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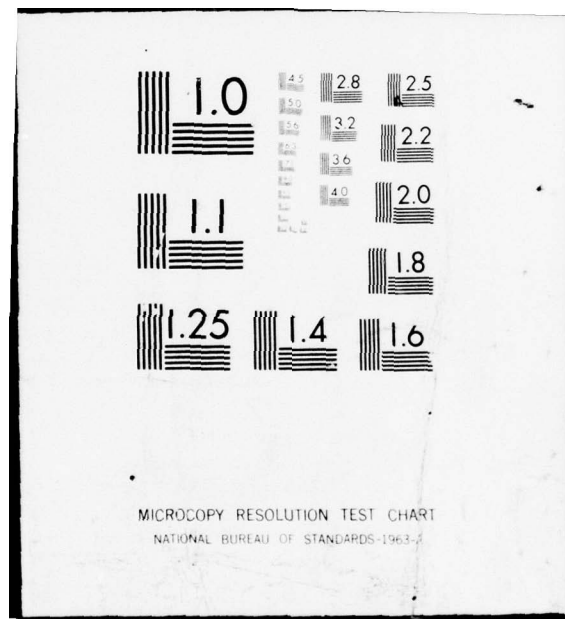UNCLASSIFIED   ONRL-R-8-77   NL

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ACUTE RHABDOMYOLYSIS FROM EATING QUAIL

J. B. BATEMAN

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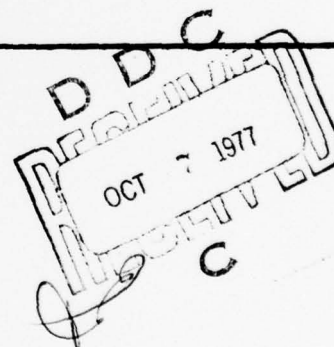
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20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*
Acute rhabdomyolysis results from susceptible persons eating quail during
the migrating season. The etiology is unknown. Muscular exercise is an
important precipitating factor. In this paper the literature on this and
related rhabdomyolytic and hemolytic syndromes is reviewed, ranging from
biblical times to the present day. It seems likely that the responsible
agent present in the quail is of dietary origin and that susceptibility
to poisoning in man is based upon an inherited biochemical defect. In view

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of the importance and seriousness of acute exertional rhabdomyolysis among
military personnel, all types of rhabdomyolytic illness are thought to
be worthy of close attention.

ACUTE RHABDOMYOLYSIS FROM EATING QUAIL

by

J.B. BATEMAN

CONTENTS

ACUTE RHABDOMYOLYSIS FROM EATING
QUAIL

by

J.B. Bateman

INTRODUCTION

This paper is about an animal and about a sickness afflicting people. The animal is a bird, the quail: most familiar as a restaurant delicacy but, in fact, an important object of current research on a variety of subjects related to human disease. The sickness too is more important than its apparently trivial nature may seem to suggest at first glance: a muscular injury closely related to a type of damage that is of increasing concern in military medicine. More about this later.

Some years ago the late Dr. John Barnes, then Director of the Medical Research Council Toxicology Laboratory, showed me a short paper in the *Journal of the American Medical Association* (1) entitled: "Some Notes on Quail Poisoning." The author was Dr. Theodore Ouzounellis of the Department of Medicine, Vostanion General Hospital, Mytilini, Lésvos, Greece. The novelty of the paper, to me, lay in my discovery that quail may be poisonous for man. The circumstances under which this can be so, and the nature of the resulting injury, seemed to point to a causative factor present only in certain quail and toxic only to certain individuals:

"Shortly after the quail has been eaten, an acute myoglobinuric syndrome suddenly appears. The patients experience sharp muscular pains and paralysis in various muscles, usually the ones in use. The urine is colored red, due to the excreted myoglobin, and this is frequently followed by oliguria, even to the point of anuria, and azothemia (myoglobinuric nephrosis).

"By all indications, in order for the syndrome to appear, it is necessary that the individual possess a sensitivity, possibly caused by enzymatic abnormality of the muscular tissue. The quail itself, or rather the substance it carries, simply constitutes the eliciting factor."

Since similar observations had already been published elsewhere, Ouzounellis' immediate purpose was to present them in the context of the biblical story of the "very great plague" which caused many deaths among Hebrews in Sinai who had eaten quail. The sudden onset and the fatal outcome are accounted for, he felt, by

extreme muscular fatigue and the privations endured by desert
nomads.

Following Dr. Barnes' suggestion that a debilitating toxicosis
of this nature, even if infrequently fatal and even if of minor impor-
tance, would be of interest to the US Armed Forces with their world-
wide deployment, I seized the opportunity during a visit to Athens
to meet Dr. Ouzounellis at Mytilini. The season was not that of quail
migration, but the discussions were rewarding. In the meantime I have
kept interest alive by wandering through the literature describing
things that might have some bearing on poisoning by quail and am compiling
the present report in the hope that the absence of a definite conclusion
will inspire somebody else with more fruitful ideas than those presented
here.

BIBLICAL AND CLASSICAL RECORDS

The biblical story to which Ouzounellis referred (1) is worth
quoting as an illustration of the vastness of the quail migration at
certain seasons, as well as the fact that these birds may be toxic
to man. Not always, evidently, for the incident was preceded by another
attended by no unhappy consequences:

"And the Lord spake unto Moses, saying, I have heard the murmurings
of the children of Israel: · speak unto them, saying, At
even ye shall eat flesh .... And it came to pass, that at even
the quails came up, and covered the camp ...." - *Exodus*, 16, 11-13.

Later, when the Lord wished to punish the children of Israel for
complaining about the food and comparing it unfavorably with what they
had had in Egypt, he used the same inoffensive bird for his purposes:

"The Lord will give you flesh, and ye shall eat. Ye shall
not eat one day, nor two days, nor five days, neither ten
days, nor twenty days; but even a whole month, until it come
out at your nostrils, and it be loathsome unto you ...." - *Numbers*,
11, 18-20.

