Radioisotope Scanning of the Liver and Spleen in Dextrocardia and in Situs Inversus with Levocardia

By Kishor D. Shah, M.D., Catherine A. Neill, M.D., M.R.C.P., Henry N. Wagner, Jr., M.D., and Helen B. Taussig, M.D.

Knowledge of the position of the abdominal organs is important in cardiac diagnosis. Thus a mirror-image dextrocardia is usually observed in a patient with complete situs inversus; this condition more frequently occurs in an otherwise normal individual than in one with a malformed heart. By contrast, when dextrocardia occurs without situs inversus, malformation of the heart is the rule. When the heart occupies its normal position but situs inversus of the viscera is present, the heart is almost always seriously malformed.

Partial situs inversus is now known to be relatively common in patients with dextrocardia and severe multiple intracardiac defects and is occasionally seen in patients with levocardia. The term “visceral heterotaxy” has been used to denote partial situs inversus with a midline cecum or a symmetrical liver and is common in association with asplenia. Asplenia, although rare, is usually associated with severe cardiac malformations. Accurate localization of the liver may be difficult, especially if its lobulation is unusual or its contour symmetrical. Although the spleen when present uniformly lies on the same side as the stomach, the diagnosis of asplenia is uncertain. An ancillary method for the demonstration of the position of the liver and spleen appeared desirable.

Radioisotope scanning of the liver was first described by Friedell et al. The basic principle of this method is the visualization of the liver by determining the spatial distribution of an intravenously injected radioisotope that is selectively taken up by the liver. The areas of maximal radioactivity are recorded as dark areas on x-ray film. By superimposition of the scanning image on a roentgenogram of the abdomen made with the patient lying in the same position on the scanning table, the size, shape, and position of the liver can be determined. The substances used for liver scanning have included rose bengal, a dye labeled with radioactive iodine, or a colloidal suspension of radioactive gold.

Radioisotope scanning of the spleen with chromium-tagged, heated red cells was first described by Wagner et al. They showed that in patients who had undergone splenectomy or who had splenic atrophy due to longstanding sickle-cell anemia, the labeled red cells were taken up by the liver instead of the spleen. It was therefore hoped that spleen scan might be of value in the detection of asplenia.

The value of scanning was brought to our attention by the following case. A newborn infant, C.F., no. 990425, was seen at The Johns Hopkins Hospital in 1961. X-ray and fluoroscopy revealed a large nonpulsatile shadow in the region of the left precordium. Angiocardiography showed the heart pushed upwards and to the right (fig. 1a). Radioisotope scanning of the liver showed that the left lobe of the liver had herniated upwards through the foramen of Morgagni and had caused the cardiac displacement (fig. 1b).

It was therefore decided as part of a continuing study on dextrocardia to evaluate the technic by undertaking liver and spleen scanning in a small series of patients with ab-
normalities in the position of the heart and viscera.

Material and Methods

A series of 10 patients was studied, five with dextrocardia and five with levo cardia and situs inversus. There were four males and six females and the age distribution ranged from 2 months to 24 years (table 1).

Dextrocardia was said to be present when the heart lay in the right hemithorax and the cardiac apex pointed to the right. Since the arrangement of the ventricles was not analyzed in this study, such terms as dextroversio n and dextrorotation are not used. Five patients had dextrocardia, two with situs inversus and three with normal position of the viscera.

Situs inversus was considered to be present when the stomach lay on the right side. The position of the stomach was determined in all patients by a barium swallow and was confirmed by the water test in all except case 8. This latter test consists of percussing for stomach tympany and then auscultating for water gurgling after the patient drinks a glass of water. The stomach lay on the right in two of the two patients with dextrocardia and in all five of those with situs inversus and levo cardia.

Scanning of the liver was carried out by the intravenous injection of 10 to 100 μc of silver-coated colloidal gold (Au^{198}). The shape, size, and lobulation of the liver were identified by the area of maximal radioactivity on the scan. On a normal scan the right lobe of the liver not only appears larger than the left but also contains a

Figure 1

Infant with diaphragmatic hernia. A, left. Venous angiogram showing heart pushed upwards and to right. B, right. Liver scan: Left lobe of liver herniated through foramen of Morgagni into left chest causing cardiac displacement.

