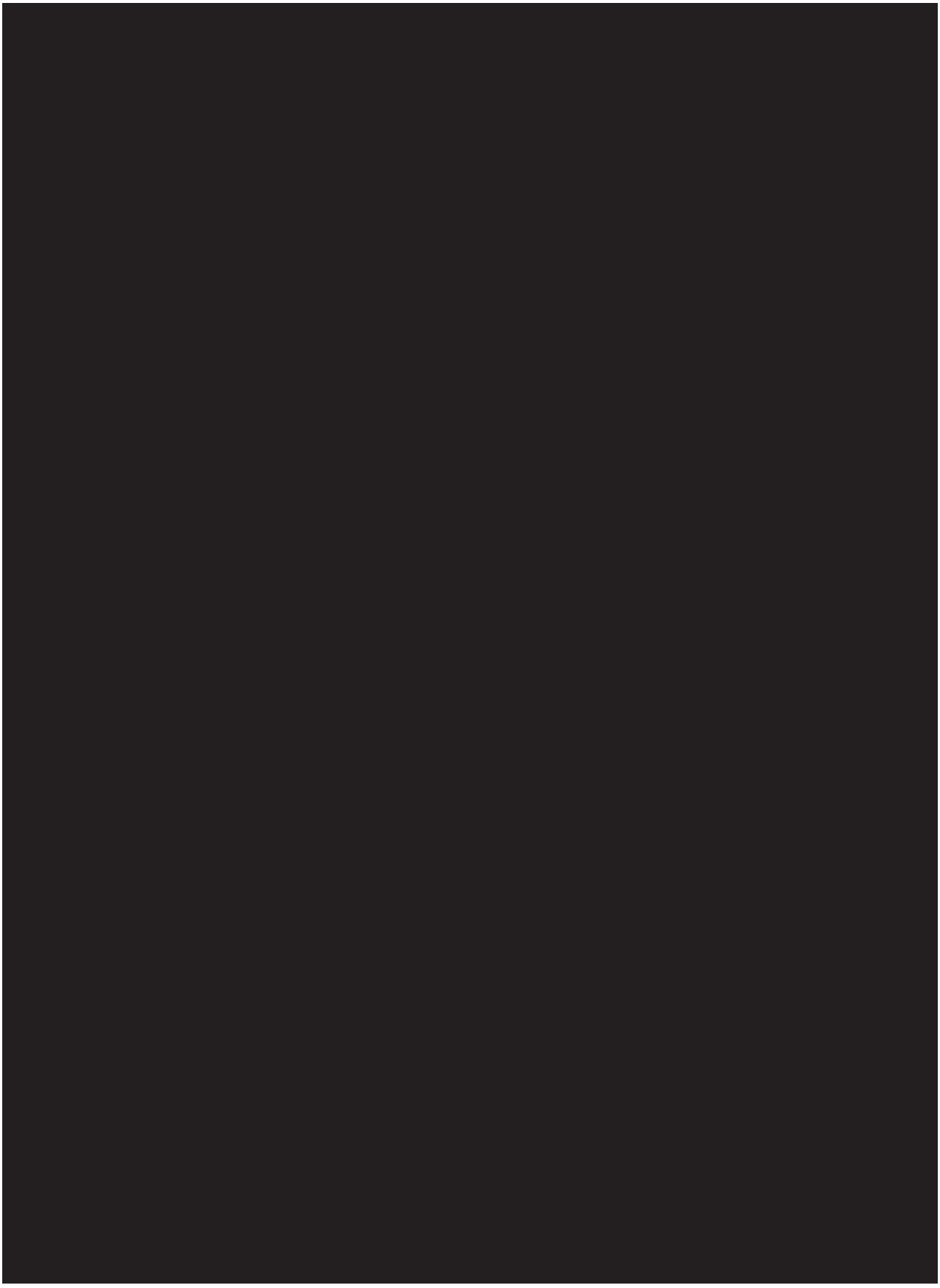


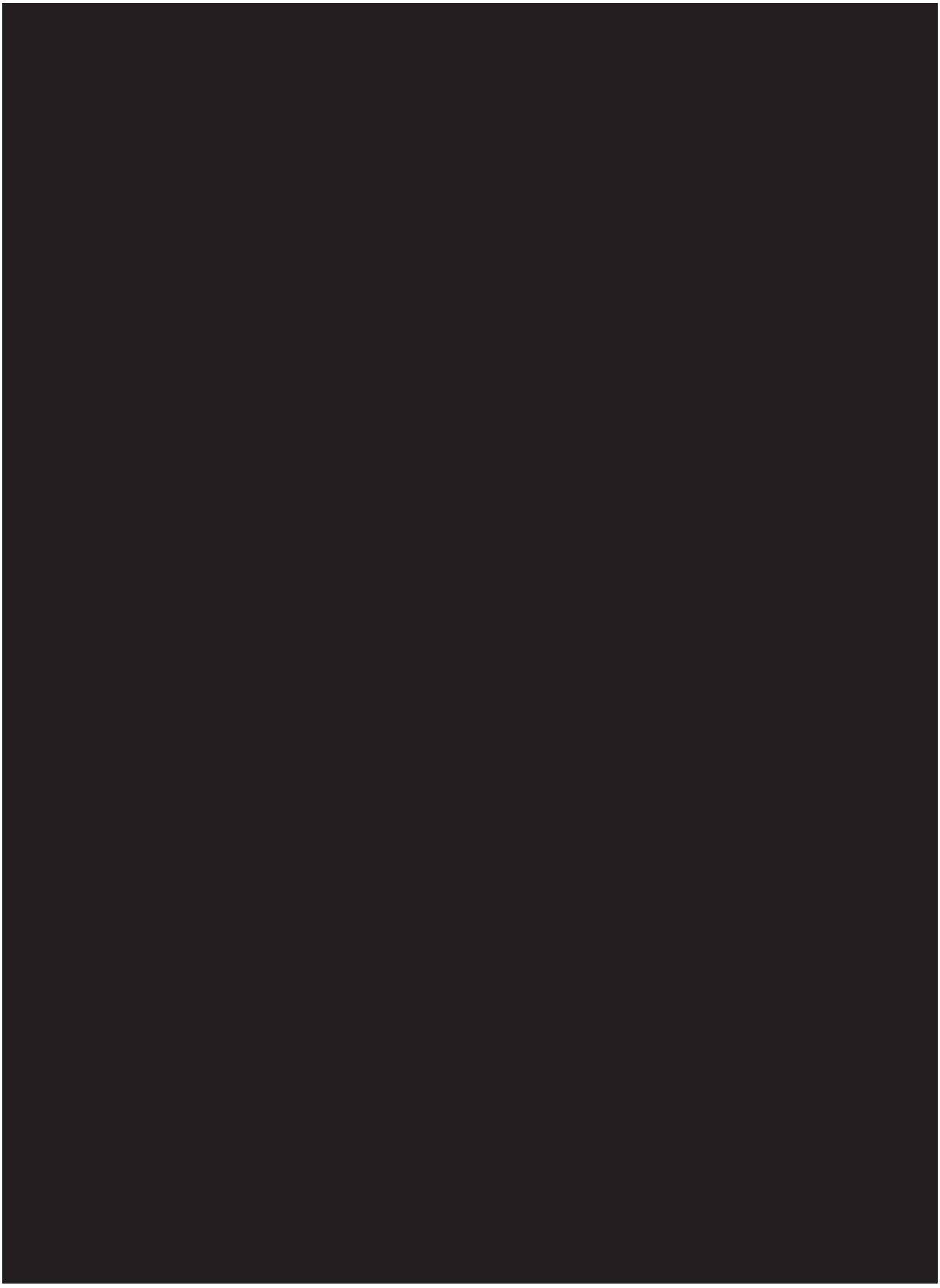


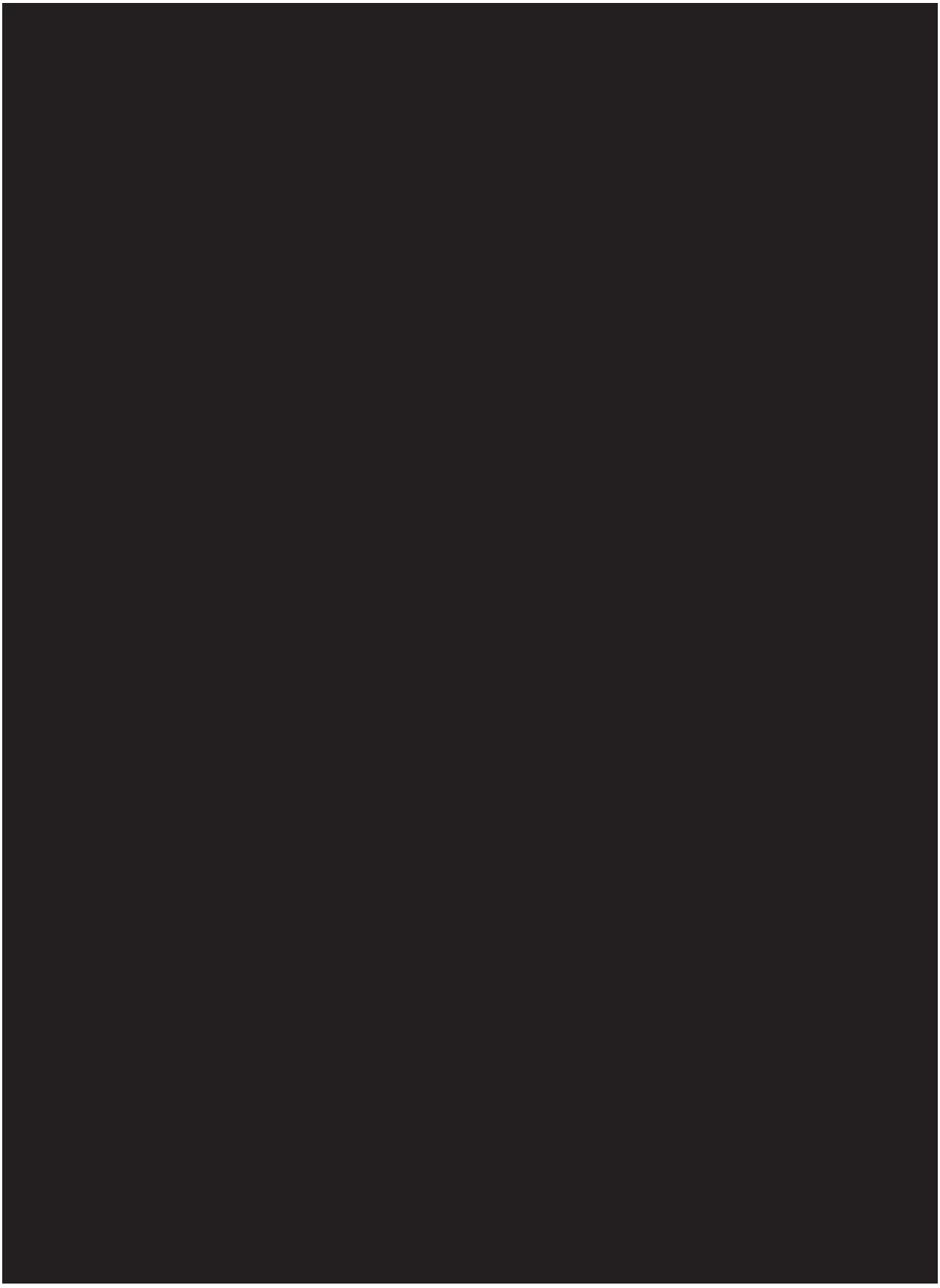


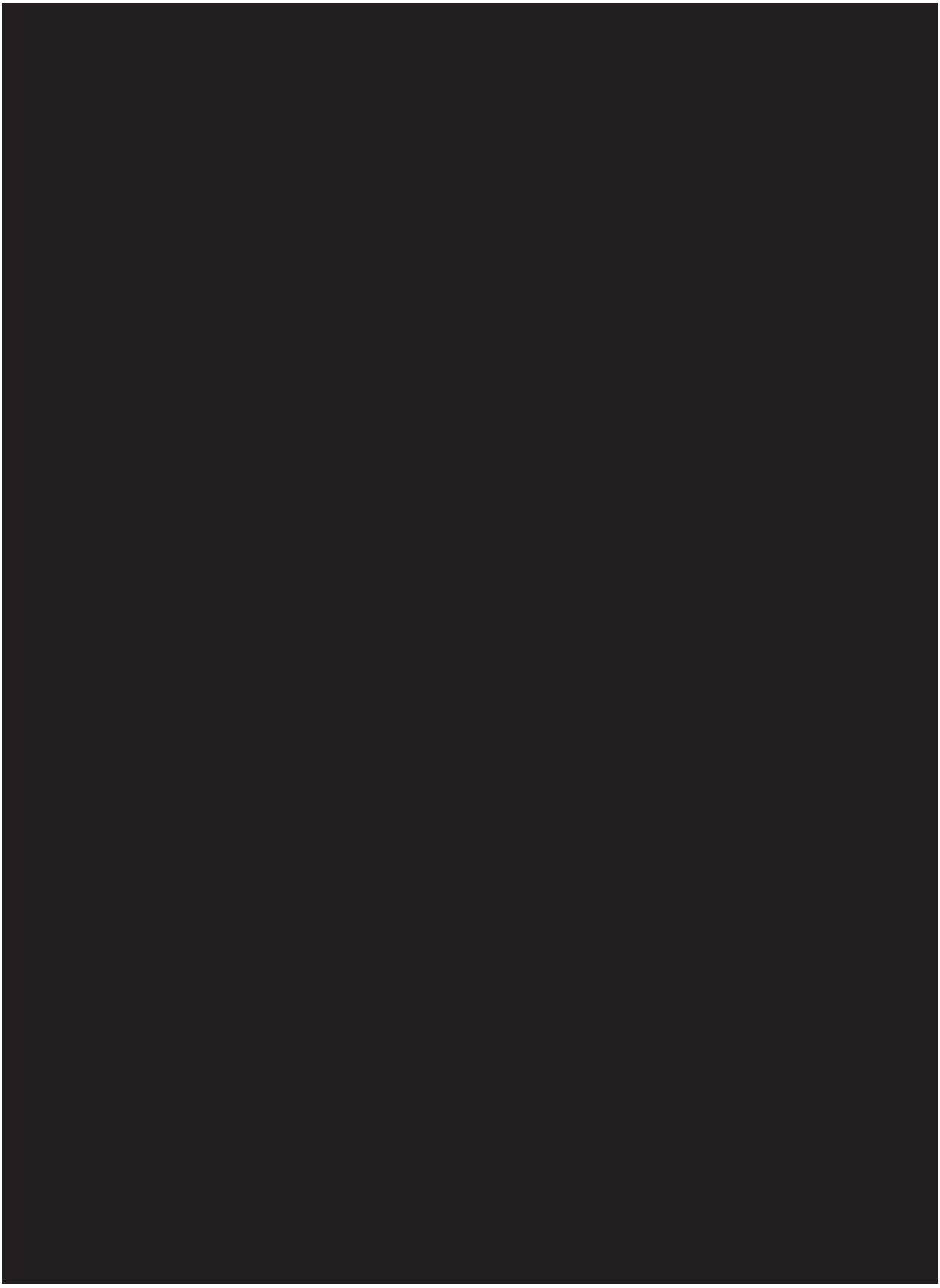


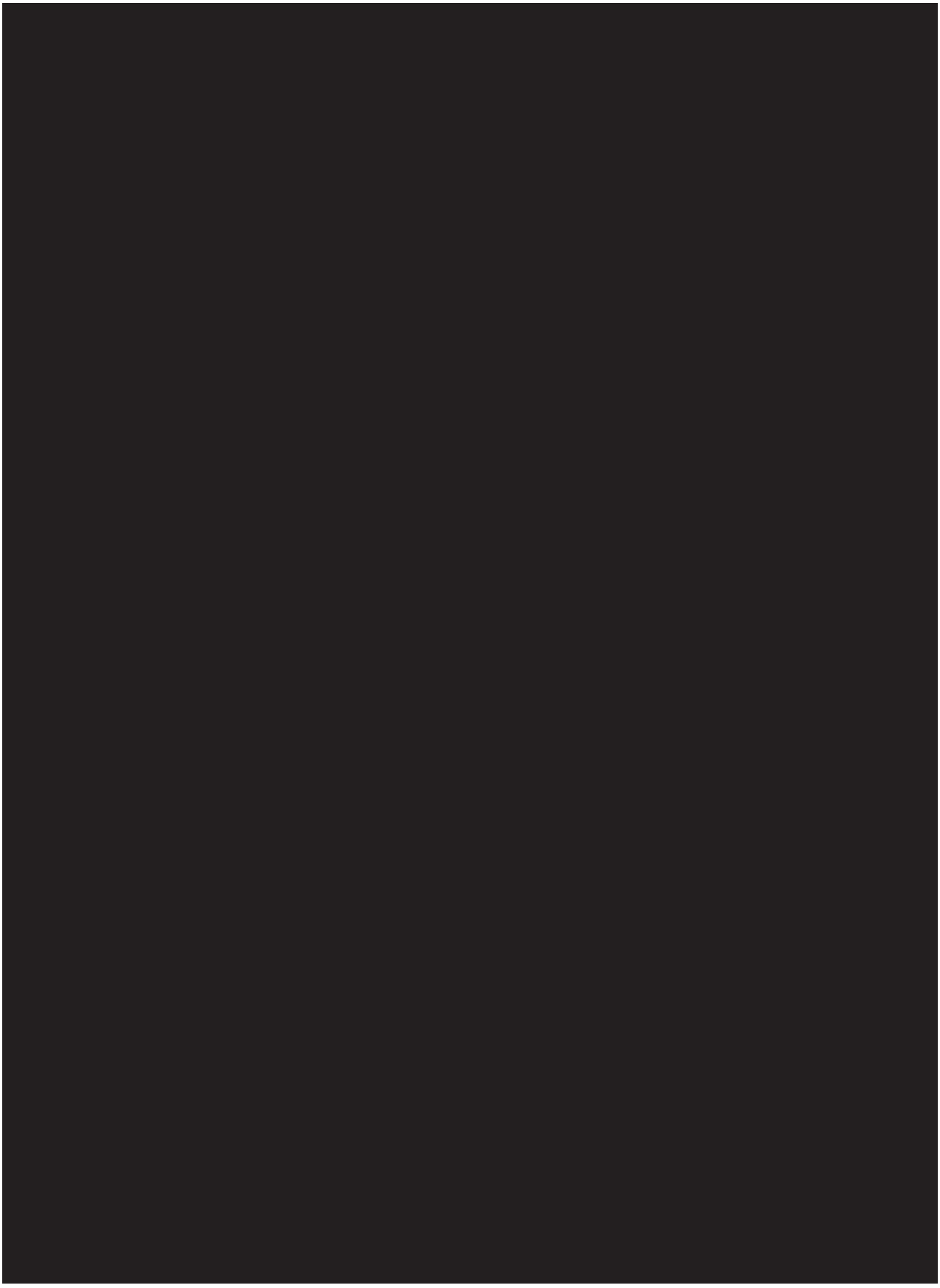