The threat was lurid enough and fulfillment was prompt, packed,
it would seem, into less than the month forecast, and leading to large
scale fatality rather than the mere discomfort of overeating:

"And there went forth a wind from the Lord, and brought quails
from the sea, and let them fall by the camp, as it were a
day's journey on this side, and ... a day's journey on the
other side, round about the camp, and as it were two cubits
high upon the face of the earth. And the people stood up
all that day, and all that night, and all the next day, and
they gathered the quails: he that gathered least gathered
ten homers: and they spread them all abroad for themselves

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round about the camp. And while the flesh was yet between
their teeth, ere it was chewed, the wrath of the Lord was
kindled against the people, and the Lord smote the people
with a very great plague. And he called the name of that
place Kibrothhattavah: because there they buried the
people that lusted." - ib., 31-34.

Ouzounellis and others have seized upon the phrase "while the
flesh was yet between their teeth, ere it was chewed" in order to show
a parallel to the rapid onset of present-day quail poisoning, but it
must surely have been a far more potent poison, even with special poten-
tiating factors at work, than the one taken in by present quail eaters.
A poison gas seems more likely, if indeed the translation is to be taken
literally. Unfortunately, the chronicler has not described the symptoms.

Other literary references to toxic quail are to be found dating
from Greco-Latin antiquity. Quotations from Lucretius (96-55 BC), Didymus
(ca 100 BC), Pliny the Elder (23-79 AD), Sextus Empiricus (ca 200 AD),
and the Arab Avicenna (980-1037) are to be found in the literature
(2) (3) including a particularly interesting passage from the Greek
physician Galen (ca 130-200) which I translate from Bréhant's French
(3):

"Hemlock nourishes starlings without inflicting mortal injury
on them, while it is fatal to us. And hellebore, upon which
quail feed, is a deadly poison for man."

And this immunity to poisons has fired the poetic imagination:

"Comme la caille, Amour, tu me fais estre Qui de poison
s'engraisse et se repaist ...." - Ronsard (1524-1585),
cited in (3)[1].

There were also stories about toxic honey, and a paper on these
by Sandulescu (4) caused Bréhant (3) to notice some similarities between
the Hebrew experiences with quail and those of the Greeks with honey.
Sandulescu describes the erratic, exhausting retreat of "the Ten Thousand,"
led by Xenophon after the death of their leader Cyrus the Young in the
battle of Cunaxa near Babylon, August, 401 BC. He quotes a passage from
Anabasis in which Xenophon recounts an incident that occurred after the
defeated army had followed the Tigris northwards and had finally commenced
their descent toward the Black Sea: again I translate from Bréhant's
French version:

"Nothing remarkable happened there except that there were
many beehives and that those of the soldiers who ate honey
lost their senses; they vomited, evacuated *par en bas*, and

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[1]Without an English edition of Ronsard at hand, the best I can
do is this: "Under your influence, Amor, I am like the quail that
fattens itself on poison and delights in it ...."

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nobody had the strength to stay on his feet. Those who had
eaten a small amount resembled persons who were completely
drunk, those who had taken a lot were like raging madmen
or even gave the appearance of being moribund. So they
remained, many stretched out on the ground as if after a
defeat, and there was general consternation. Next day, however,
nobody had died and at about the same hour of the day they
regained their reason. On the third and fourth days they
could remain on their feet, as if emerging from a drugged
state."

Others travelling in the same region of the Black Sea and
also in parts of the United States and Switzerland have suffered sim-
ilarly: giddiness, delirium and sometimes death. There is a Greek
word for it, *mainomenos*, or honey that causes madness. The bees pro-
ducing this honey, it is said, have plundered toxic plants such as
azalea, rhododendron pontique, monkshood (*Aconitum*), etc. In recent
times, according to Sandulescu, Russian work has narrowed this down
to the nectar of toxic plants of the family Ericaciae which contains
the glycoside andrometoxin.

I include this reference to poisoning by honey in the poison
quail context only because others have done so: the evidence for a
common toxic agent is flimsy, amounting to little more than the fact
that the victims in antiquity were all travelers who had endured
severe privations.

THE MIGRATIONS OF QUAIL

It has been noted that poisoning by quail occurs in North Africa
only in spring, when the birds are returning at their leisure from the
center of the continent, with plenty of opportunity to eat poisonous
weeds. On the other hand, it has been said that in the autumn they are
well fed from the cornfields of Hungary, Rumania and Russia (2). But
it is precisely in the autumn that poisonous quail are found in Lésvos.
The contrast has been remarked upon by Hadjigeorge (5).

The migration of the quail *Coturnix coturnix* is a most impressive
phenomenon when one remembers that this small bird crosses the Mediter-
ranean and the deserts of North Africa twice a year while migrating
to and from its breeding grounds "all across central and southern Europe,
Asia Minor, Syria and Siberia" (6). A lecture by R. E. Moreau in 1927
(6) contains many interesting details which are probably still quali-
tatively valid, although disturbances in the breeding grounds, combined
with the intensive trading in quail for sale in the luxury markets of
Great Britain, France and Italy, have further depleted a population
which had already begun to decline as long ago as 1912 (6).

Moreau is concerned mainly with Egypt, but from Sergent (2)
and others it is clear that much the same picture can be seen in

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Algeria. Moreau records the "immense horde" arriving on the north coast of Egypt in the two hours of each morning just before sunrise, from the last week of August until the middle of October. There are unexplained "blind stretches" which vary from year to year. The greatest numbers are found between Gaza and Port Said, but they are also numerous all along the coast to Tunis and beyond. Since they have been seen flying over the sea at 30-40 miles per hour, Moreau calculates that the crossing must have taken ten hours, with take-off from Europe and Asia Minor a little after sunset.

After reaching land, the birds apparently disappear with little trace, diluted as it were by the great deserts, and apparently to a large extent bypassing the oases and the shores of the Red Sea where one might have expected them to seek shelter. The scanty evidence cited suggests that they pass the winter much further south, some even crossing the equator but few going beyond a line crossing the continent from the Gambia to equatorial Sudan and thence up to Ethiopia and northern Somaliland.

During the spring migration, between January and March, quail are found throughout Egypt, especially along the Nile valley, and are abundant all over what Moreau calls Palestine, meaning, perhaps, the coastal zone west of the Dead Sea and the river Jordan. Moreau accepts this as evidence that the northerly overland passage in spring is not marked by particular urgency, but he does not discuss the oversea part of this journey. Perhaps there is nothing to say. One could imagine from the abundance of the birds in "Palestine" that many use an overland route.