Figure 2

### Table 1

<table>
<thead>
<tr>
<th>Case no. and J.H.H. no.</th>
<th>Race, sex</th>
<th>Age (yr.) at time of scan</th>
<th>RA</th>
<th>IVC</th>
<th>SVC</th>
<th>Cardiac findings, diagnosis</th>
<th>Card. cath.</th>
<th>Angio</th>
<th>Stomach x-ray and water test</th>
<th>Liver X-ray Scan</th>
<th>Spleen Scan</th>
<th>Hb</th>
<th>Autopsy</th>
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<tr>
<td><strong>Dextrocardia without situs inversus</strong></td>
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<tr>
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<td>W/F</td>
<td>10</td>
<td>L</td>
<td>Ab</td>
<td>L</td>
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<td>+</td>
<td>+</td>
<td>L</td>
<td>R</td>
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<td>L</td>
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<td>2. S.V. 377702</td>
<td>W/F</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td>?TGV + PS, ?T/F RBTS '45</td>
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<td>L</td>
<td>R</td>
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**Dextrocardia with situs inversus**

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<tr>
<th>Case no. and J.H.H. no.</th>
<th>Race, sex</th>
<th>Age (yr.) at time of scan</th>
<th>RA</th>
<th>IVC</th>
<th>SVC</th>
<th>Cardiac findings, diagnosis</th>
<th>Card. cath.</th>
<th>Angio</th>
<th>Stomach x-ray and water test</th>
<th>Liver X-ray Scan</th>
<th>Spleen Scan</th>
<th>Hb</th>
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<tr>
<td>4. R.R. 899054</td>
<td>W/M</td>
<td>13</td>
<td>“L”</td>
<td>Ab</td>
<td>R</td>
<td>TGV + PS, single ventricle, large ASD</td>
<td>+</td>
<td></td>
<td>R</td>
<td>L</td>
<td>L</td>
<td>Tri-lobed</td>
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<td>5. D.D. 885870</td>
<td>W/F</td>
<td>14</td>
<td>L</td>
<td>Ab</td>
<td>L</td>
<td>TGV, + PS, VSD, single atrium</td>
<td>+</td>
<td>+</td>
<td>R</td>
<td>L</td>
<td>R</td>
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**Situs inversus with levocardia**

<table>
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<th>Case no. and J.H.H. no.</th>
<th>Race, sex</th>
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<th>RA</th>
<th>IVC</th>
<th>SVC</th>
<th>Cardiac findings, diagnosis</th>
<th>Card. cath.</th>
<th>Angio</th>
<th>Stomach x-ray and water test</th>
<th>Liver X-ray Scan</th>
<th>Spleen Scan</th>
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<td>W/F</td>
<td>11</td>
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<td>Ab</td>
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<td>Ost. primum, Cleft MV</td>
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<td>R</td>
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<td>L</td>
<td>AVComm., TGV, PS</td>
<td>+</td>
<td></td>
<td>R</td>
<td>L</td>
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The apparatus used is shown schematically in Figure 2. Liver scan was performed on five patients. Details of the technic were as described by Wagner et al.4

Liver scan was performed on five patients (Table 1). Scanning of the spleen was performed in a total of eight patients. In seven, the patient's own red cells were withdrawn, labeled with radioactive chromium (Cr51), heated at 50°C for 1 hour, and then reinjected intravenously.5 In one patient, the red cells were labeled with Cr51, damaged with N-ethyl maleimide, and reinjected intravenously without heating. Results

<table>
<thead>
<tr>
<th>Case</th>
<th>Dextrocardia without Statis Inversus</th>
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**Abbreviations:** R, right; L, left; Ab, absent; HB, Heinz bodies; Sym, symmetrical; bilat. activ., bilateral activity; RA, right atrium; SVC, superior vena cava; IVC, inferior vena cava; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; RBTS, right-sided subclavian pulmonary anastomosis; P. atresia, pulmonary atresia; MV, mitral valve; TAVR, total anomalous pulmonary venous drainage; TGV, transposition great vessels; PS, pulmonary stenosis; AVComm., atroventricular communis; Ost. primum, ostium primum defect; T/F, tetralogy of Fallot; PV, pulmonary vein; Portal V, portal vein; Cor biloc, Cor biloculare; Cong. ht. block, congenital heart block.