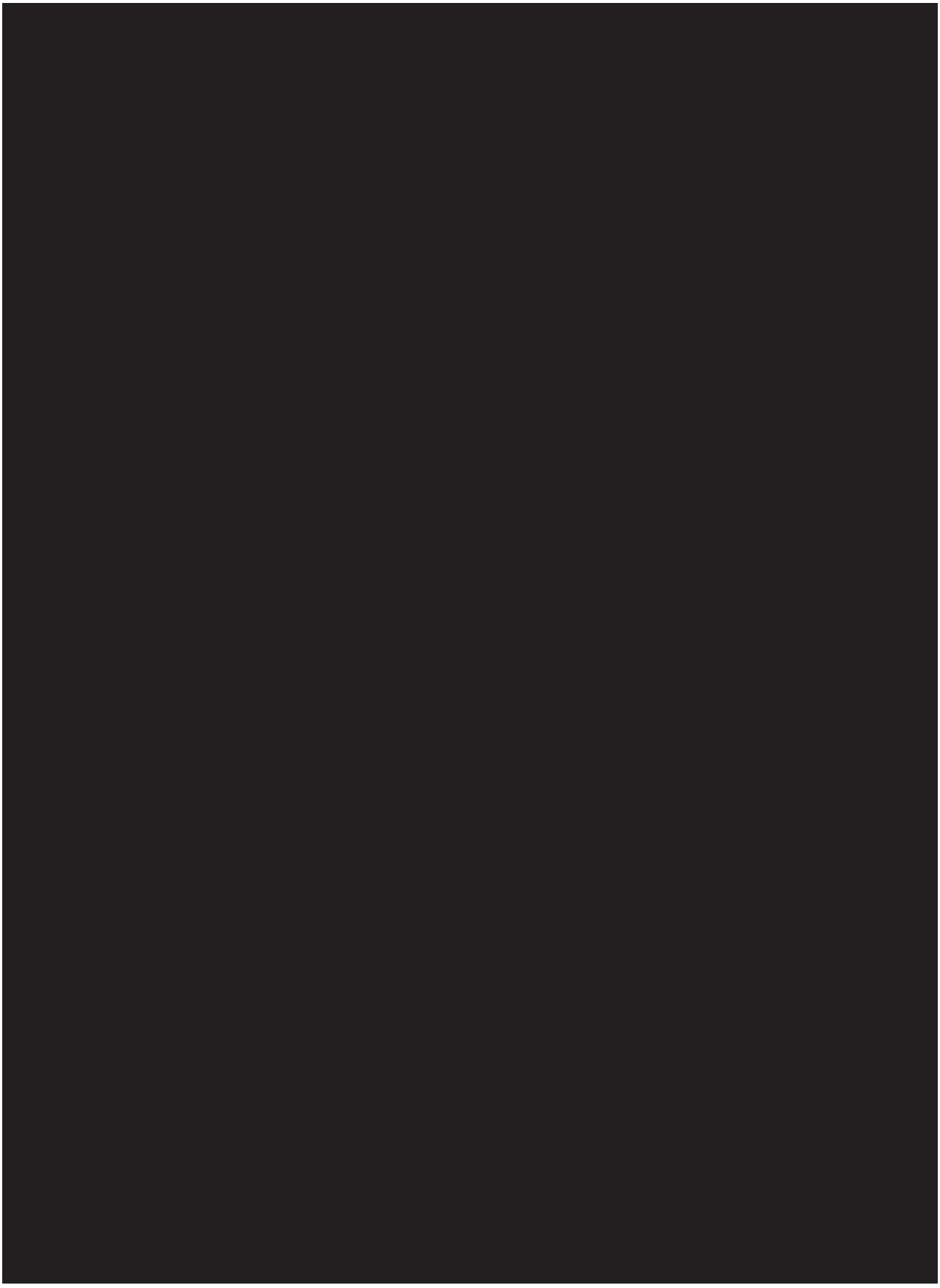


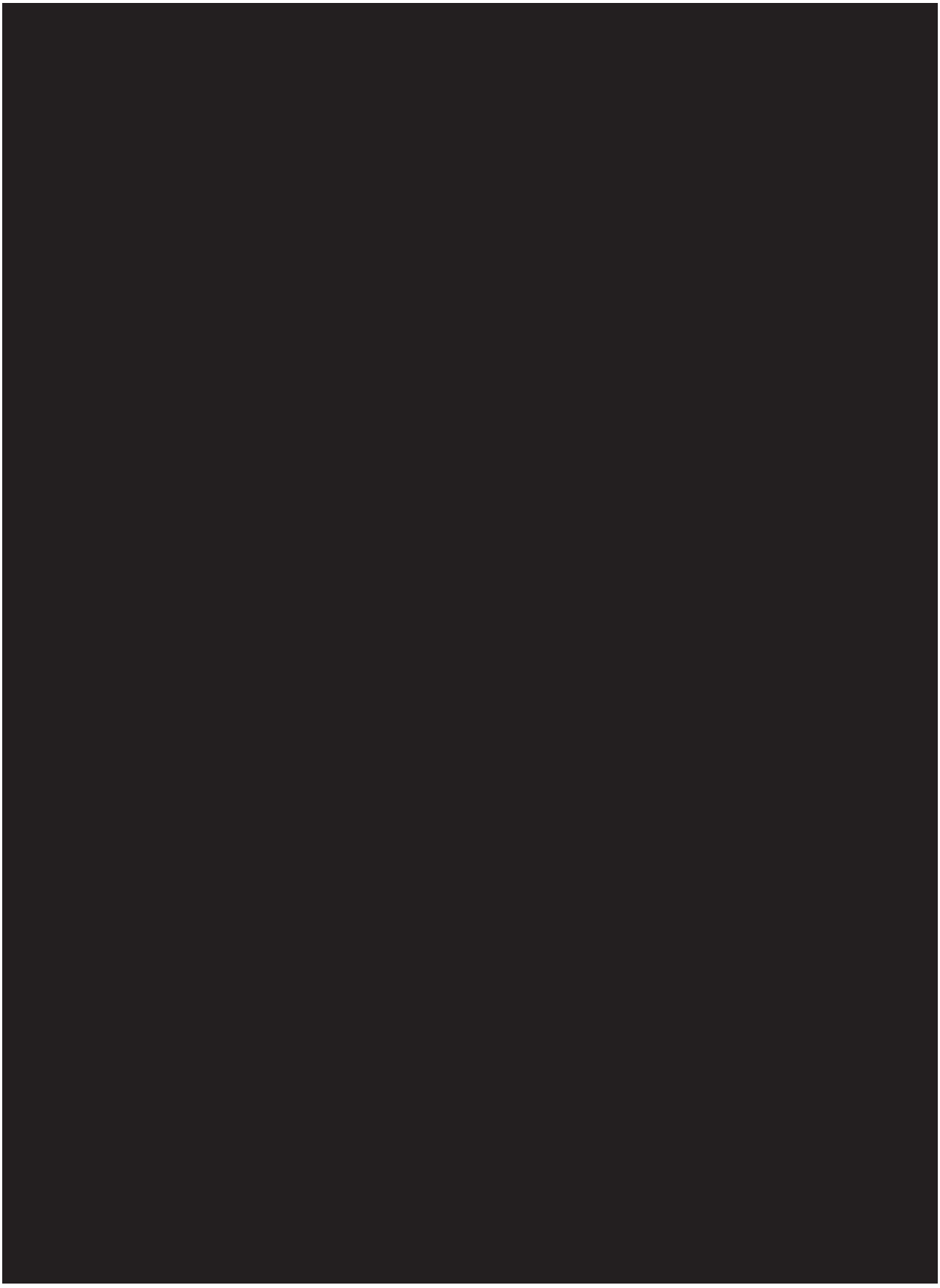


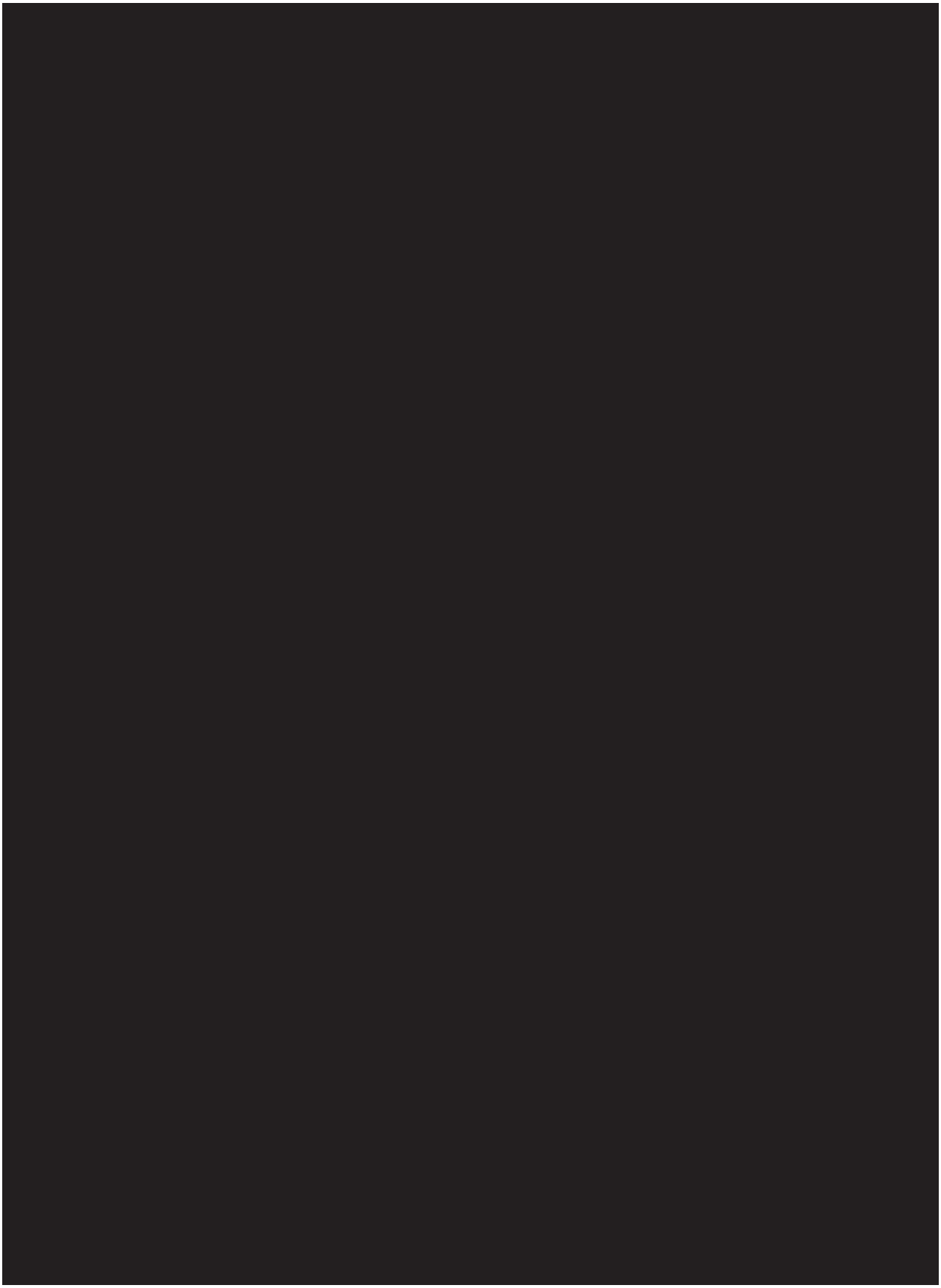


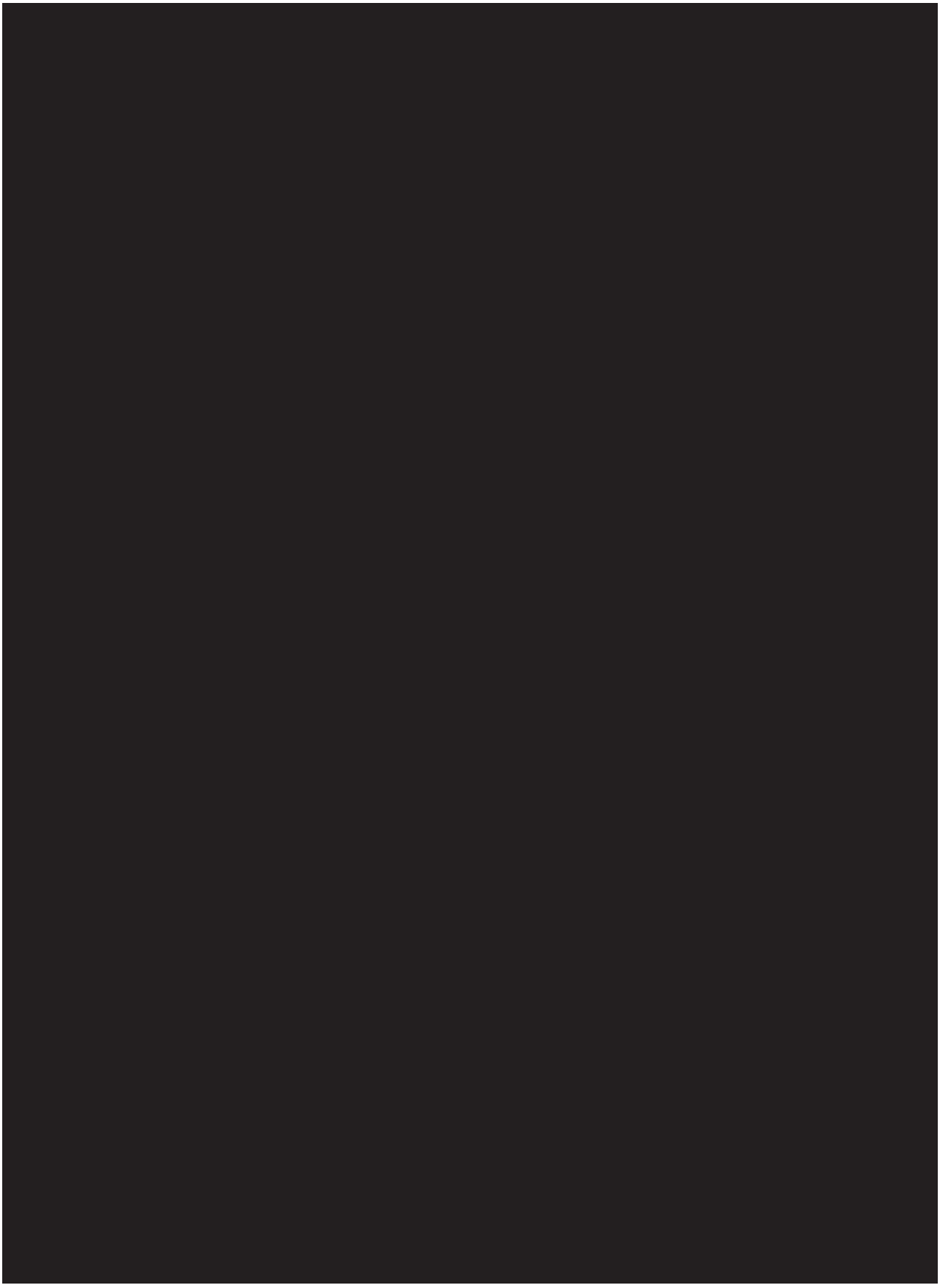