In any event the whole performance is extraordinary on the part of a most improbable creature, equipped as it is "with round heavy bodies and little wings which have to be flapped at a great rate to lift them into the air at all. Quail are of just the build to feel adverse winds most severely"(6). So the mortality must be very great on long journeys, with wholesale losses from time to time when conditions of wind and fog at sea and sandstorms in the desert are especially severe. Statistical, rather than individual, survival must be what matters for the quail.

So much for North Africa. The situation in the Greek islands must be very different in both spring and autumn, for in neither case is there any reason for the birds to have flown a great distance over sea or inhospitable land. However, I have come across no discussion of this point. The island of Lésvos, within sight of Asia Minor, is to all intents and purposes part of the mainland.

QUAIL HUNTING

The quail, being good to eat, "is known and watched by every fellah and every Bedouin in Egypt" (6). In North Africa the trapping of quail arriving during their autumn migration extends over virtually the entire length of the coast. In rough weather the exhausted birds drop on the

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shore and are easy prey (6). While various devices for snaring and trapping are used on a large scale, there is also a good deal of shooting.

POISONING BY QUAIL AND ITS SYMPTOMS

The first recent mention of poisoning by quail seems to have been that of Sergent (2) in 1941 who says that in Algeria it is so well known that in certain regions the hunters refrain from eating spring quail, while quail from other localities are not harmful. The birds look healthy, are flying normally but (as he says in another place) are thin and fatigued. He describes a number of cases of illness, noting the rapid and alarming onset. The symptoms may be digestive, or paralytic, or both. Complete paralysis (sic) may occur for more than half a day, during which it is impossible to move or speak, although hearing is unimpaired. There is "lipothymia," vomiting, diarrhoea. Ascending paralysis leading to dyspnoea and suffocation. Muscular pains. No rise in temperature. The symptoms recede in reverse order.

According to Ouzounellis (7) food poisoning caused by quail was first observed on Lésvos by J. Rally (unpublished, ca 1948) and then described in a Greek publication in 1951 by Karamanos. Hadjigeorge (5) described the symptoms as similar to those seen by Sergent, including vomiting, colic, hypotonia, stiff neck, etc., with some renal complications. A further Greek paper, by Komvos and Giotsas in 1953, is mentioned in (7).

It was Ouzounellis who first stated that myoglobinuria is a significant accompaniment of poisoning by quail (1)(7) (8). He also, admittedly on the basis of a small number of cases, noted a tendency for the illness to occur within particular families and to recur in certain individuals; the fact that most were males he attributed to predisposing muscular fatigue among hunters. He described four cases in some detail, including that of an elderly diabetic who died while the myalgias were receding. He tabulated the frequency of occurrence of various symptoms and circumstances among 28 cases which represented the incidence of the illness over 15 years among a population of 100,000. Here are the main points (8):

    Symptoms start 1.5-9 hours after meal.
    Violent myalgias invariably occur: trunk and extremities,
      never the head.
    Cramps in legs in some cases.
    Muscular asthenia or even paralysis of groups of muscles
      may follow the myalgias.
    Sensation of cold may precede the myalgia.
    Red urine was seen in 31% of cases; in others it may
      have escaped observation.
    Vomiting in 27% without other digestive upset.
    Absence of fever or other mental disturbance.
    Children and adolescents: only 2 cases, 13 and 19 yrs.
    Men suffer more often than women.

Exercise predisposes: 14 out of 20 men had been hunting.
  Symptoms start in group of muscles most used.
Benign course. Regression of symptoms after a few hours,
  recovery in 24-28 hours.

In the same paper (8) which contains the detailed description
of four cases, it is remarked that

"the fact that this is a typical myoglobinuric syndrome
appears from clinical observation only .... The presence
of myoglobin in the urine (first case) was proved by
laboratory examination."

In fact, even in this one case the presence of myoglobin
was only shown qualitatively by fractional precipitation with ammonium
sulfate, the quantity of urine available being insufficient for
spectrophotometric and electrophoretic tests. The raised levels of
serum glutamic oxalacetic transaminase (SGOT) and glutamic pyruvate
transaminase (SGPT) in this patient and in one of the others, a 77 year
old housewife whose urine was yellow, are also compatible with a
myoglobinuric syndrome; so, too, the renal complications which occasionally
follow. A short paper in *The Lancet* gives details of such a case which
had to be referred to a hospital in Athens for treatment of acute renal
failure (9).

Since the foregoing facts were put on record, the number of incidents
of poisoning by quail investigated in Lésvos has mounted to over 104
(10).

The appearance of papers on poisoning by such a popular bird
has of course brought in news of additional cases not perhaps always
reliably reported. Sergent (11) received word from a hunting family
in Chénérailles, central France. Because of a scarcity of pheasants,
these hunters had turned to quail and were poisoned on 18 September
after eating them stuffed with buckwheat. Again in September there
were two cases from Brive, also in central France: in these there was
a skin eruption but no paralysis and no pain. Finally, Dr. Ouzounellis
(10) informs me of a report from Bordeaux of four cases of myoglobinuria
in persons who had eaten skylarks. Muscle biopsies were taken and electron
microscopy revealed nuclear degeneration and alteration of the Z-line.

Little discussion of the subject has reached the standard books
on muscle diseases. No mention is to be found in Walton (15), and Hughes
(18) includes in his brief reference to the paper by Billis *et al* (9)
the astonishing statement that the quail myopathy is "often fatal."

POISONING BY FISH: HAFF DISEASE

Writers on poison quail have been impressed by the similarity
of the symptoms to those of Haff disease, so named because of an

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extensive epidemic which occurred in 1924-5 among the population of
fisherfolk on the shores of Koenigsberg Haff (= bay) in East Prussia -
Koenigsberg being presumably that important town now more often called
Kaliningrad or Krolewiec. Berlin (12), reporting on a later outbreak
of the disease in Sweden, describes the earlier occurrences in some
detail, with reference to original sources which for the most part are
to be found in rather inaccessible places. He names the disease
myoglobinuria paroxysmalis. He notes a major recurrence in autumn 1932
and early 1933 and a few cases in 1940; more than 1000 cases in all.
There were reports of something similar in 1934 near Lake Onega in the
USSR, a couple of hundred miles northeast of Leningrad.