Blank space (as in case 2, S.V.); no information available.

* Bilateral distal inferior venae cavae noted at autopsy but no direct connection with atrium demonstrated.

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leads first suggested the presence of atrial inversion. Angiocardiography and catheterization studies confirmed this. The patient has thus been diagnosed as having atrial inversion without abdominal situs inversus, an extremely rare combination. Her electrocardiographic and other cardiac findings are reported in detail elsewhere.9, case 7

Case 2, a 24-year-old cyanotic woman, had been followed since childhood with a tentative diagnosis of either tetralogy of Fallot or transposition of the great vessels with pulmonic stenosis. A liver scan showed a normal right-sided liver with a slightly enlarged left lobe. Despite severe cyanosis, she refused further investigation.

Case 3 was a severely ill, cyanotic infant suspected of asplenia because of the association of a complex cardiac malformation with isolated dextrocardia and a midline symmetrical liver demonstrated both clinically and by x-ray.10 Heinz bodies were found in the peripheral blood.11, 12 The findings on spleen scan were compatible with asplenia and are discussed in detail later with the analysis of cases 8 to 10.

Dextrocardia with Situs Inversus

Both patients in this group had complex cyanotic cardiac malformations associated with pulmonic stenosis and transposition of the great vessels. One had only a liver scan performed and the other only a spleen scan.

Case 4, a 13-year-old cyanotic white boy, was found on physical examination to have a slightly enlarged heart lying in the right hemithorax. X-ray and water test showed the stomach on the right. The liver was enlarged and bilaterally symmetrical on clinical examination and by x-ray. Selective angiocardiography showed the inferior vena cava to be absent; the catheter was passed from below the diaphragm to enter the superior vena cava by an azygos vein. Three hepatic veins (fig. 4a) could be seen entering the right atrium immediately to the right of the midline. The left hepatic vein seemed slightly larger than the other two. Liver scan (fig. 4b) showed a trilobed liver, the maximum intensity of radioactivity being on the left side. The right border of the liver did not reach the lateral abdominal wall, suggesting that the spleen was located in this region; a spleen scan, however, was not performed.

In addition to single ventricle, transposition of the great vessels, and pulmonic stenosis, a very large atrial septal defect was present. The systemic venous atrium appeared to lie to the left of the midline although the only superior vena cava demonstrated entered it from the right. Although abdominal situs inversus was present in that the stomach lay on the right and the larger lobe of the liver was on the left, it is of great interest that the liver appeared midline and symmetrical due to three lobes of approximately equal size. This
case may represent an intermediate stage between a true situs inversus and what is known as visceral heterotaxy.

Case 5 underwent a spleen scan with Cr\textsuperscript{51}-labeled, heated red cells; this revealed a normal-sized spleen lying in the right hypochondrium (fig. 5).

\textbf{Situs Inversus with Levocardia}

The five patients in this group all had major cardiac defects. Four were cyanotic. Because of the high incidence of asplenia in such patients a spleen scan was performed in each of this group.

A right-sided spleen was visualized in cases 6 and 7. The spleen scan in case 6, an 11-year-old girl with an ostium primum defect, is illustrated in figure 6. The spleen, which is of normal size, lies in the right hypochondrium near the stomach gas bubble. This scan was obtained with Cr\textsuperscript{51}-labeled, heated red cells.

Asplenia was diagnosed in the remaining three patients in this group and the diagnosis was confirmed at autopsy in case 8. This 2-month-old white infant had been cyanotic from the first day of life. The stomach lay on the right and the liver was thought clinically and on x-ray to lie on the left. Barium enema revealed a midline cecum. Asplenia was thought probable on clinical grounds because of the cardiac diagnosis of cor biloculare and pulmonary atresia, a midline cecum, and furthermore because of the presence of Heinz bodies in the peripheral blood. Spleen scan was performed with Cr\textsuperscript{51}-labeled, heated red cells. The spleen was not visualized and the labeled red cells were taken up by the liver (fig. 7). Similar findings were obtained on a spleen scan in the other autopsy-proved case of splenic agenesis (case 3), in whom no visualization of the spleen was obtained following intravenous injection of chromium-tagged, heated red cells but the tagged cells were taken up by the midline symmetrical liver.