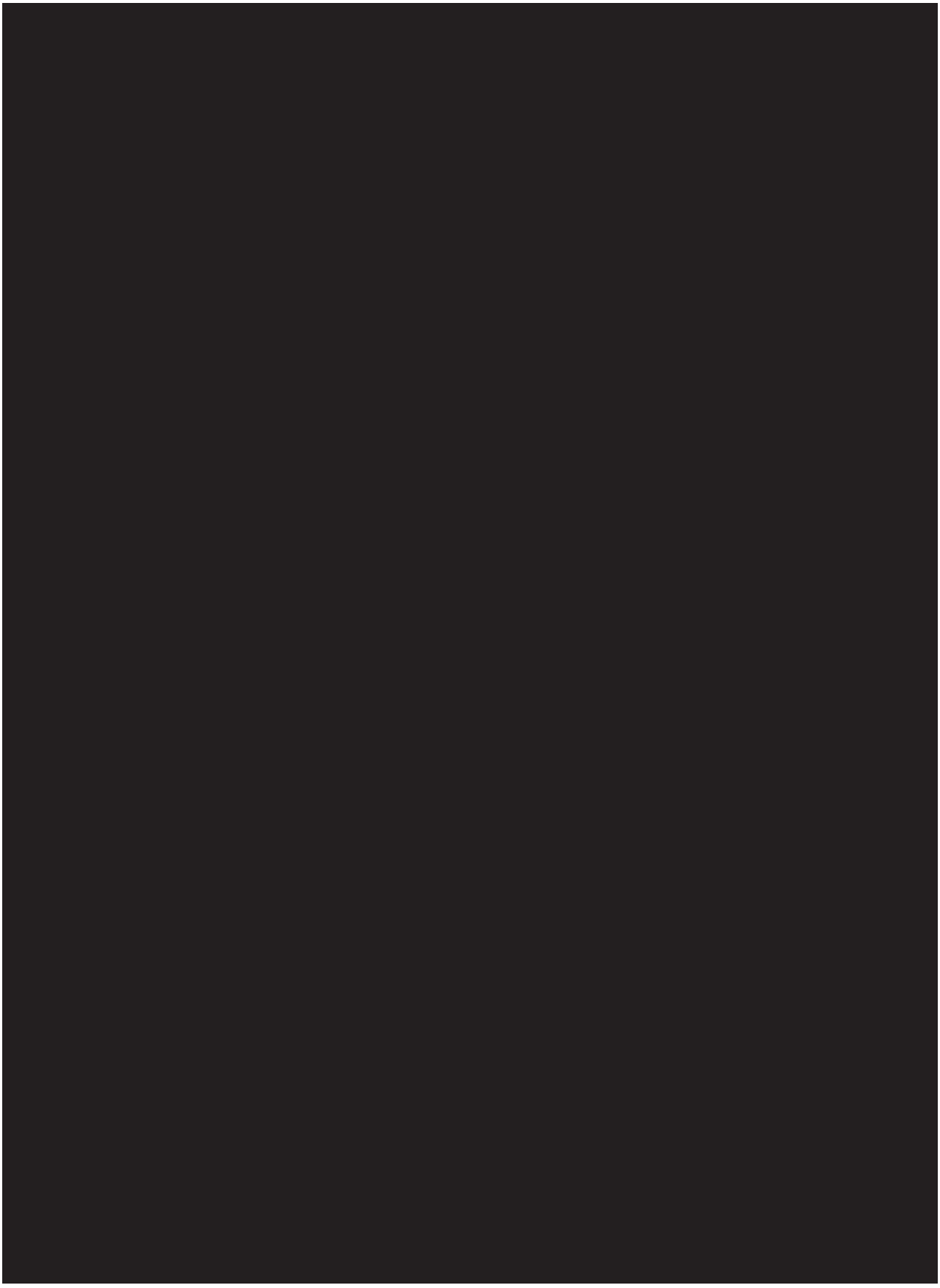


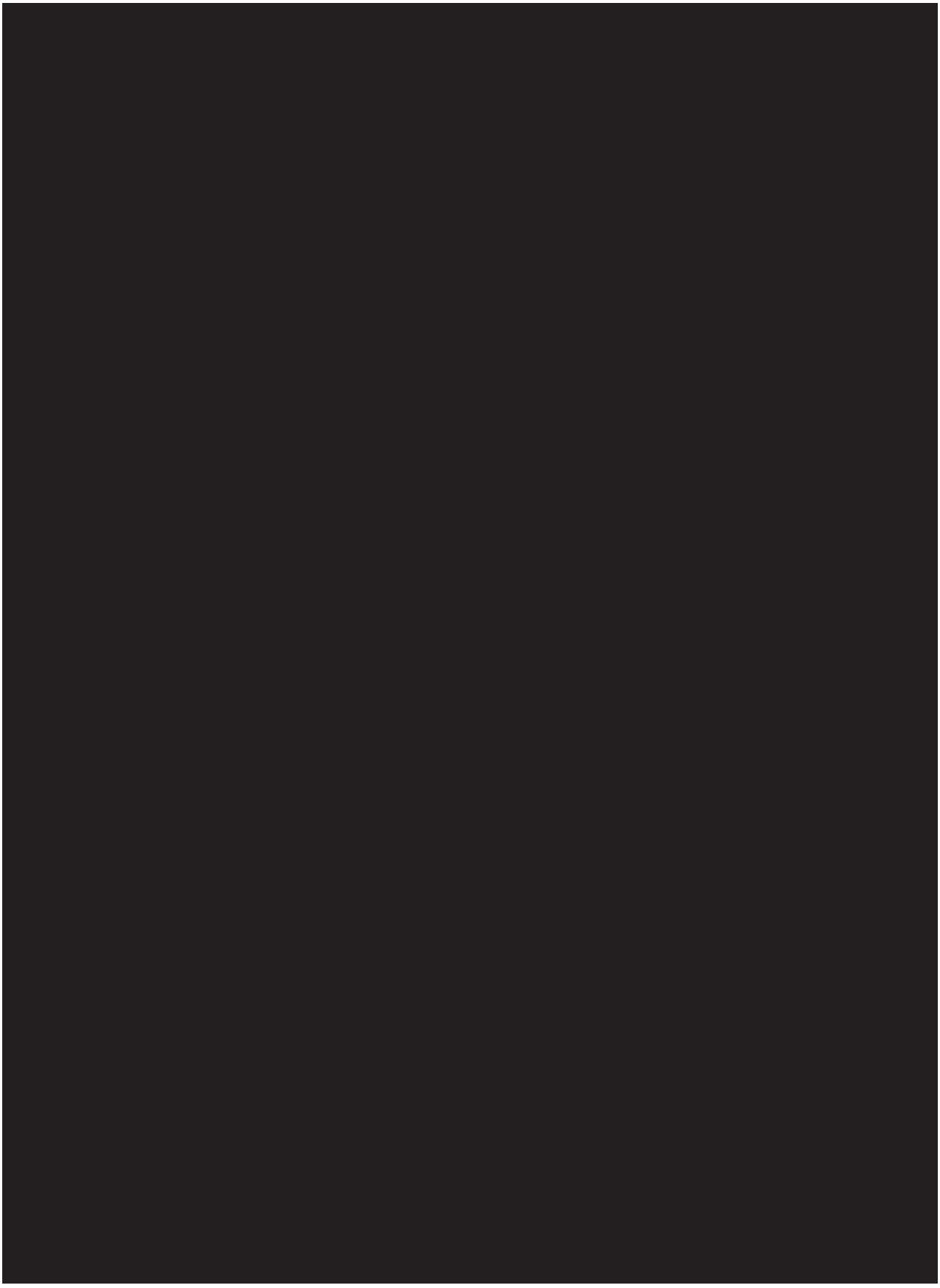


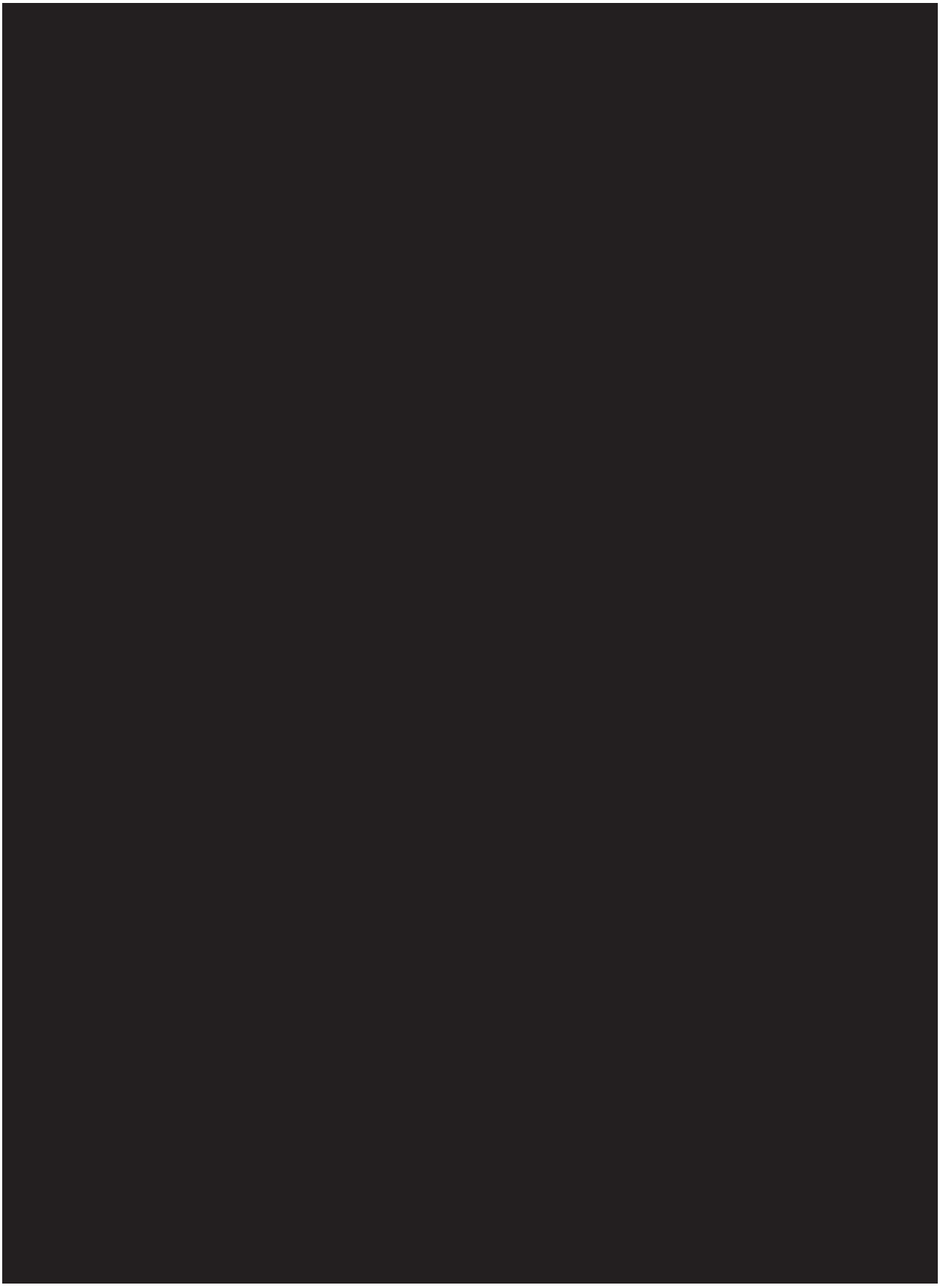


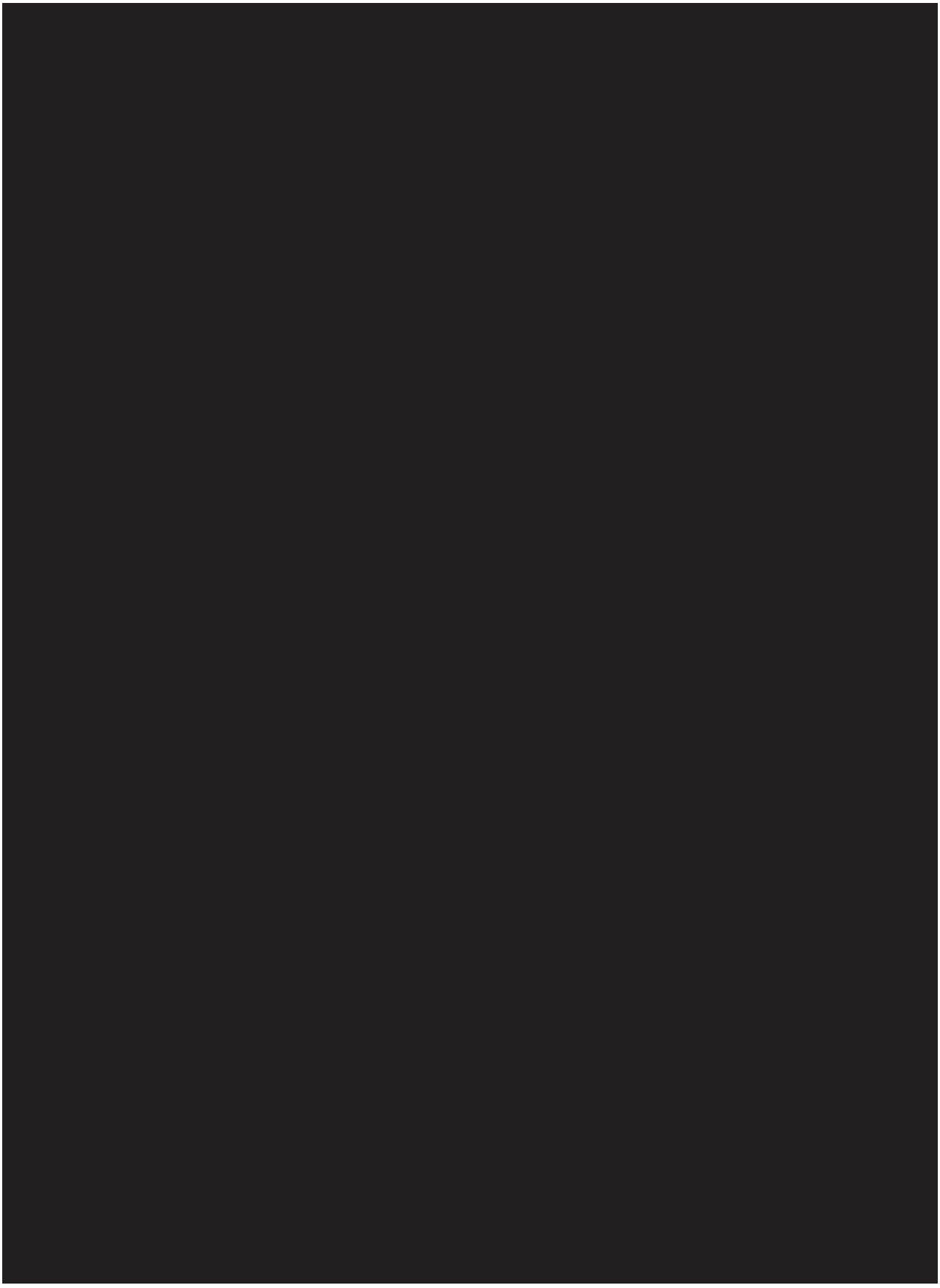


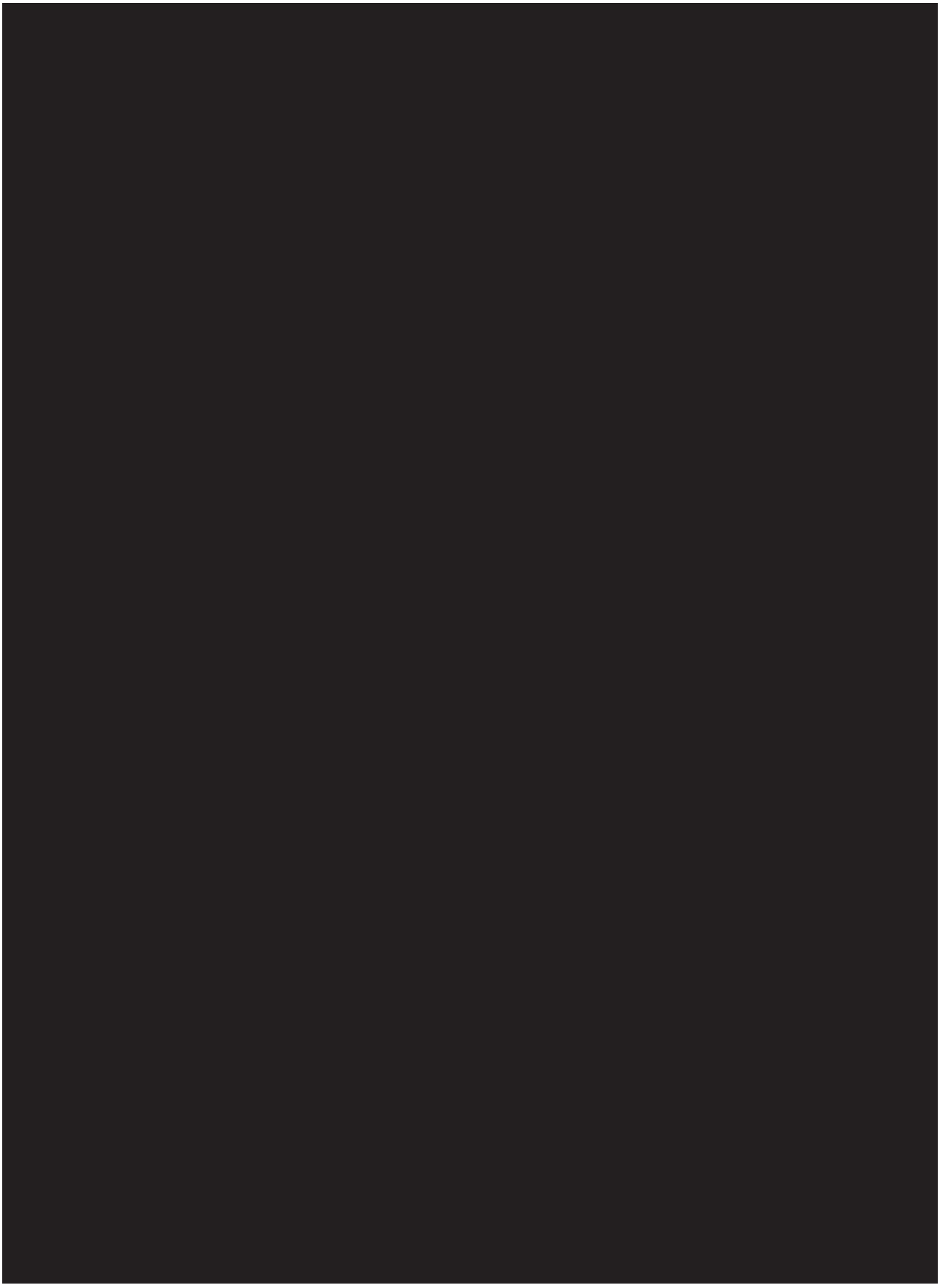