The illness starts suddenly some 18 hours after the victim has
eaten certain kinds of fish, especially burbot liver and eel, and sometimes
pike. Muscular pain, starting in calves, arms, back of neck, etc.,
spreads until within minutes or hours all muscles except those of the
head are involved, becoming excruciatingly sensitive to touch; however,
the muscles are not hard and the joints are flexible. There is no head-
ache, no fever, and no mental disturbance. Respiration may be difficult.
Vomiting may occur. Urination, impossible at first, releases a brownish-
black urine containing a few white and red cells and granular casts.
The absorption bands are stated to be those of myoglobin, at higher
wavelengths than those of hemoglobin. In most cases recovery occurs
within hours or a few days, but about 1% develop renal complications
leading to uremia and death while fully conscious. There is a personal
predisposition. The same person may experience several episodes and
occasionally relapses occur without the patient having again eaten fish.

Among the animals, cats were found to suffer from paralysis of
the hindquarters; they often died. Fish, seabirds and foxes died.

The Swedish outbreak described by Berlin (12) occurred early in
1942 around Ymsen Lake (which I cannot find on my map), situated in
a non-industrial area and accommodating one of the largest fish stocks
in Sweden. The symptoms have been described above. The particular
features of the Swedish incident can be summed up as follows:

Period covered: Feb. 1942 to April 1943. No cases in winter.
Victims: Fishermen and families; fish, water birds, cats, foxes.
Fish eaten: Eel; burbot liver; bream. (No pike)
Number of cases:
      One attack: 7
      Two attacks: 1
      Three attacks: 2
      Seven attacks: 1
      Total: 11
Deaths: 2, one from uremia, one from "sepsis."
Individual sensitivity: Usually only one or two members of a
                                    family afflicted.

This brief account of Haff disease may not be quite up-to-date though the accounts given by Adams (14) (16) and McArdle (17) are based solely on the early literature, without reference to Berlin's key paper, while Hughes (18) reproduces the main points made by Berlin without adding anything. In the USSR it has evidently been rechristened Haff-Uiksov Disease, and an article which I have not seen (13) deals with its occurrence in the Trans-Urals.

CAUSATIVE AND PREDISPOSING FACTORS

The resemblance between Haff disease and poisoning by quail is so close that a common etiology suggests itself. The early descriptions in both cases seemed to rule out bacterial (and probably also viral) infections: Sergent (2) remarked that quail are eaten freshly killed so that microbial spoiling is unlikely. All are agreed that toxic agents are responsible. In Haff disease the early suspicions of industrial poisoning were disarmed by the Swedish outbreak on a lake remote from industry, but it has been pointed out to me that airborne pollution from the Ruhr valley is known to fall into Swedish lakes. Berlin (12) decided against botulism, the symptoms of which in Western Duck disease are quite different, against an allergic reaction to fish, and was unable to find selenium, another suspect, in burbot liver. He favored a thiamine inactivating factor such as that known to be present in carp, and thought to be responsible for Chastek paralysis of captive silver foxes fed upon raw fish. However, positive evidence in favor of this hypothesis is lacking. It is difficult to reconcile the symptoms of Haff disease and of the quail myopathy with those of thiamine deficiency as usually described and difficult in any case to believe that an inactivating factor would be able to cause a clinically evident deficiency within a matter of hours.

In the case of the quail myopathy, observers in Africa and Lésvos are equally conscious of the variety of the seeds eaten by quail and of the possibility that one or more may contribute a poison harmless to the bird but toxic to man—or, at least, toxic to persons predisposed by some enzyme deficiency, in the view put persuasively by Ouzounellis (7) (8). Perhaps because of Socratic prejudices, hemlock has been considered a primary candidate by Sergent (2) (11) and by others, excluding Ouzounellis, who quote him without contributing anything further to the scant sum of available evidence. In what follows we shall give hemlock its due, but shall also describe the search, not yet successful, for other toxic substances present in the quail diet; then the role of muscular exercise and of inborn factors in the production of myoglobinuria will be discussed.

Hemlock poisoning

Sargent (2) directed his attention to hemlock ("la grande ciguë") because the season for poisoning by quail in Algeria coincided with the flowering and fructification of the plant; the later occurrence of cases in France at a different time of year, poorly documented though

it was, reinforced his suspicions (11). He tested his hypothesis ex-
perimentally, after having first established that the toxicity of the
seeds diminishes during a few months' storage. He triturated some seeds
with 4 to 8 volumes of water (the technique used by the Athenians at
the time of Socrates). These extracts were poisonous for dogs and lethal
if given in sufficient quantity: weakness in the hind legs, trembling,
vomiting, excessive salivation and, finally, convulsions. Fresh seeds,
given abundantly to quail by force-feeding over many days, caused no
symptoms, but powdered seeds produced vaguely described paralytic dif-
ficulties. Quail that had been fed on fresh seeds, then cleaned and
roasted, produced in dogs the same symptoms (marked paresis of hind
limbs) as those which followed direct intake of the aqueous extract.

Assuming that sufficient care was taken to remove seeds before
roasting the birds, these experiments raise interesting questions con-
cerning the relative susceptibilities of quail and dogs to hemlock poi-
soning, and they deserve more attention than they have received; but
as a contribution to the solution of the toxic quail problem they have
little to offer. The symptoms do not seem to include the intense myalgia
recorded in cases of poisoning by quail in man. Indeed the active sub-
stance, coniine, or α-n-propyl piperidine, $C_5H_{10}N(C_3H_7)$, is a neuro-
muscular blocking agent. Its action was said to include a loss of sensation
(23).

Some confusion may arise from the varied pharmacological actions
found among the different plants known collectively as hemlock. The
implication in Sergent's paper is that his grande ciguë is *Conium
maculatum*, known (23) as poison hemlock, St. Bennetts's herb, or fool's
parsley. It contains coniine, as already mentioned. However, Plichet
(24) in discussing Sergent's work refers to the effects of cicutoxin,
which is present in the leaves and rhizomes of plants of the genus
Cicuta: his authority is Keizer (25) who describes two cases of hemlock
poisoning and identifies the responsible grande ciguë as *Cicuta virosa* L.
The symptoms include vomiting, colic, convulsions, foaming at the mouth,
pupillary dilation and loss of the light reflex. Miller (23) mentions
the strychnine-like convulsions associated with poisoning by the common
swamp plant *Cicuta maculata* L (water hemlock; cowbane) and the dilated
pupils.