Case 9 was an infant of 7 months with cor biloculare in whom Heinz bodies were demonstrated in the peripheral blood. Spleen scan with red cells labeled with Cr\textsuperscript{51} and damaged by N-ethyl malleimide showed activity in the left hypochondriac region and a little activity in the right hypochondrium. The scan was at first interpreted as indicating a left-sided spleen: inasmuch as the stomach lay on the right, this interpretation was recognized as untenable. A liver scan with colloidal gold clearly showed bilateral symmetrical ac-
asplenia, the evidence for this must be considered as inconclusive.

Discussion

The development of the abdominal viscera, especially the liver, is closely related to the growth of the venous system and also to atrial position. Multiple systemic and sometimes pulmonary venous anomalies are characteristic of visceral inversion.

The development of the liver begins in horizon 11. The hepatic diverticulum arises ventrally from the entodermal lining of the gut during the fourth week of embryonic life. As early as 6½ weeks the bilateral symmetry characteristic of the primitive liver and primitive posterior cardinal veins are normally replaced by a right-sided dominance, the right lobe of the liver being the larger and the inferior vena cava, on the right, having replaced the bilateral posterior cardinal veins. Little is known of the embryology of dextrocardia or of situs inversus. As Taussig has stated, however, the presence of a normal inferior vena cava is dependent on the simultaneous development of the major lobe of the liver on the same side as the right or systemic venous atrium. The high incidence of absence of the inferior vena cava in the present series confirms Taussig's observation. In addition, cases 4 and 5 suggest that the inferior vena cava may also be absent when situs inversus and dextrocardia are associated with complicated

Figure 5

Case 5, D.D. Spleen scan showing right-sided spleen in patient with dextrocardia and situs inversus. Note stomach gas bubble on right.

tivity. Superimposition of the spleen scan over that of the liver showed similar contours, indicating that the n-ethyl maleimide-damaged red cells had all been taken up by the liver. The diagnosis of asplenia remains unproved in this patient but is considered highly probable because of the similarity of the scan to that in the two proved cases of asplenia.

Case 10 was a slightly cyanotic 6-year-old girl with a cardiac diagnosis of single atrium and congenital heart block in whom both liver and spleen scans were performed. The patient was in chronic congestive failure and the enlarged liver could be felt to extend almost to the umbilicus and appeared midline and symmetrical. A liver scan (fig. 8) confirmed the midline liver but suggested that it was a multilobular rather than a strictly bilobed structure and that more activity was present on the left than the right. Twenty-four hours following this test a spleen scan was performed with chromium-tagged, heated red cells. Slight activity seen in the left hypochondrium was attributed to persistence of radioactivity in the liver. Unlike the other cases of asplenia, the red cells were not clearly taken up by the liver, possibly attributable to inadequate heating of the red blood cells. The child died in congestive failure before the study could be repeated and no autopsy was obtained. Although the scan was thought suggestive of

Figure 6

Case 6, C.V. Spleen scan showing right-sided spleen in patient with situs inversus and levocardia.
cardiac anomalies including major defects in atrial septation. When the hepatic portion of the inferior vena cava is absent, the hepatic veins enter the atrium directly while the subhepatic venous drainage travels by a vein, which probably represents a persistent posterior cardinal vein, to enter the superior vena cava via an enlarged azygos.\textsuperscript{17, 18}

The development of the spleen is closely associated with that of the stomach. Splenic primordia appear about the end of the fourth week (horizon 15) as poorly defined irregular areas of thickening in the dorsal mesogastrium.\textsuperscript{19} These thickened areas or hillocks subsequently fuse to form a smooth spleen. The high incidence of asplenia in situ inversus with levocardia and the severity of the cardiac malformations associated with this condition were emphasized by Ivemark.\textsuperscript{2} Teratogenic agents, as yet unknown, are assumed to arrest splenic development completely and simultaneously arrest normal cardiac and conotruncus partitioning.