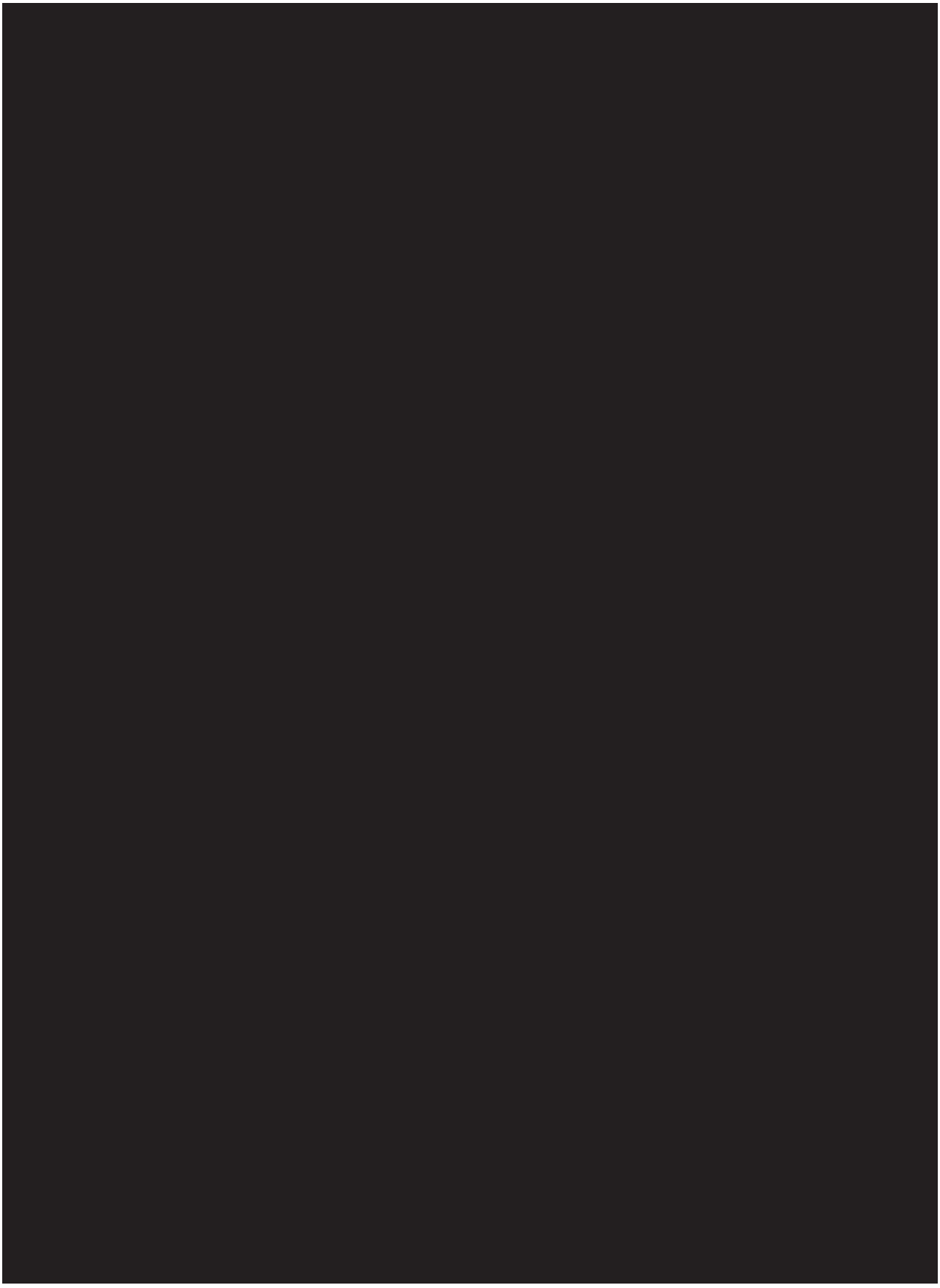


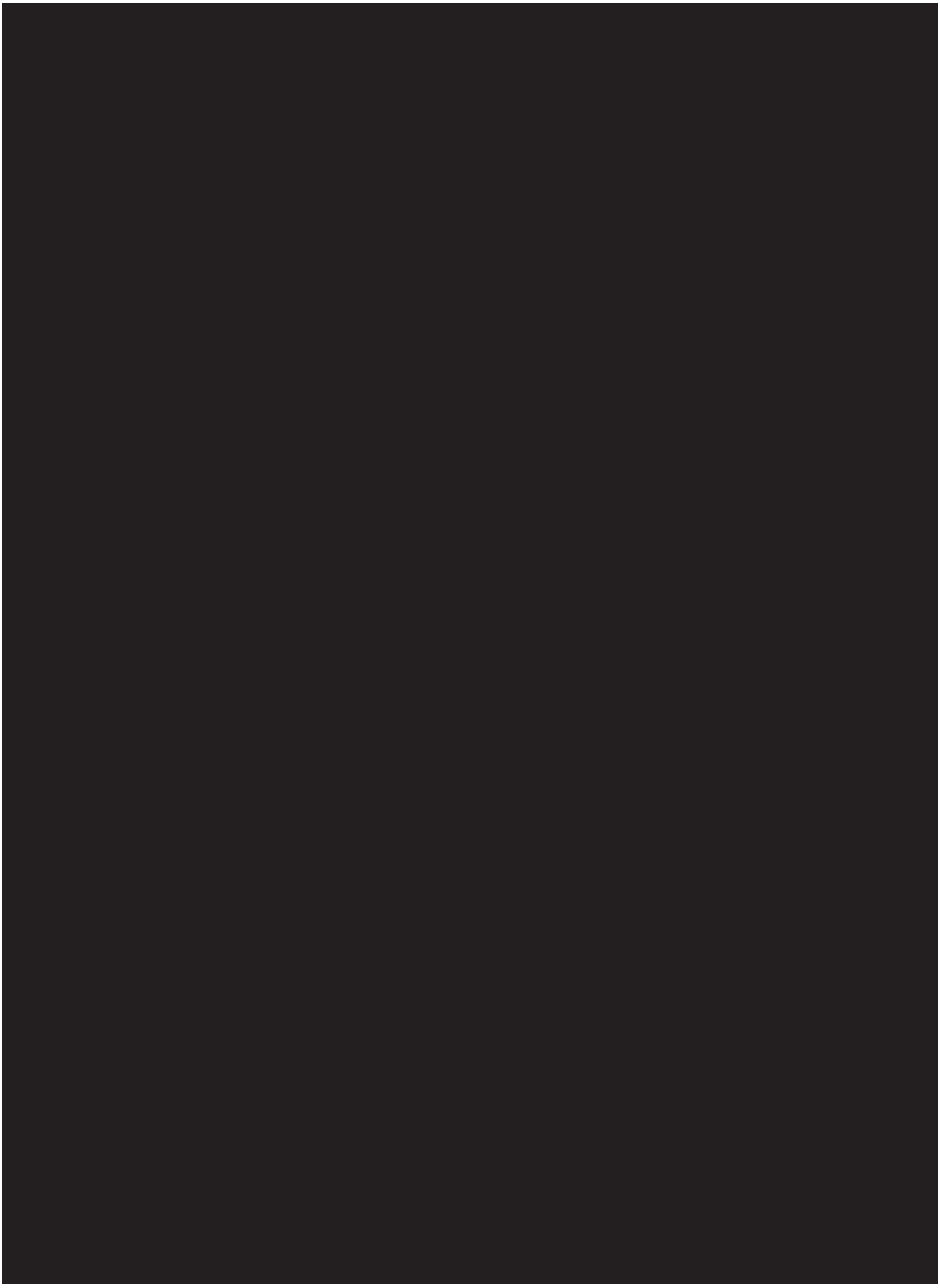


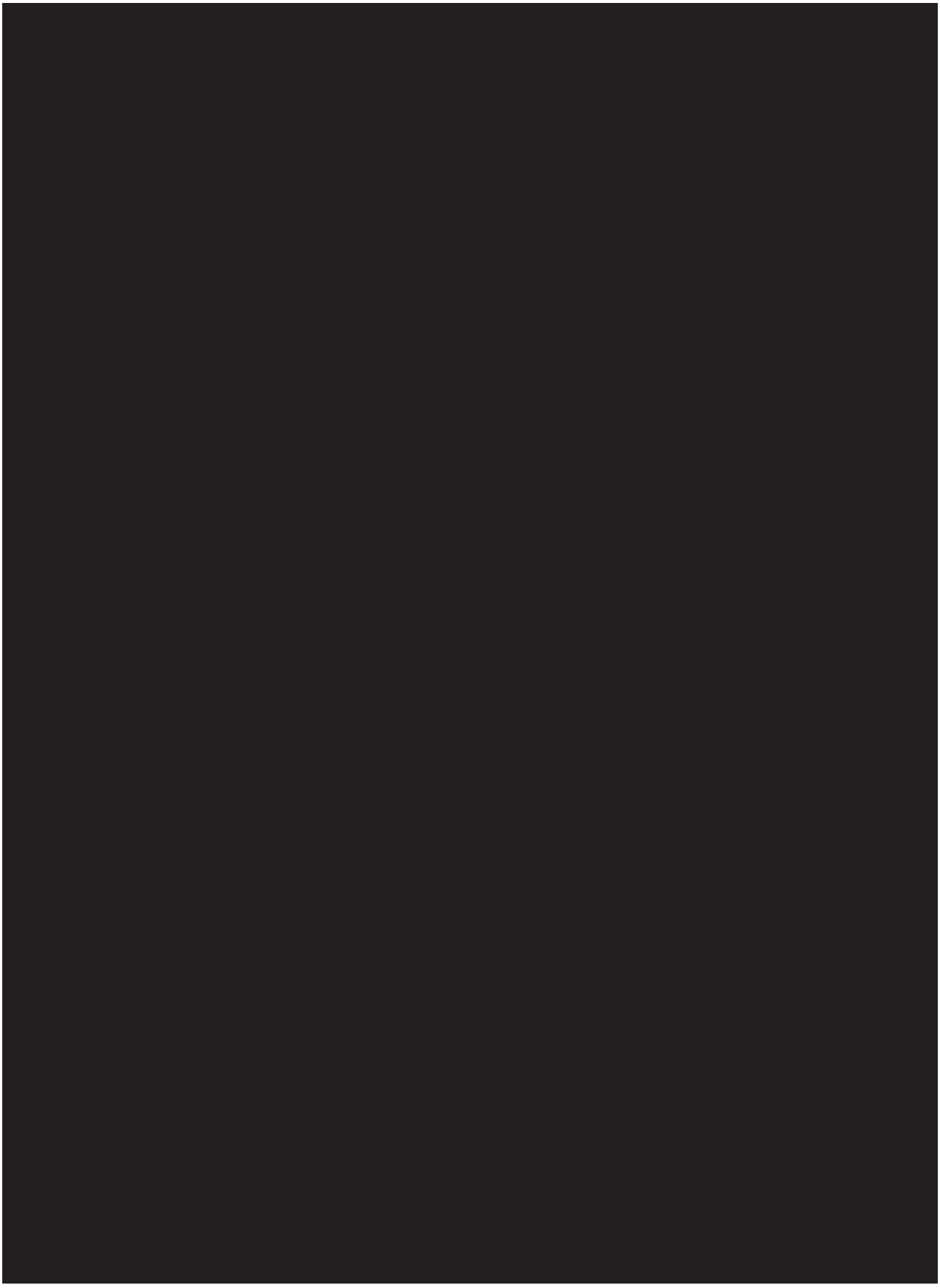


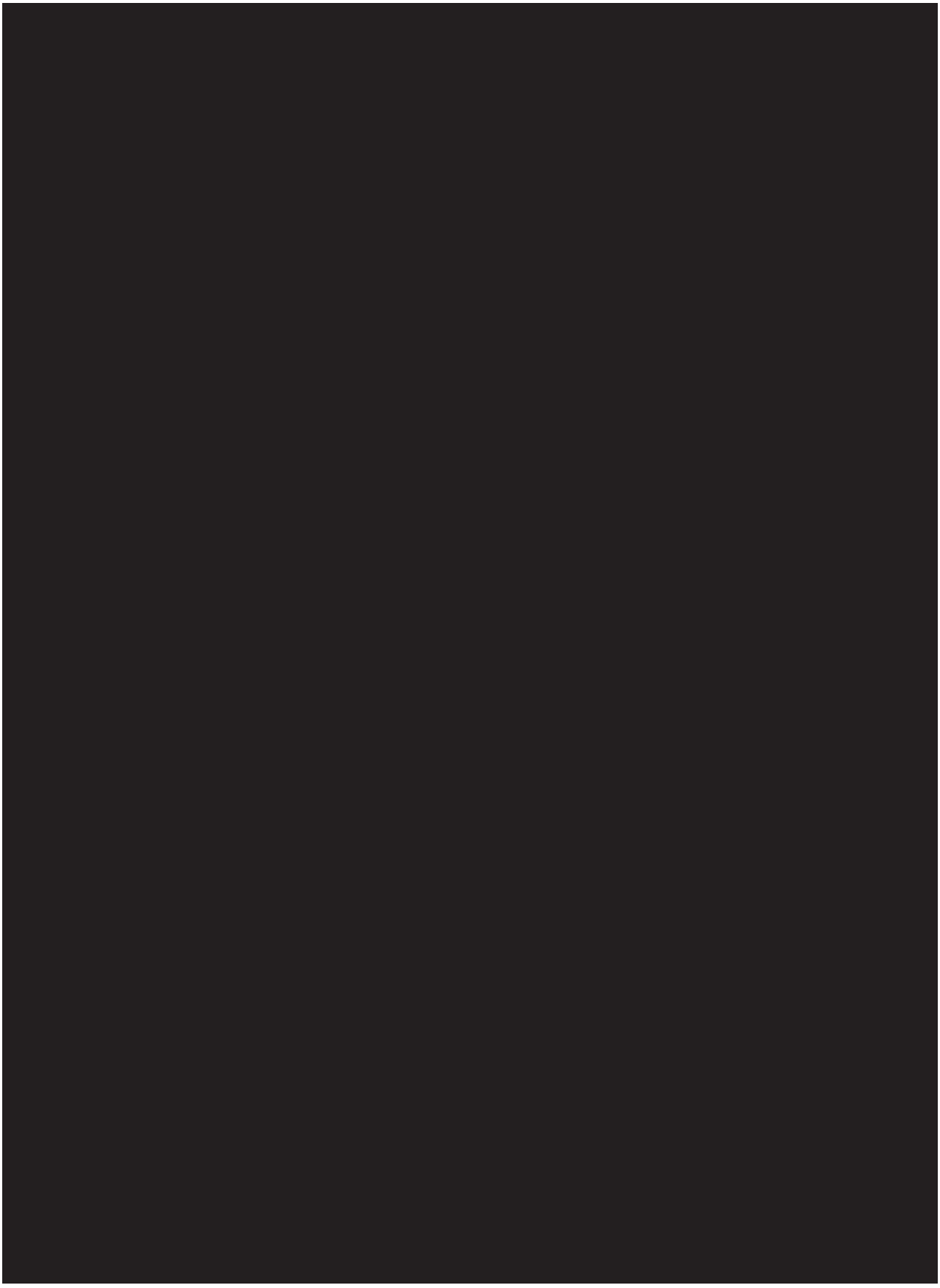