Seeds Eaten by Quail

Sergent (2) says that quail fly always on an empty stomach, citing
Lavanden as his authority. This may account for the fact that only birds
on the spring migration are poisonous in N. Africa and those on the autumn
migration in Lésvos. It also suggests that poisonous seeds found in
the quail gut must be of local origin. Sergent (2) goes on to mention
that in addition to fruits and grain, quail eat insects, larvae, terres-
trial molluscs and all sorts of seed: knotgrass, goosefoot, spurrey,
dock, stellaria, vetch, brassica. Some may be poisonous. Among these
he names as examples (whether actually found or merely surmised is not
clear) hellebore, aconite, nightshade, stramonium, henbane and hemlock.

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As far as I can tell, none of the active substances in these plants can be held responsible for the quail myopathy. Hellebore contains the hypotensive *Veratrum* alkaloids. Aconite, the active principle of *Aconitum*, is a cardiac depressant. Henbane and other nightshades, members of the Solanaceae, contain various alkaloids of the atropine and scopolamine class; the thorn-apple *Datura stramonium* or Jimson-weed also contains atropine. The symptoms of poisoning by these alkaloids have practically nothing in common with those of quail myopathy, and they include signs such as pupillary dilation and blurring of vision that could hardly have been overlooked had they occurred.

A preliminary effort has been made to identify seeds collected over several years from quail "stomach" in Lésvos by Dr. Ouzounellis and sent to me in London in 1973. At the suggestion of Mr. P.K.C. Austwick of the Nuffield Institute of Comparative Medicine the 36 samples were submitted to Professor J. Heslop-Harrison, Director, Royal Botanic Gardens, Kew. His colleague, Dr. J.P.M. Brenan, was successful in identifying one or more constituents of all but 4 of the samples with varying degrees of precision between family and species, while Miss Rosemary Angel noted those known to have poisonous properties. In the following, the occurrence of these poisonous seeds is indicated in parentheses after each item in Miss Angel's report:

Setaria sp. The millets have caused poisoning from time to time, but apparently only to horses. (*Setaria* sp. found in 4 samples)

Polygonum Persicaria. This and other species of *Polygonum* may cause gastro-enteritis. (*P. persicaria* L in 2 samples; *P. convolvulus* L. in 2; several *P.* spp. in 1 sample)

Trifolium species. These have caused poisoning in animals. (*Trifolium* in 5 samples including one identified as *T. arvense* L)

The seeds of *Trigonella foenum-graecum* contain trigonellin, $C_7H_7NO_2$. (?*Trigonella* sp. in 1 sample)

Vicia sativa causes photosensitization or "trifoliosis" in animals. (*Vicia* sp. in 1 sample, pods of *Vicia* sp. in another)

Some *Galium* species contain coumarin. (*Galium* sp. in 1 sample)

Lathyrism may be caused by eating the seeds of *Lathyrus sativus* and other species of *Lathyrus*. (*Lathyrus* sp. in 1 sample)

The American species, *Crotalaria sagittalis*, definitely causes poisoning. (*Crotalaria* sp. in 1 sample: "but the nearest locality for this is in Egypt")

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The remaining, presumably relatively non-toxic, seeds named by
Dr. Brenan are the following:

> *Lithospermum arvense* L
> Gramineae. (Two samples)
> Nutlets of Boraginaceae or Labiateae, probably.
> ? A pyrene of *Crataegus* sp. (Two)
> *Onopordon acanthium* L.
> *Milium* sp.
> ? Boraginaceae. (Two)
> ? *Stachys* sp. nutlets.
> *Amaranthus* sp.
> *Carthamus tinctorius* L
> Leguminosae (Three)
> ? Caryophyllaceae

The absence of seeds of *Conium* spp. and *Cicuta* spp. is noteworthy,
reinforcing the impression gained from the symptomatology that
hemlock cannot be implicated in the quail myopathy. Equally, the guilty
seed seems not to be among those listed above. The presence of *Crotalaria*
in birds from Lésvos is a little puzzling, but the toxic effects of
the alkaloids of *C.spectabilis* have been thoroughly studied in animals
(19) and are known in man to include veno-occlusive disease of the liver
and cirrhosis. It is of some interest, however, that quail will not eat
C.spectabilis seeds offered with their food or in the field (20). As
many as 40 seeds had to be given by force-feeding before the birds became
sick while 80-160 seeds caused death in 1 to 3 days. The seeds of other
Crotalaria species were not toxic to quail in 10-g doses (20). Data
from US Fish and Wildlife Service cited by Nestler and Bailey (20)
showed that out of 3,669 crop analyses, 108 contained seeds of *Crotalaria*
of which only one was known to be toxic, present in only a minute pro-
portion of the whole crop contents. Some quail will in fact starve
rather than eat the toxic seeds.

Lathyrism, in its neurological form, is caused by substituted
amino acids which occur not only in the "parent" organism *Lathyrus*
but in two species of *Crotalaria*. Another substance present in *Vicia
sativa* and other *Vicia* species also causes the characteristic convulsions
and muscular rigidity of neuro-lathyrism (21).

Although they may avoid extremely poisonous seeds, quail are said
to eat forbs which contain phytoestrogens. The interesting observation
has been made, in California (22), that these isoflavones (non-steroid
estrogens) are produced in increased amounts in stunted desert annuals
during a dry year. The increased intake of such substances by the
California quail *Lophortyx californicus* under such inimical circumstances
inhibits reproduction and so results in a lowered demand upon the available
food resources. If the European quail is similarly susceptible to
this mechanism of population control it seems likely that the flesh
of birds coming from the African desert in spring or from southern
Europe in autumn after an unusually dry season would contain isoflavones.
There is no immediate reason to connect these substances with quail
myopathy, but from the experts I have asked, I gathered that there is

little information about their effects on man, and probably none at all about individual idiosyncratic sensitivity due to a biochemical defect.

Finally, the mycologist, Mr. Peter Austwick, was kind enough to examine the specimens from Lésvos. He found nothing to warrant further mycological investigation. This was of course another shot in the dark. The best known mycotoxin, aflatoxin, does not come into consideration since its primary short-term action is on the liver.

Notes on Rhabdomyolysis

Berlin (12) calls Haff disease "myoglobinuria paroxysmalis;" Ouzounellis (9) regards poisoning by quail as a "myoglobinuric syndrome." Both diseases appear to be selective in their incidence, some exposed persons being affected and others not. Muscular exertion predisposes susceptible persons to poisoning by quail, and muscular exertion may well be a factor in precipitating Haff disease which is common among fishermen.