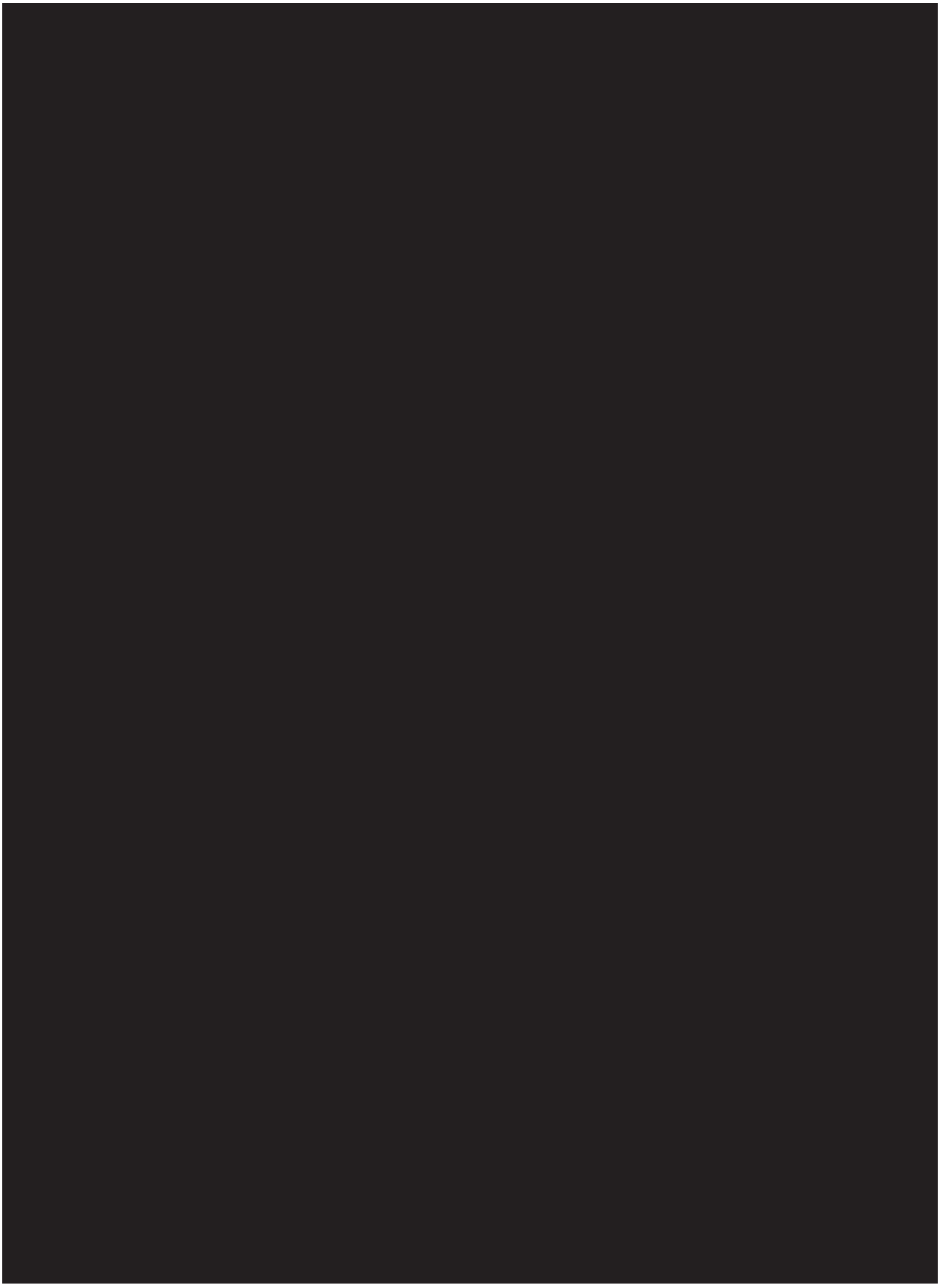


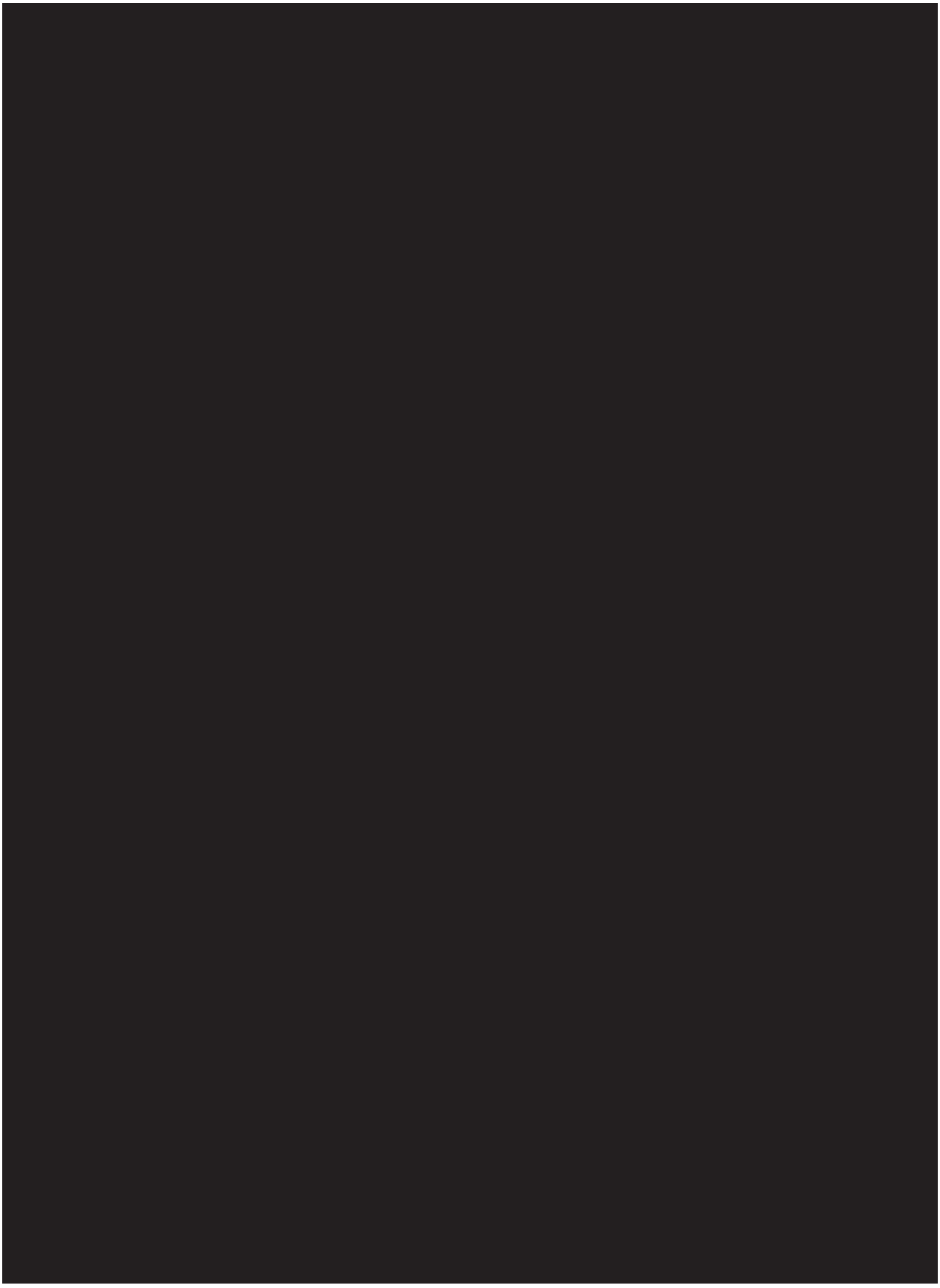


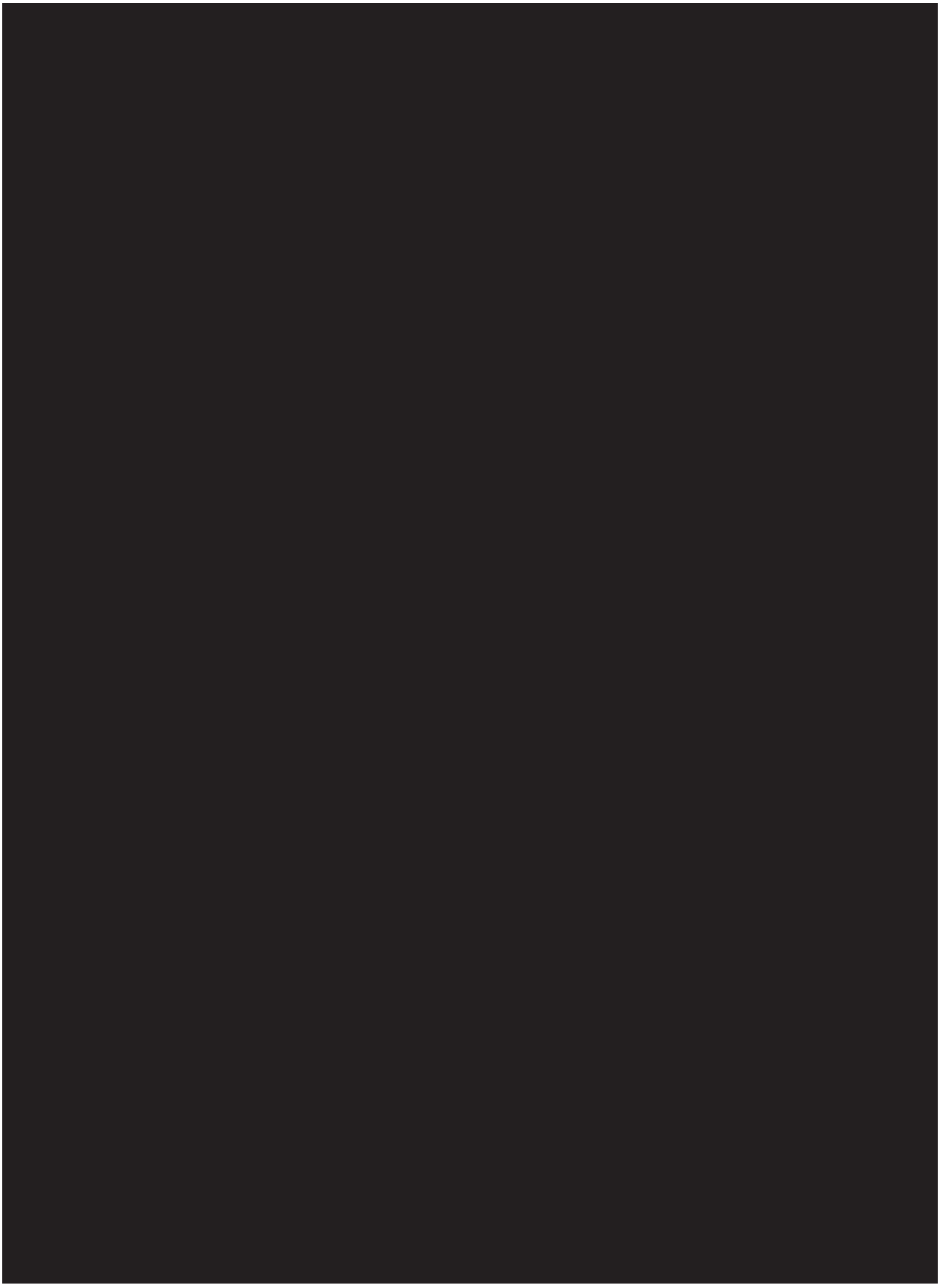


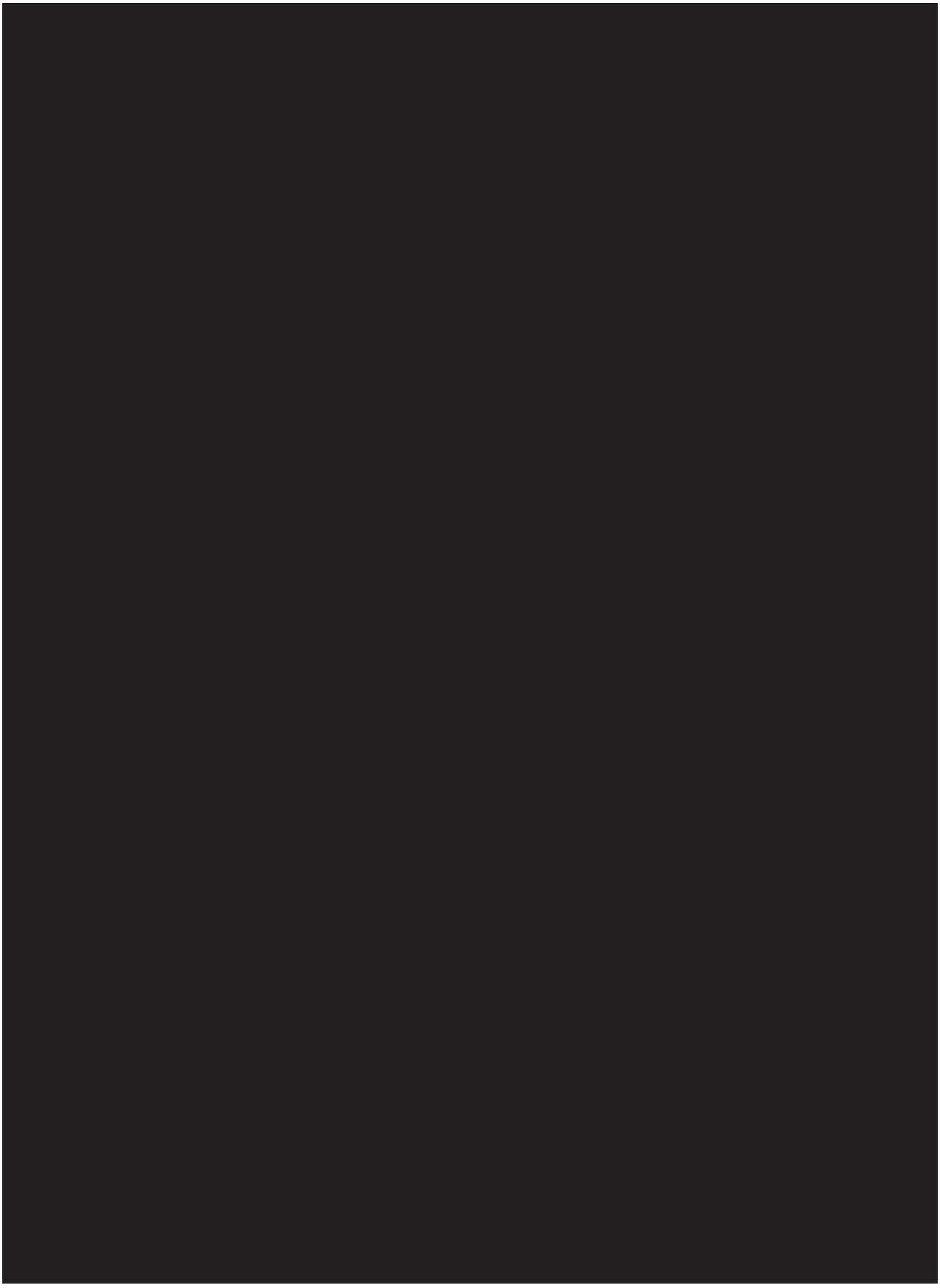


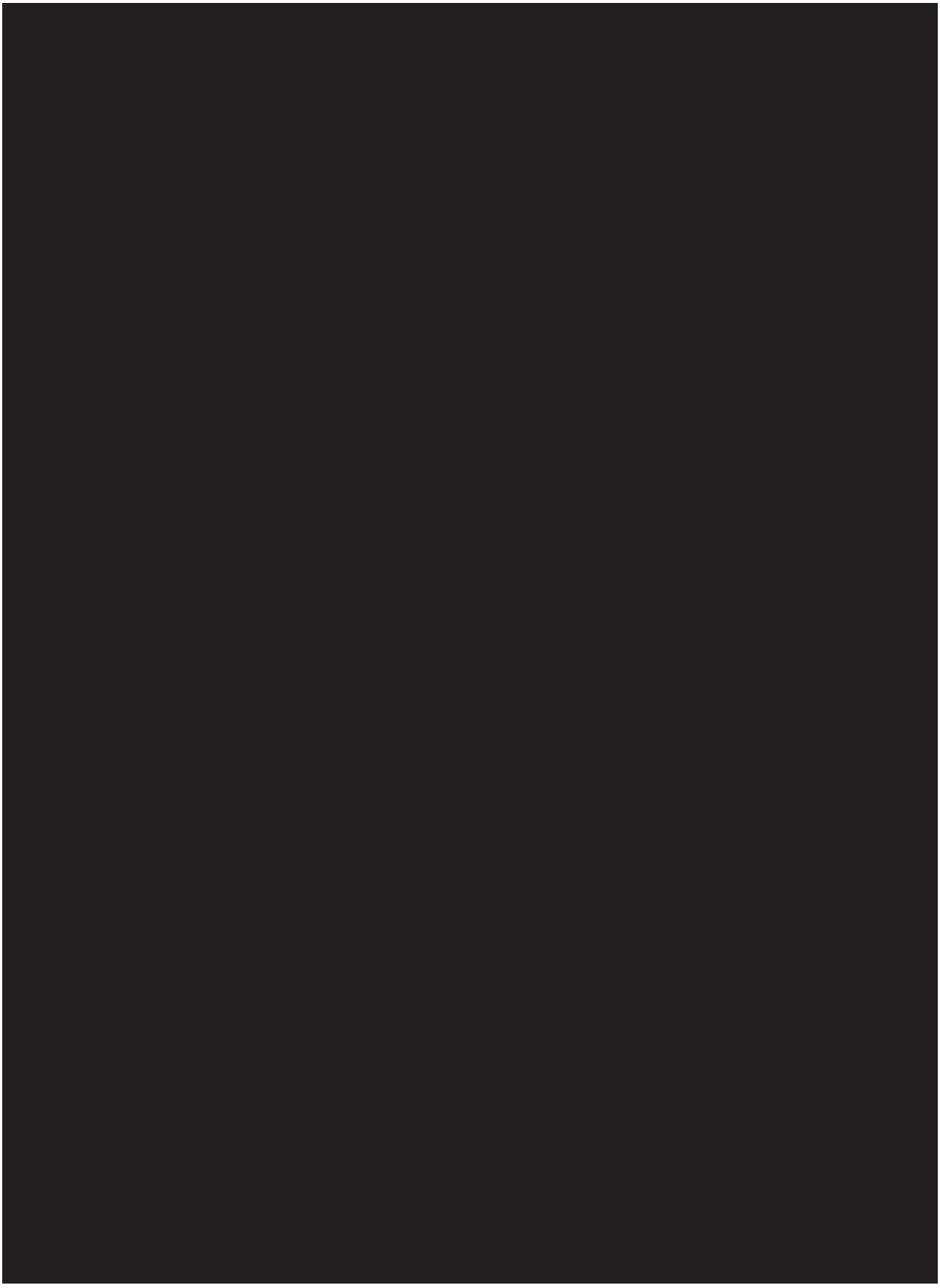


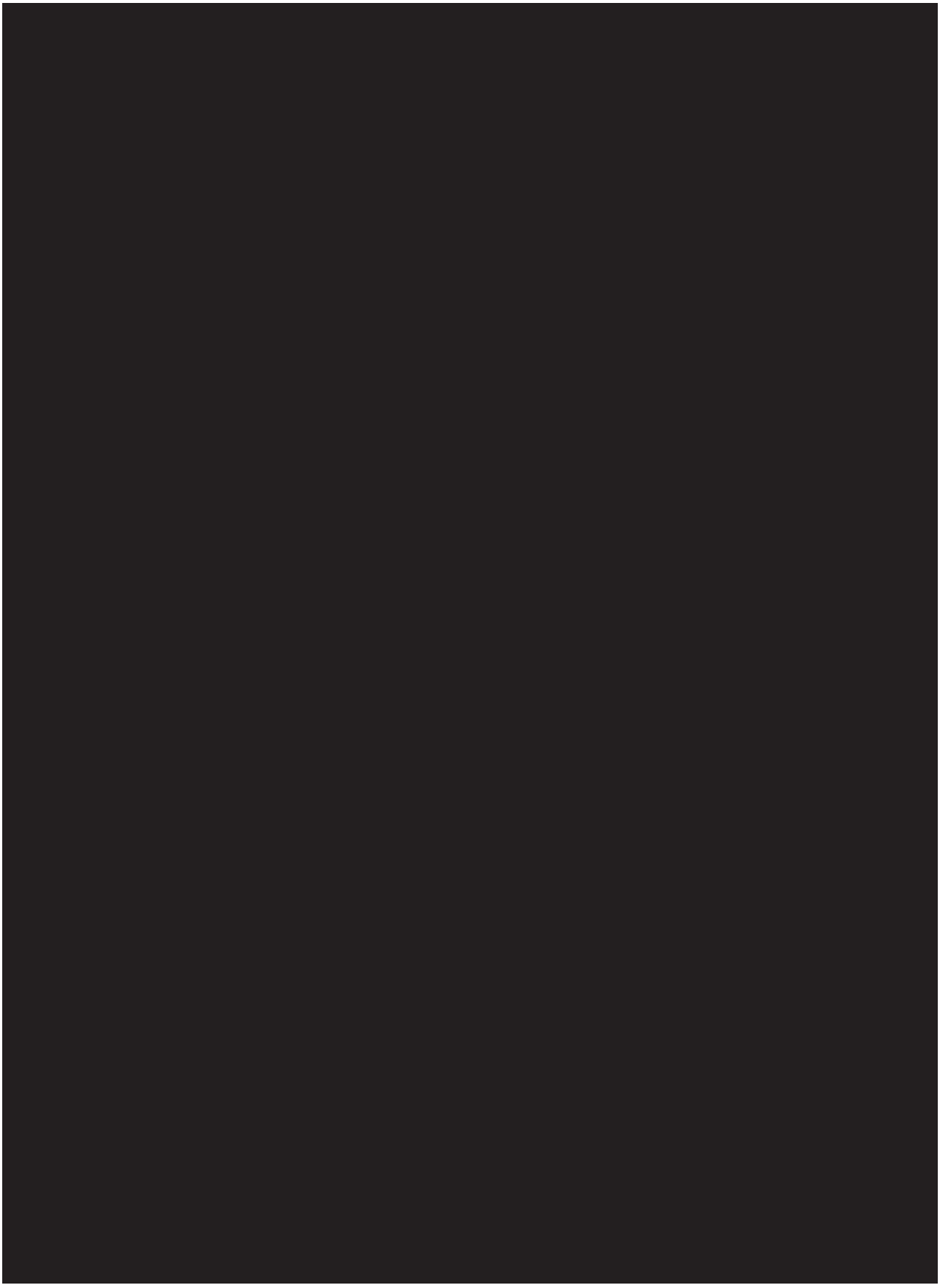


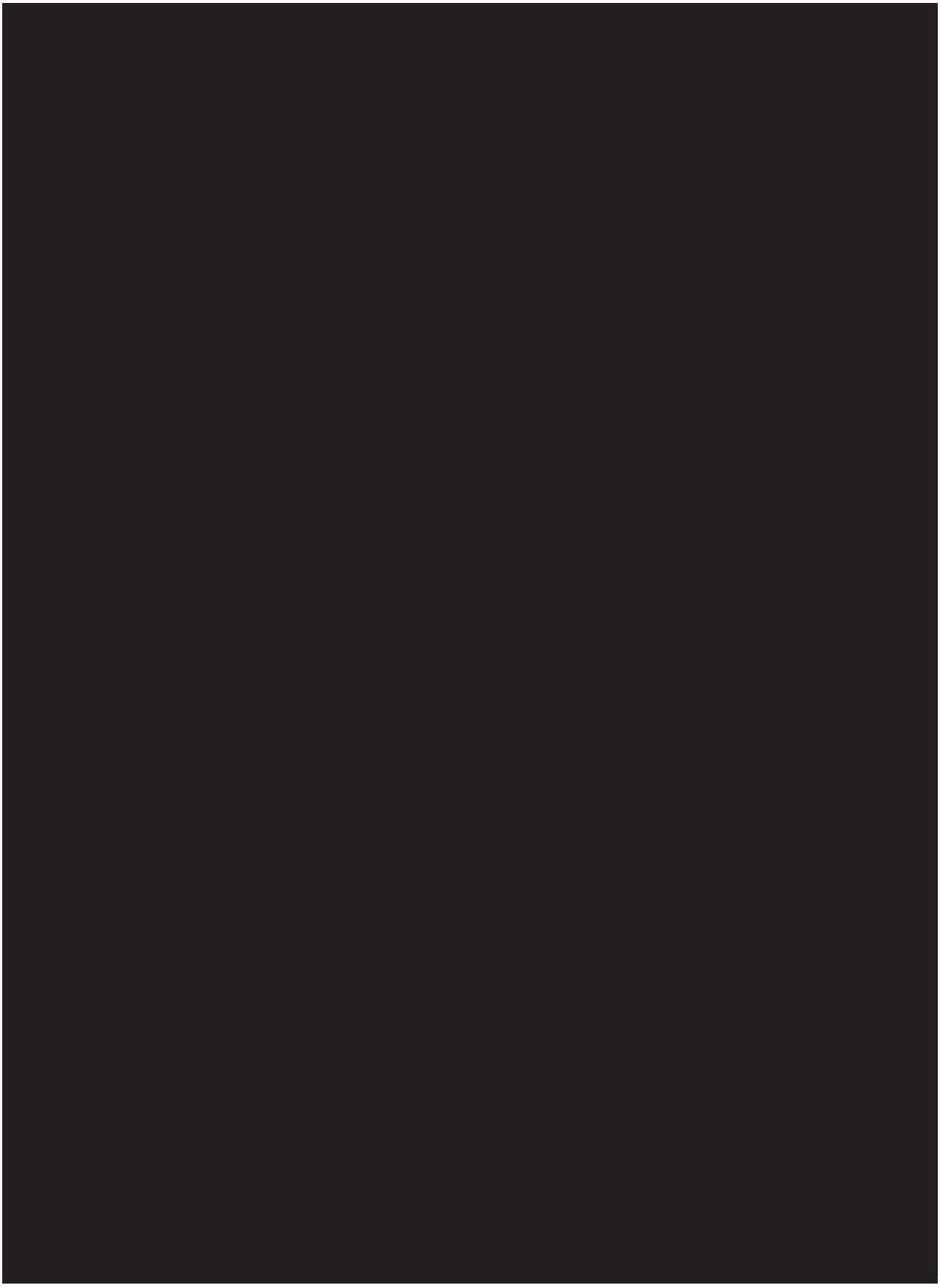


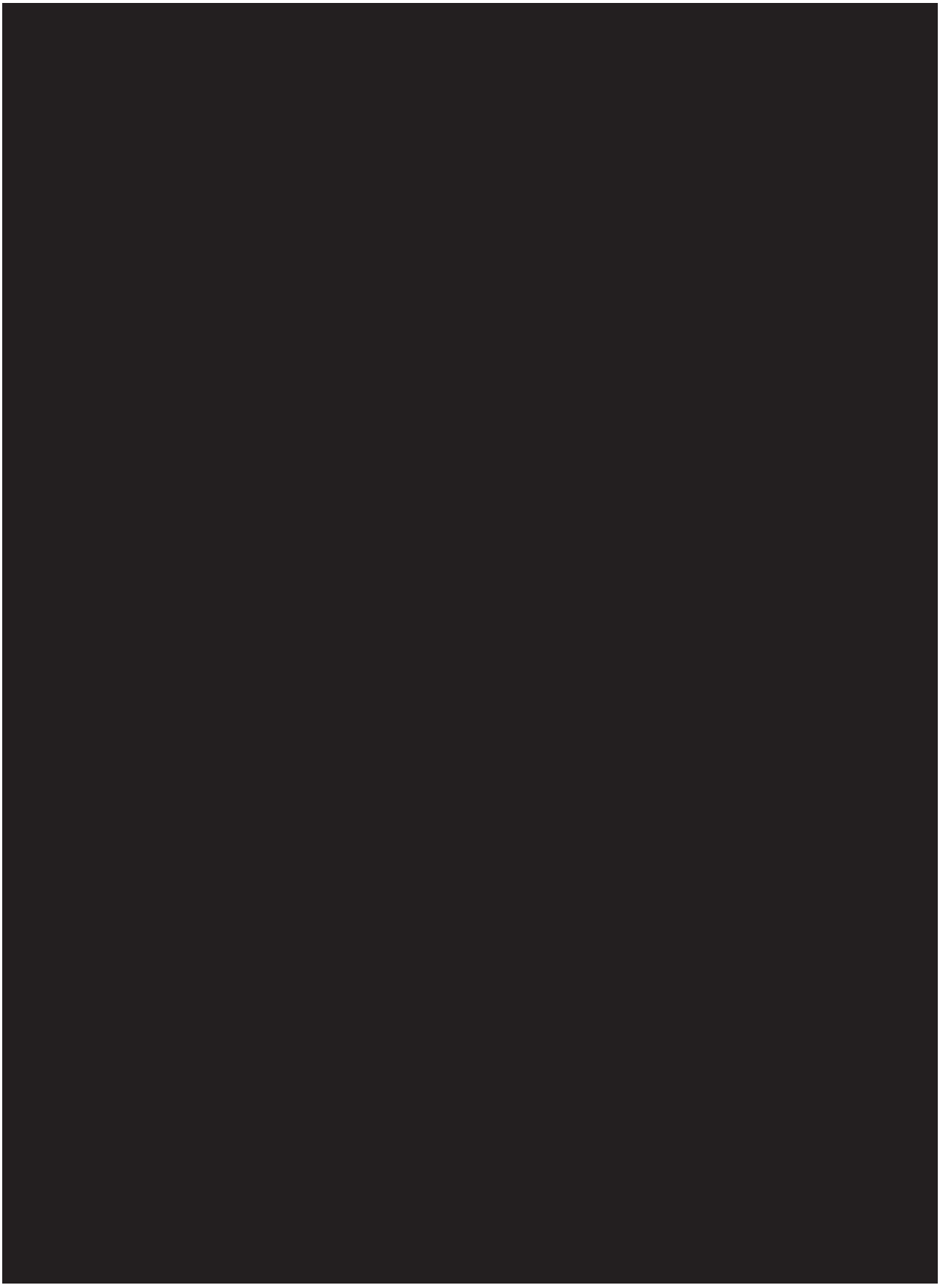


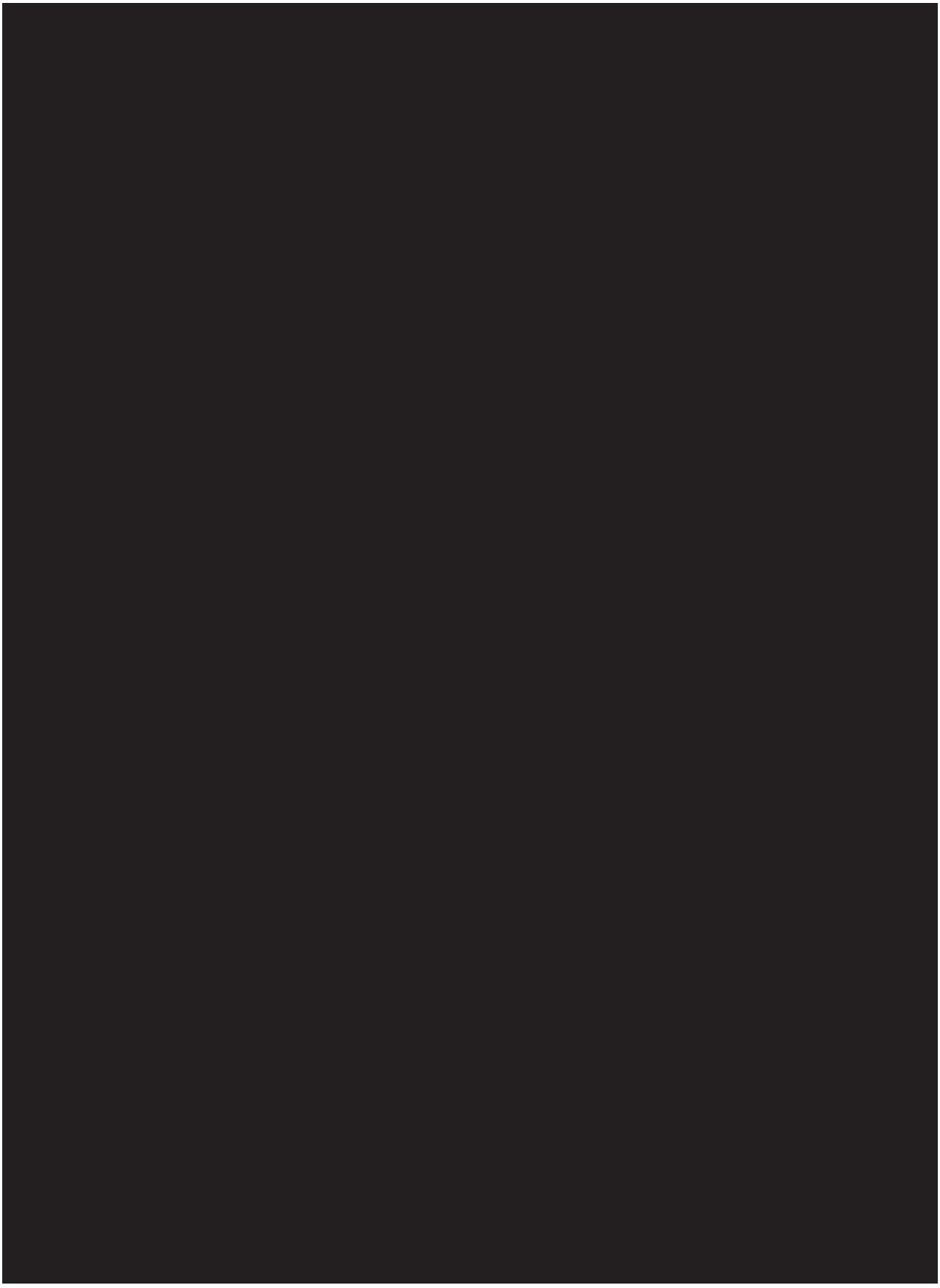


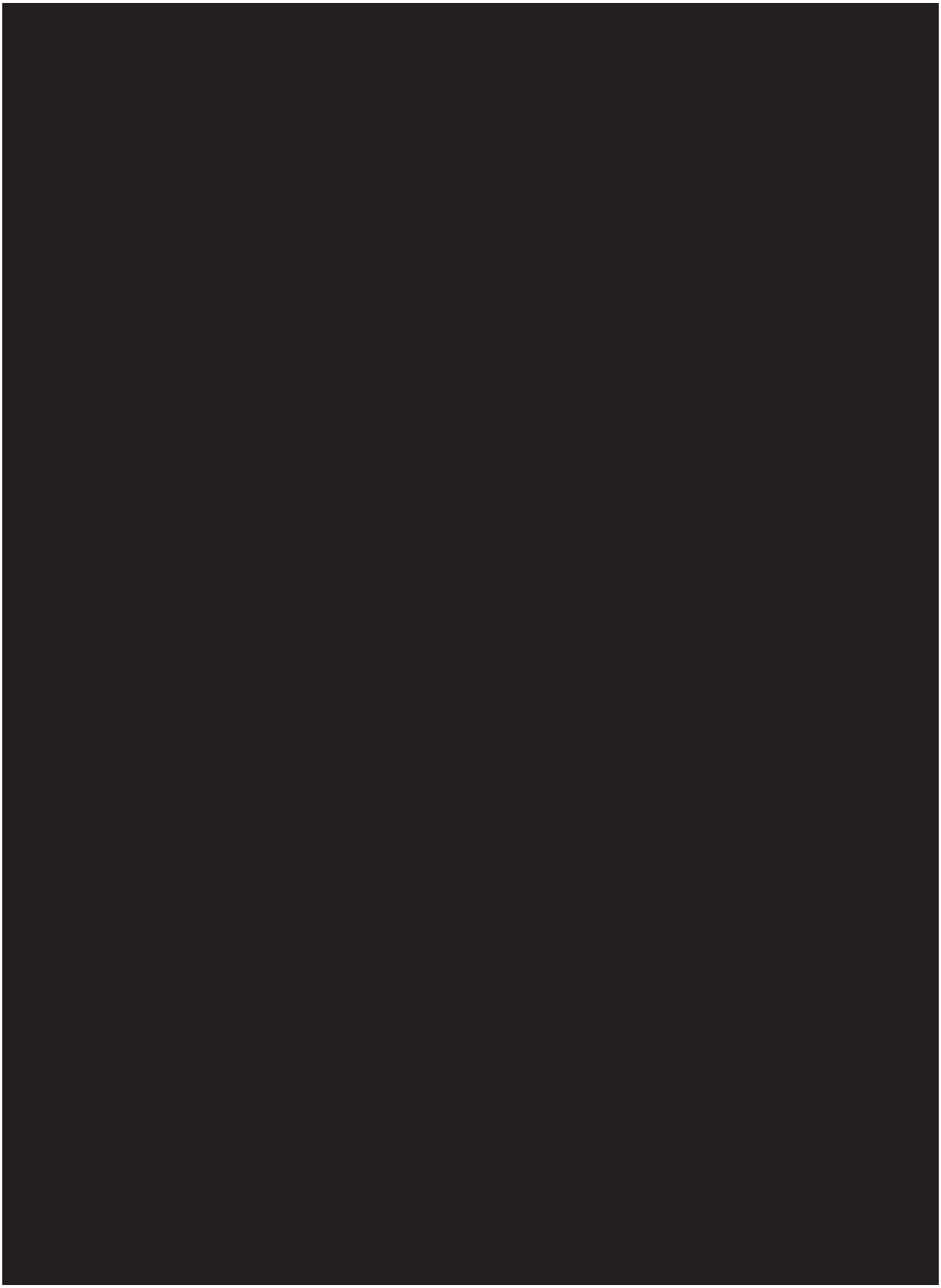