Myoglobinuria is a sign of disease, not the disease itself. It is a result of injury to skeletal muscle, and we shall follow the recommendation of Gitin and Demos (26) by discussing rhabdomyolysis, the disease, rather than the myoglobinuria, which is a frequent but not invariable feature.

As noted by Adams. (14), "the whole subject of the disorders giving rise to myoglobinuria remains unsettled." Injury to skeletal muscle being the common feature, it is not surprising that exertion frequently plays a part as main cause or as a contributing influence. Exertion if sufficiently severe can probably cause rhabdomyolysis in absence of other predisposing factors: it has been recorded after a baseball game (27), after Conga drumming (28), and after kicking a wall in karate practice (29). Professor Walton tells me that extreme exertion often results in local injury of the anterior tibialis muscle in physically unfit persons, with necrosis and myoglobinuria, leading to acute kidney failure and sometimes death. Now that the syndrome has been recognized and given a name, acute exertional rhabdomyolysis (30), its incidence among people occupationally forced into excessive physical exertion is attracting increasing attention. Its importance in military medicine (26) has been established in two studies of Marine recruits undergoing training in California (31) (32) and in South Carolina (30). In SC myoglobinuria was found at least once in two thirds of the trainees despite absence of clinical symptoms, and in California the proportion was 39.2%. In uncomplicated cases the main symptoms are proximal muscle pain and weakness, and excretion of dark urine. Biochemically there are increases in serum creatine phosphokinase (CPK), lactic dehydrogenase (LDH), and glutamic-oxalic transaminase (GOT) which correlate well with the serum myoglobin concentrations (28). Although only a few recruits had to be hospitalized, the dangers of repeated episodes of myglobinuria are well known, with oliguria, anuria and death ensuing in extreme cases. When inborn defects are

present, other dangers as yet unrecognized may eventually manifest themselves. A case in point is a recorded death from sickle-cell disease precipitated and exacerbated by exertional rhabdomyolysis (33). A point of particular interest in connection with poisoning by quail is that acute exertional rhabdomyolysis may affect healthy individuals who have had no previous episodes of muscular pain, weakness or dark urine after exercise, and no family history of muscle disease (26).

At the other extreme there are the spontaneous acute attacks of muscle necrosis, brought on sometimes, but not always, by mild exertion. These were described in 1910 by Meyer and Betz and, the etiology being unknown, have since been dubbed "idiopathic primary recurrent rhabdomyolysis" or some permutation of these and other terms. Sometimes they are called, more simply, Meyer-Betz disease. The disease is characterized by paroxysmal attacks of generalized muscle pains, accompanied by myoglobinuria, and leading sometimes to permanent muscular degeneration (34) (35) or to circulatory collapse and anuria (14) (34). Genetic factors may enter, and on the basis of cases in three brothers, two sisters, and a brother and sister, an autosomal recessive pattern of inheritance has been discerned (35).

Between the extremes of primary inborn rhabdomyolysis and the acute exertional rhabdomyolysis of normal persons there are a number of types of rhabdomyolytic occurrence in which causes other than exercise can be identified or strongly suspected—although, to be sure, exercise even then may sometimes be a contributing influence. Aside from those involving gross insult to the muscles (e.g., crushing, electric shock, myocardial infarction) or the intervention of parasites (e.g., trichinosis), the causes can be described in terms of (a) inborn metabolic (bio-chemical) defects or (b) uptake of toxic substances. Typically these two classes are distinct. Toxic effects are readily identified, for instance, in cases of snake bite (36)(37), wasp sting, or alcohol (26). Inborn metabolic defects on the other hand will be detectable only by the demonstration of unusual gross differences in susceptibility among exposed members of a population and establishment of a pattern of inheritance of an abnormal muscular response to (for example) exercise or diet.

Writing in 1967, Lapresle *et al* (38) identified six muscular diseases associated with enzymatic anomalies. Of these, the so-called McArdle syndrome has attracted attention in relation to the subject of this paper. The syndrome is a form of rhabdomyolysis brought on by light exercise (39). The original description (39) noted in a single patient the resulting muscular pain, weakness, stiffness and swelling. Ischemic work led to contracture. Blood lactate and pyruvate fell during aerobic exercise. These results were attributed to an inability of the muscle to convert glycogen to lactic acid. McArdle also thought it worth mentioning that the patient had three normal daughters. The presence of a glycogenolytic defect was confirmed by Schmid and Mahler (40). They removed a sample of muscle from a patient who could not do moderate exercise without suffering cramps and producing urine

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containing myoglobin. A homogenate of the muscle when incubated was unable to produce lactic acid at the normal rate, but this could be corrected either by adding the enzyme phosphorylase or by providing glucose-l-phosphate, a normal intermediate following the phosphorylase-catalyzed breakdown of glycogen. Subsequent work substantiated this and showed that the muscle sample could synthesize glycogen from uridine diphosphate and glucose *in vitro* (41). A most unusual circumstance (42) made it possible to typify the disease genetically in a convincing manner. Three cases occurred among 13 siblings of a family of Portuguese extraction, the parents of whom, both normal, were first cousins from the Azores. Furthermore, six out of 31 members of the third generation were medically examined and the histories of the remainder were available: none of them showed any unusual response to exercise. The disease, accordingly, was attributed to "a single, *completely recessive, rare, autosomal gene*" (42).

The diseases associated with eating quail or fish under circumstances already described seem to have some of the properties of both toxic and exertional rhabdomyolytic syndromes. The consequences of an enzymatic defect are triggered both by physical exertion and by the action of substances which are toxic only in presence of the defect, while they are innocuous to the "normal" person.

FAVISM

Inborn sensitivity to otherwise harmless substances, such as that postulated above in the case of Haff disease and poisoning by quail, has been much studied in the case of favism, the hemolytic anemia that results from eating the broad (fava) bean *Vicia fava.* This, as well as the hemolysis caused in some persons by primaquine and certain other antimalarial drugs, is a condition based upon a lack of normal concentrations of glucose 6-phosphate dehydrogenase in the red blood cells. There is no evidence that this is the defect underlying the toxicity of fish and quail, but the prevalence of G6PD deficiency and favism among the Mediterranean peoples make the comparison an obvious and an attractive one. Favism is common in Lésvos: Hadjigeorge and Ouzounellis (43) have described 60 cases, with 8 deaths. They note the extreme variations in sensitivity among susceptible persons and, in some, its sporadic nature. Others, referred to in (44), have reported that the incidence of clinical favism in a random group of G6PD-deficient subjects is less than 30%. Prolonged malnourishment may be a contributing factor (43).