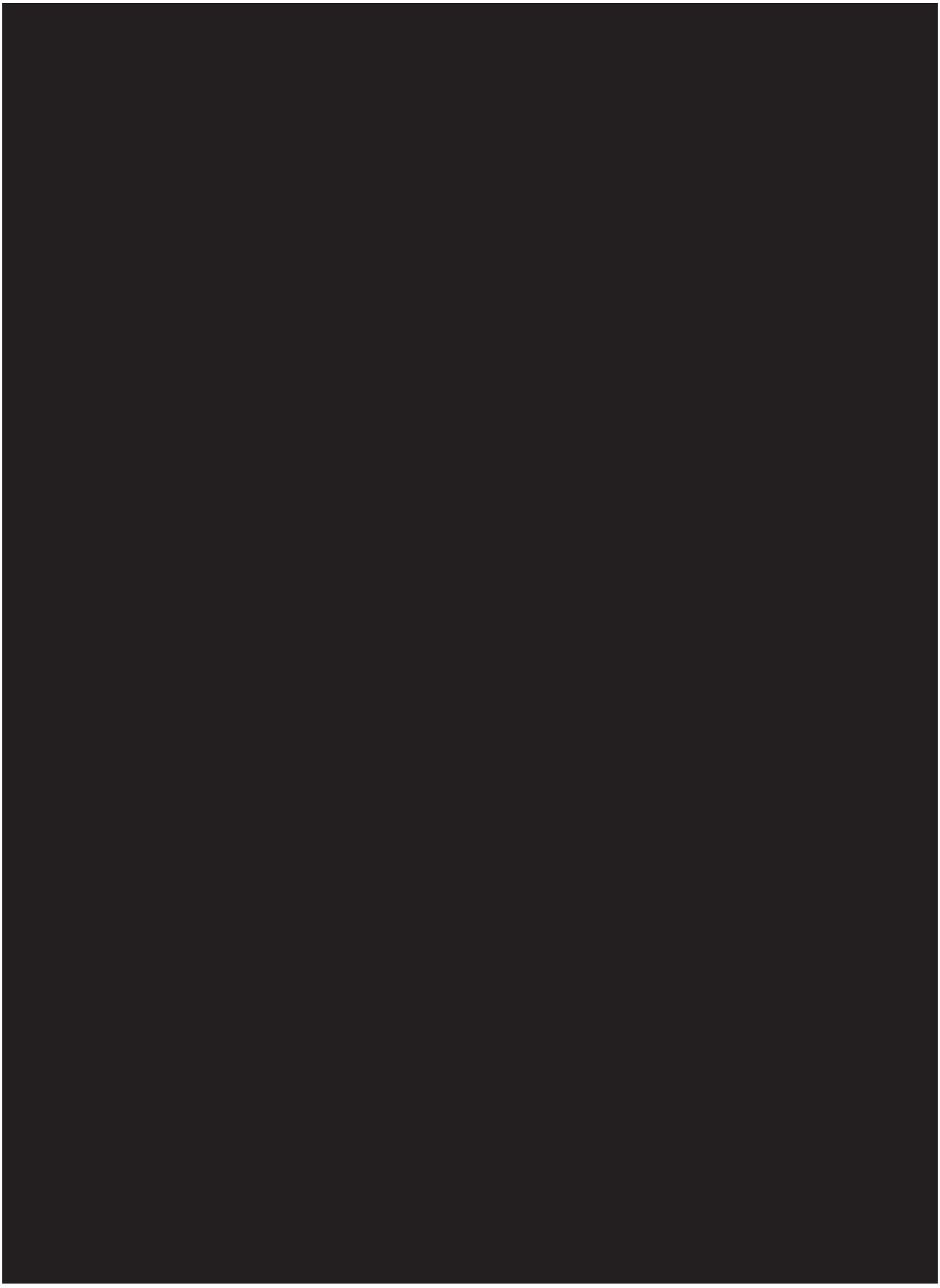


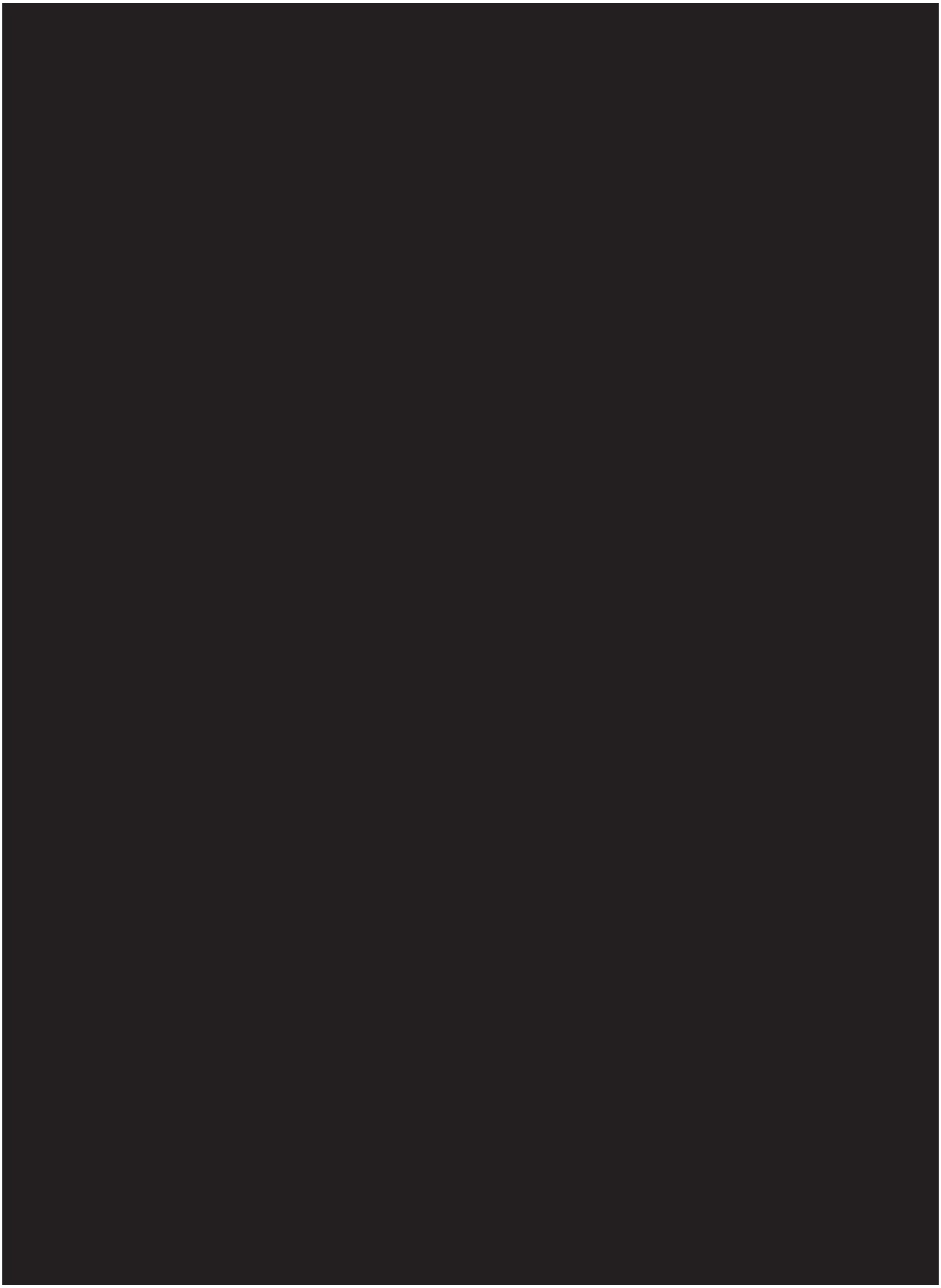


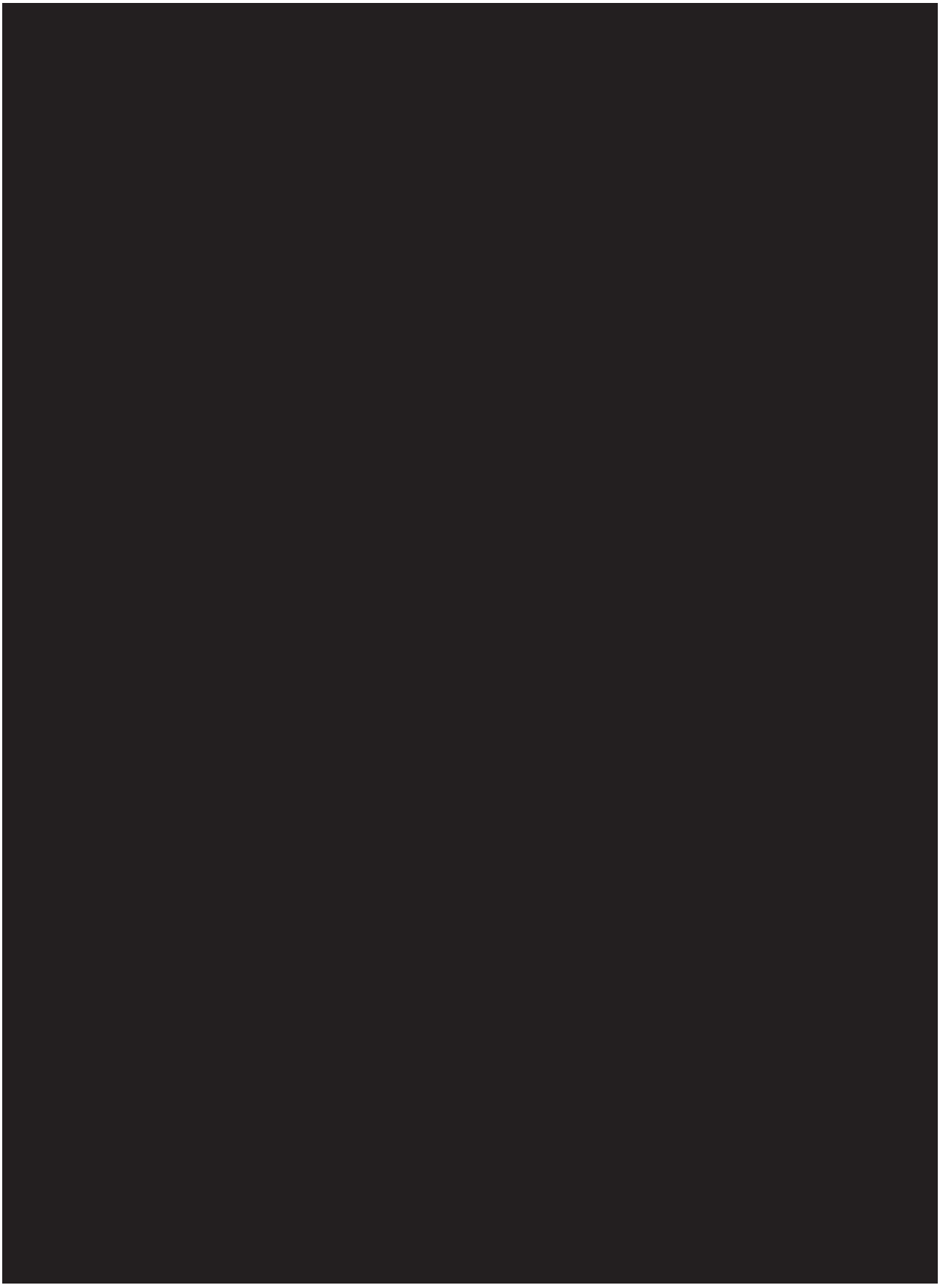


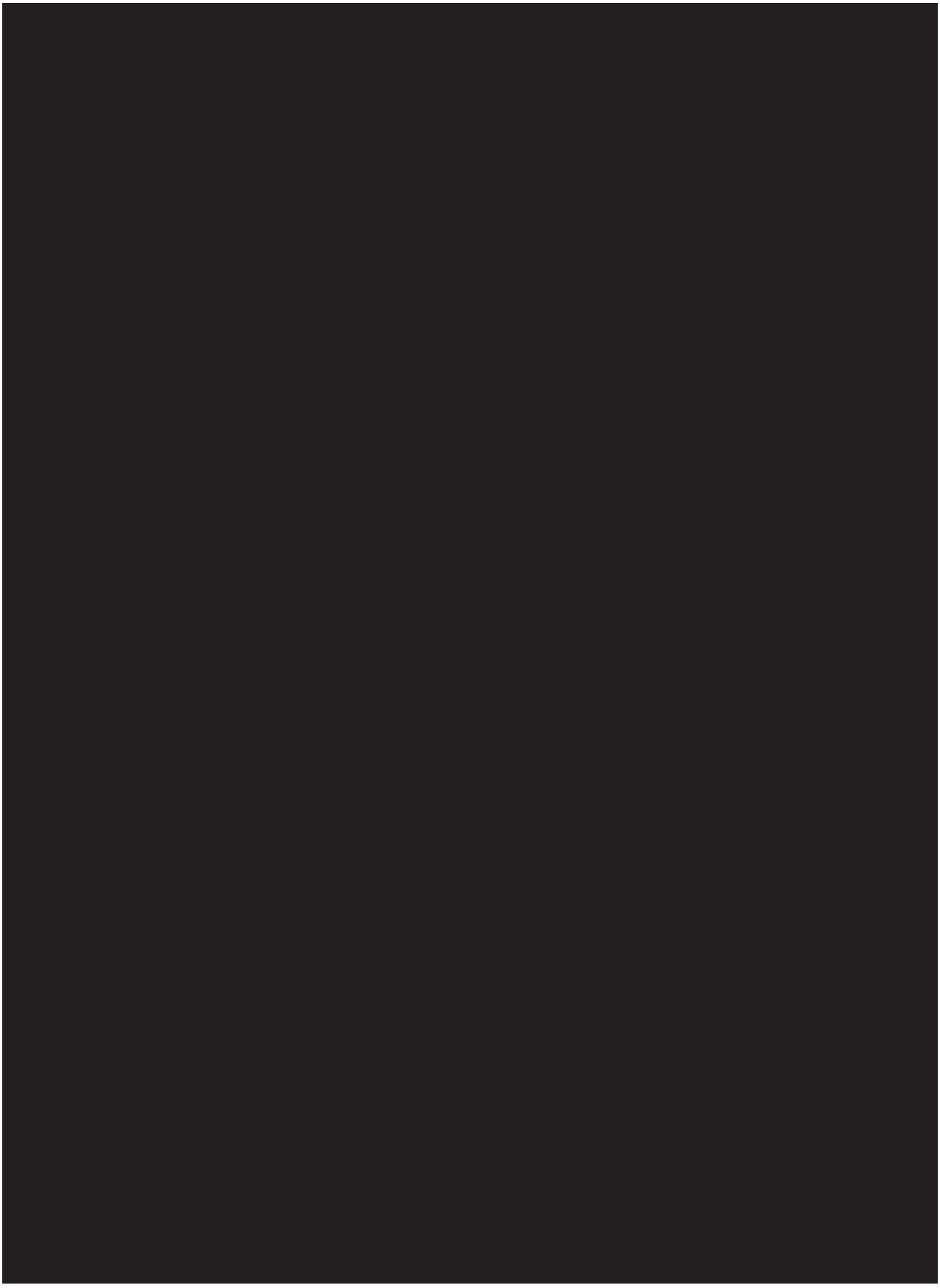