It was of interest, if only a shot in the dark, to see whether there might be a pattern of G6PD deficiency in patients who had had a rhabdomyolytic episode after eating quail. I was able to carry samples of blood from such persons and normal controls in B-D "vacutainers," packed in ice, from Lésvos to Genova. There they were delivered to Professor Emanuele Salvidio of the Department of Hematology, University of Genova, whose colleague Dr. Franco Ajmar screened them for certain enzymes and for abnormal hemoglobins. Use of an unpublished

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screening routine devised by Dr. H. Frischer revealed no differences
among the samples in the following enzymes:

glucose 6-phosphate dehydrogenase   G6PD
6-phosphogluconate dehydrogenase   6PGD
glutathione reductase   GSSG-R
adenylate kinase   AK
phosphoglucose isomerase   PGI
phosphofructo kinase   PFK
fructoaldolase   FA
glyceraldehyde 3P dehydrogenase   GA3PD

The negative results for G6PD were confirmed by starch gel electro-
phoresis at pH 8.6 by Bowman's method, revealing no variants; G6PD
was type B+ and 6PGD was type A. Electrophorsesis using the same
system showed absence of abnormal hemoglobins.

These negative findings should not deter us from the pursuit
of clues offered by the study of favism. There are two considerations
that may be worth suggesting with due caution:

First, the myoglobinuric manifestation of rhabdomyolysis arises
presumably from muscle cell lysis, and it may be guessed that cell lysis
and repair are dependent upon factors *analogous* to those causing or
preventing hemolysis. The hemolysis of favism is brought about, by
a still unknown mechanism, as a result of G6PD deficiency. This may
well be the case also for myolysis, but I do not know (though perhaps
it is known) whether muscle G6PD is the same as red cell G6PD, nor do
I know whether demonstrated red cell G6PD deficiency necessarily means
a similar deficiency in the skeletal muscle cells, or a different pattern
of distribution of isozymes. To this extent the negative results just
reported on the blood enzymes are not relevant to the question of poisoning
by quail. The importance of G6PD in the repair of muscle is shown,
however, by the recent observation of Wagner, Kauffman and Max (45)
that G6PD activity rises "dramatically" during the early stages of
regeneration after injury caused by a myotoxic local anesthetic.

Second, it is now known that the severity of the hemolytic crisis
in favism is dependent, *inter alia*, upon the phenotype of erythrocyte
acid phosphatase present in the G6PD-deficient subject, the frequency
of carriers of certain alleles of the autosomal gene (P^a and P^c) being
higher in people subject to clinical favism than in the general population
(46). At the same time the presence of a high level of type A2 hemo-
globin typical of the β-thalassemia trait, exerts a protective effect
on carriers of the P^a allele (47). A clue to the mechanism of this
association between favism and the genetic make-up of the subject in
regard to the production of particular isozymes lies in the observation
that the various isozymes of red cell acid phosphatase are not identical
in their sensitivity to partial inactivation by oxidized glutathione
or acetylphenylhydrazine. The same may be true of the effects *in vivo*
of the toxic substances in the fava bean. As Bottini *et al* remark (48):

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"... the different sensitivity of the isozymatic fractions towards toxic agents could result, in special environmental conditions, in a different viability of the different acid phosphatase genotypes, the genotype which causes the most stable isozymatic combination being the most viable one." It is possible though not proven that these differential sensitivities of the phosphatase isozymes may underlie the occurrence of "favism minor," or non-hemolytic favism, a syndrome recognized by mild headache, uneasiness, weakness, vomiting and dizziness. The hypothesis of a type of favism determined by a recessive autosomal factor without *G6PD* deficiency was suggested by Sartori, cited by Bottini (44); the latter, however, mentions the difficulty of arriving at a clearcut diagnosis of favism minor and questions its occurrence in Italian populations other than those in Sardinia studied by Sartori.

CURRENT WORK ON POISONING BY QUAIL

Ouzounellis is pursuing his studies as cases of poisoning occur. In some respects, in the present state of knowledge, it is a matter of patient detective work - seeking, for instance, the guilty kind of seed in flocks of quail among which toxic specimens have been found; examining the geographical distribution around the Mediterranean of the plants which were identified at Kew (p. 11))and seeking a correlation with the incidence of poisoning in those areas.

The identification of susceptible individuals has become rather more reliable as a result of a recent practice intended to protect them against severe poisoning without denying them the pleasure of eating quail. Each bird is divided so as to provide equal servings for each member of the party - a difficult feat, I should think, and quite tiresome for those with healthy appetites who may well be in the habit of eating several whole quail in one sitting. However, Dr. Ouzounellis assures me that it is being done, and the results have been interesting. "Many cases of intoxication was observed....Always one person was affected wherefor the others did not present any symptoms. *In some cases in which two or more persons were affected those persons belonged to the same genetical tree*" (10).

One of these families has unwittingly provided an additional bit of information which may prove to be significant. This concerns an infant child whose father had been poisoned twice and the grandfather three times. The infant vomited after feeding and developed jaundice, hepatomegaly and gross ascites and, in serious condition, was sent to London for treatment after efforts elsewhere had failed. There the cause of the trouble was found to be sucrose, and it was cured by giving glucose instead. Further tests led to identification of the syndrome as hereditary fructose intolerance (49). The initial difficulties in treatment were due to a secondary disturbance of tyrosine metabolism which had suggested a diagnosis of the rare disorder tyrosinosis in which tyrosine is excreted instead of being degraded to

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homogentisic acid. Members of this family also submitted to chemical
tests which showed that their blood lactate concentration increased
in a normal manner during anaerobic exercise, distinguishing them from
cases of McArdle's syndrome where blocked glycogenolysis prevents lactic
acid accumulation (42).

External cooperation is available to a limited extent. Enzymological
studies of muscle taken from victims of poisoning by quail are projected
in cooperation with the neurologist Professor Theodore Papapetropoulos
of Aiginition Hospital in Athens. In the USA the subject has attracted
Dr. Louis Grivetti of the Department of Avian Sciences, University
of California, Davis. Grivetti's research student, Bruce W. Kennedy,
having returned to Davis from a visit to Lésvos, is setting up a program
for investigation of two alternative hypotheses: the toxic seed hypothesis
and the hypothesis, which I have not discussed in this paper, of a
toxic metabolite produced under the stress of migration.

THE QUAIL IN RECENT BIOLOGICAL AND BIOMEDICAL RESEARCH

The quail, its survival threatened by the depredations of hunters,
has been granted a reprieve consequent upon its new popularity as an
object of research in atherosclerosis, embryology, endocrinology,
photoperiodicity, immunology, and many other subjects. Though of course
largely restricted to the Japanese quail, *Coturnix coturnix japonica*,
bred in captivity and thus not subject to the stresses of migration,
the bird is available for controlled experimental work relevant to
the question of toxicity. By the same token, a solution to the problem
of the toxic quail under natural conditions would be useful in laboratory
studies, many of which concern genetic polymorphism and the effects
of toxic materials, from heavy metals and selenium all the way to alfalfa
saponins, DDT, and ochratoxin.

The unsupported hypothesis of a toxic metabolite produced under
stress—mentioned in the preceding section—could be tested under labo-
ratory conditions by extending published experiments on the metabolic
effects of heat and cold. It has been found, for example (50), that
if food intake is restricted, cold stress induces glycolysis, lipolysis,
and perhaps proteolysis with the possibility of gluconeogenesis from
the products of protein breakdown. No doubt the energy for flight
during migration comes from metabolic stores rather than from food
recently eaten, and in birds with particular enzymatic abnormalities
the production of unusual metabolites, toxic perhaps to man under some
conditions, is conceivable.

DISCUSSION

Recapitulation

The flesh of certain quail during the migrating seasons apparently
contains the agent which causes, in susceptible individuals, a

rhabdomyolytic illness when they eat the flesh. Susceptibility is inherited according to a pattern yet to be established. It is enhanced, or the attack precipitated, by muscular exertion. The lytic process, as in other rhabdomyolytic syndromes, is specific for skeletal muscle cells and evidence of hemolysis is generally lacking.

This lytic syndrome resembles no other in every detail, but has important similarities to, and differences from, some. It resembles most closely Haff disease, also of unknown etiology, caused by eating certain fish, though the part played by muscular exertion has not been stressed in the published accounts. Exercise alone, if sufficiently strenuous, can produce acute rhabdomyolysis in normal persons. Very light exercise or none at all can do the same in some people (Meyer-Betz disease). A deficiency in muscle phosphoryase is a predisposing condition for a rhabdomyolytic response to mild exercise (McArdle's syndrome). Substances which are toxic for everybody, like alcohol or snake venom, may also produce rhabdomyolysis.

The selectively toxic agent in quail is analogous to the substance or substances in fava beans which cause hemolysis in persons deficient in glucose 6-phosphate dehydrogenase, the severity of the hemolytic crisis being greater when the person's acid phosphatase is of certain relatively unstable isozymatic types. Hemolytic crises of different sorts are also characteristic of thalassemia and sickle-cell disease, which deserve mention here because the susceptibility to favism is lessened in presence of the thalassemia trait, and, indeed, by other factors in the genetic background of the individual.

Questions and Approaches

The mysteries surrounding poisoning by quail are not solved by this comparison with other rhabdomyolytic and hemolytic illnesses, but it is useful to show that it has a place in the field of biochemical genetics, especially when one considers that some of the most evident parallels and analogies are to be found in hereditary defects that are prevalent among the peoples of the Eastern Mediterranean. It would be interesting to discover whether, despite the apparent specificity of some of these defects for red blood cells or for skeletal muscle, there may be some common ground which would emerge in some sufficiently comprehensive study. It would be useful to do for myoglobin and the enzymes of muscle what has already been done in considerable, but still insufficient, detail for hemoglobin and the red blood cell. One thinks of Guido Modiano, Egidio Bottini and their colleagues in the Centre for Studies in Evolutionary Genetics, University of Rome, whose extensive work on red cell enzyme polymorphisms in relation to hemolytic disease and malaria provides a pattern for an attack on the cross-reactions between inherited defects responsible for lytic disease of muscle, and their possible manifestation or concealment in hemolytic systems.

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At the level of specific limited questions posed by toxic quail, observational or experimental points can be raised; for instance:

(1) The frequent association of rhabdomyolysis after eating quail with severe and perhaps unaccustomed muscular exertion during the hunting season suggests that in some instances, at least, the apparent toxic effects of the quail may be coincidental and perhaps unreal. The illness should then be diagnosed as simple exertional or non-toxic rhabdomyolysis. This possibility should be considered when evaluating collected data with regard to incidence within families, etc.

(2) The analogy to favism suggests that the search for seeds known to have toxic properties may be irrelevant. Attempts to identify an otherwise harmless substance which is toxic only to susceptibile persons is hampered by lack of independent criteria for detection of susceptibility, but attention might be directed to compounds known to be ingested by quail under exceptional circumstances, such as the plant estrogens or the phytohemagglutinins. There may well be some among them for which idiosyncratic sensitivities exist. An experimental approach is possible: Extracts of quail muscle could be tested for their effect on muscle enzymes, with the thought that any inhibitory effects observed might be decisive only in individuals possessing unusually low concentrations of these enzymes or unusually high proportions of particularly sensitive isozymes. The analogous case of red cell acid phosphatase and susceptibility to favism has been mentioned.

(3) The symptomatology of poisoning by quail as described by different observers is not entirely consistent, especially between the disease in Algeria as described by Sargent and in Lésvos by Ouzounellis. A cooperative study covering the two areas, and seasons, is much to be desired, as well as more assiduous reporting of cases elsewhere. It is interesting that cases have occurred in Lésvos alone among the Greek islands, although there are many other islands along the route southwards from there to the open sea. There are apparently no records from the east coast of Asia Minor.

Beyond the framework of these limited considerations are the many unresolved questions raised by the migratory habits of the quail. An understanding of the aerodynamics of flight, so surprisingly efficient for such an ungainly object, must underly any reliable formulation of the energetics and of the metabolic mechanisms involved. Water conservation is likely to prove of major importance—water loss being controlled in this animal by a muscular flutter in the throat rather similar to panting—and the modification of metabolic pathways when the bird is dehydrated could be significant. With the recent popularity of the Japanese quail as a research object these questions could at least be approached, if not exhaustively explored, in the laboratory.

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