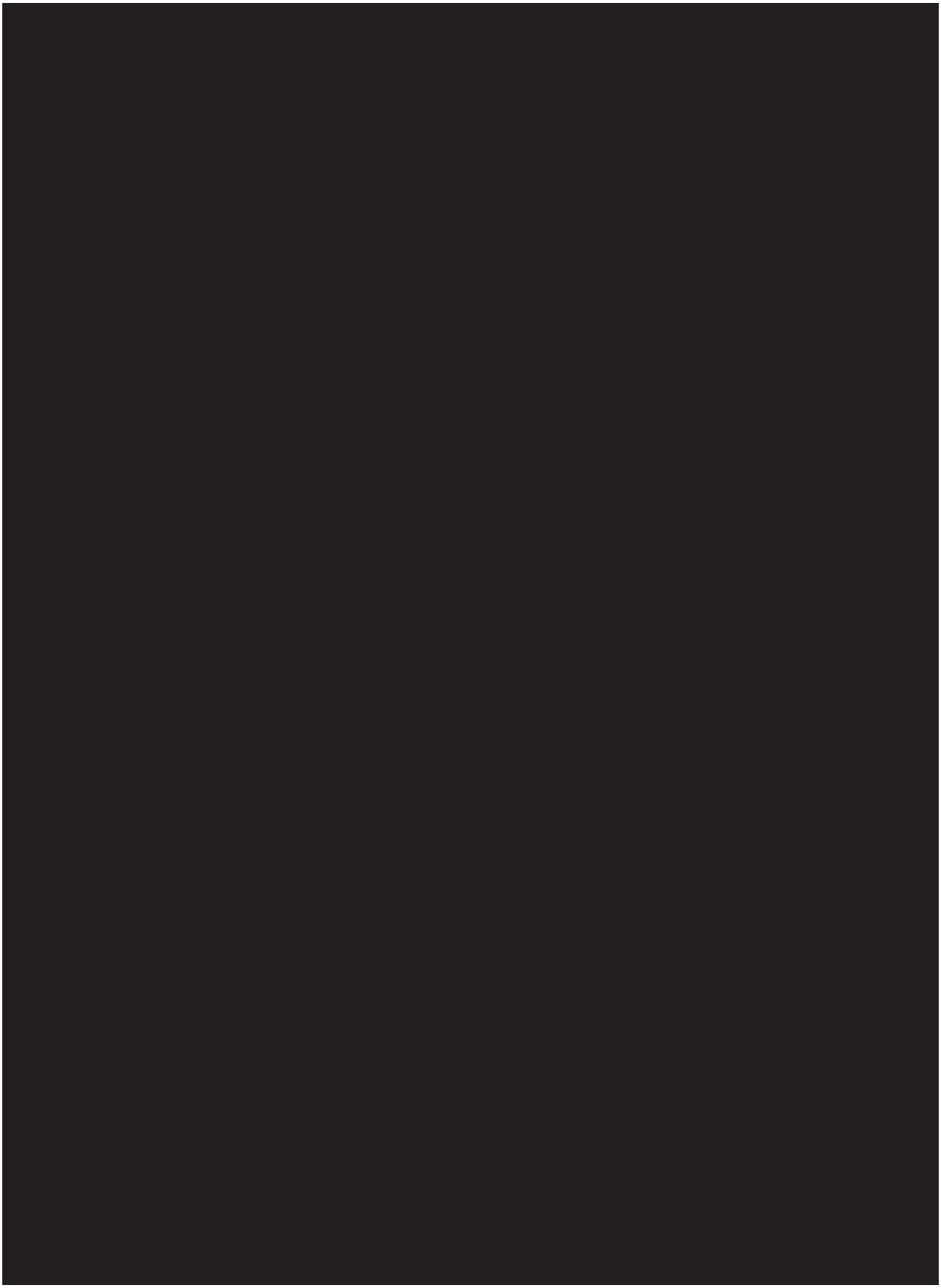


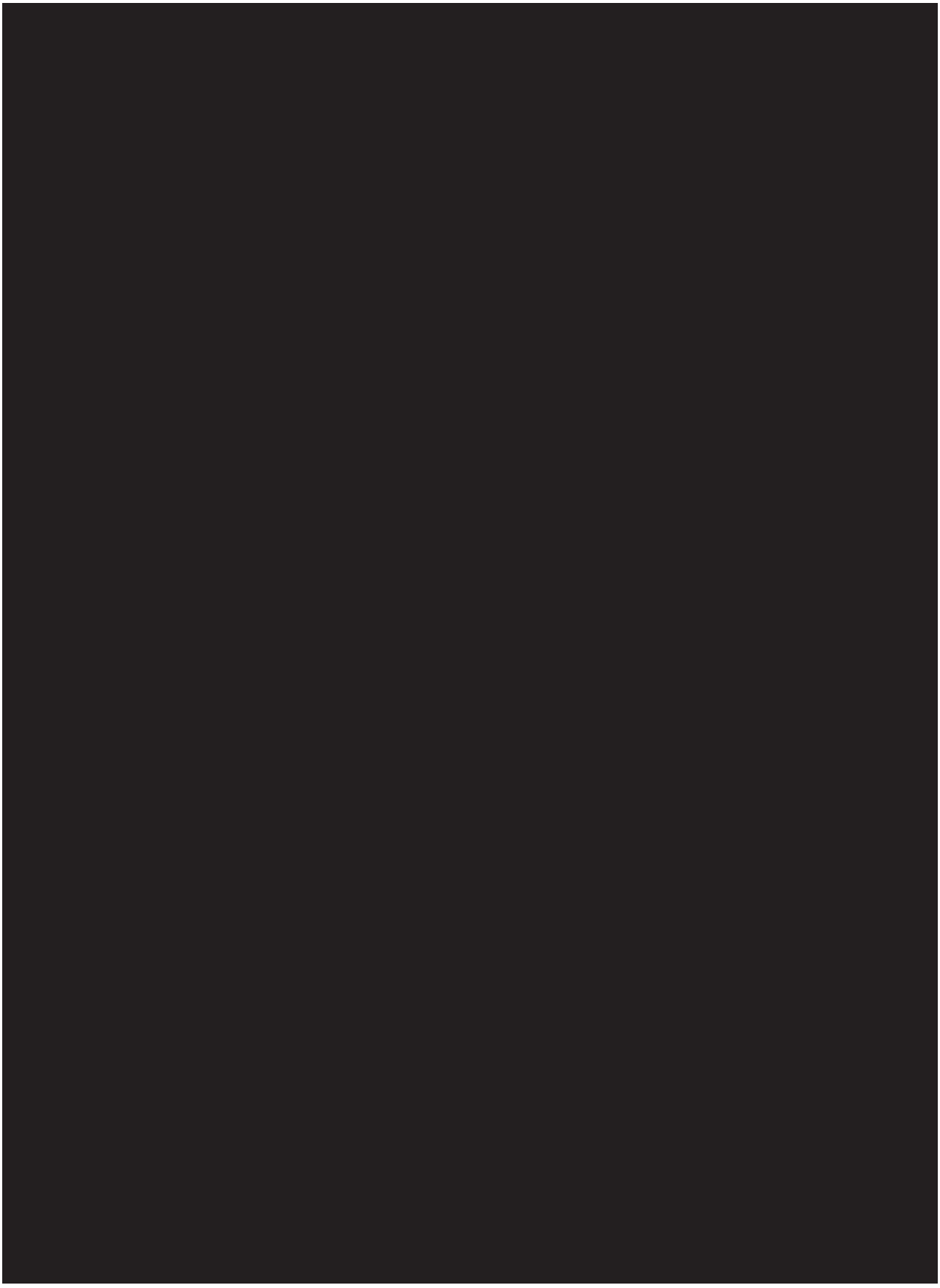


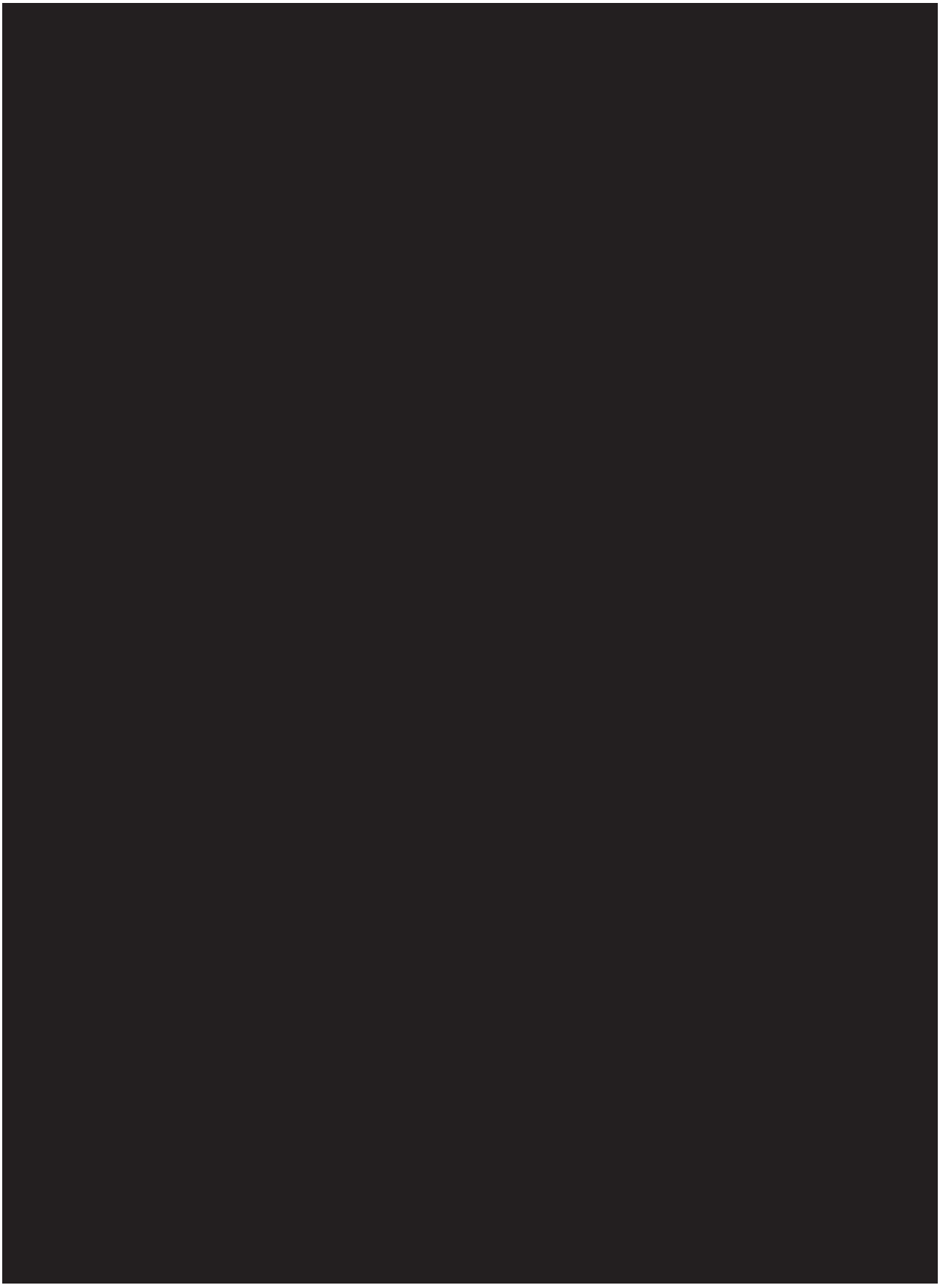












22 APPENDIX 5

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