Asplenia and visceral heterotaxy can be thought of as a primitive arrest of development at the symmetrical stage. (Although symmetry is characteristic of the external appearance of the mammal,\textsuperscript{*} the development of internal asymmetry is an essential part of evolutionary and embryonic maturity.) In its most extreme form, well illustrated by cases 3 and 8, there are asplenia, bilateral symmetrical liver, midline cecum, and malrotation of the gut. The heart may show dextrocardia (case 3) or levocardia (case 8) but the intracardiac malformations are very similar, consisting of a cor bilocular due to a large atrioventricular communis-type of defect with a single atrioventricular valve. Major anomalies of both systemic and pulmonary venous return occur with such lack of partitioning of the atrium and variation in venous return as to make identification of either atrium as “right” or “left,” “systemic” or “pulmonary” meaningless.\textsuperscript{1} This abnormal symmetry occurs in the viscera, the venous system, and the atria. The arterial anomaly most frequently encountered and exemplified in case 3 is an extreme conotruncus malformation with a large anterior transposed aorta arising from the ventricle with the trabeculated internal structure characteristic of the right ventricle. The pulmonary artery is a thin fibrous atretic cord arising posteriorly close to the defective ventricular septum.\textsuperscript{1, 2}

The importance of asplenia is of more than academic interest, as a number of investigators

\textsuperscript{*} Blake (on the tiger): “What immortal hand or eye dared shape thy fearful symmetry”
RADIOISOTOPE SCANNING OF LIVER AND SPLEEN

have stressed the disposition to infection in asplenic patients. Serious meningeal infections have been reported under the age of 10 months in such patients. Such infections are also known to occur after splenectomy. Of the 10 cases reported by Hjelt and Hakosalo,12 only three had escaped infections. All four patients with asplenia in our series gave a history of frequent respiratory infections.

The hematologic findings in peripheral blood in patients with asplenia were stressed by Willi and Gasser.11 They consider Heinz bodies and Howell-Jolly bodies in erythrocytes and numerous erythroblasts in peripheral blood pathognomonic for asplenia. Heinz bodies were found in two of our cases, erythroblasts were not seen in any case.

Asplenia with pulmonary stenosis or atresia, classified as type II by Ivemark,2 may mimic tetralogy of Fallot, and death has occurred after minor surgical procedures, tonsillectomy, adenoidectomy, etc. in these cases. These have usually occurred under 1 year of age. The prognosis of asplenia is poor. In this series, three patients died at the ages of 2½ months, 14 months, and 6 years, respectively, while one is alive and is 8 months old. In 31 cases reported in the literature the mortality rate was 50 per cent before the age of 3 months and 75 per cent before the age of 9 months.

Liver scanning with colloidal gold appeared adequate for delineation of the liver in the five cases in the study. No particular difficulties of interpretation were encountered. The liver was right sided in the two cases of dextrocardia without situs inversus although the left lobe was somewhat larger than normal. The liver was left sided and trilobed in case 4 with dextrocardia and situs inversus. These three cases had dextrocardia associated with transposition of the great vessels and the lobularity of the liver in each was neither normal nor a true "mirror image" of the normal, just as the hearts were not "mirror images" of the normal. These cases suggest that the more complicated types of dextrocardia may show variation in lobularity of the liver comparable to the variations seen in the evolutionary development of this organ in the anthropoid.20

The role of scanning in the demonstration of these more subtle variations of lobularity may prove to be of great interest.

Bilaterally symmetrical livers were shown on scanning in the remaining two patients (cases 8 and 10): one has been proved and one is thought to have asplenia. Liver scanning thus seems to be of value in confirming the bilateral symmetry of the liver as a sign of asplenia.10

Pitfalls in interpretation may occur in the presence of marked hepatic insufficiency when the parenchymal and reticuloendothelial cells of the liver may fail to concentrate the radioactivity normally. This difficulty was, however, not encountered in the present series.

Spleen scanning was considered satisfactory in seven of the eight cases. A normal left-sided spleen was clearly visualized in case 1: technically better delineation probably would have been obtained had there been a longer time interval between liver and spleen scans. A right-sided spleen of normal size was visualized in cases 5, 6, and 7. In the two proved cases of asplenia (cases 3 and 8) the spleen was not visualized and the radioactive red cells were taken up by the bilaterally symmetrical liver. In one probable case (case 9) similar findings were observed. The accumulation of labeled red cells in the liver in these cases is similar to that described in patients in whom normal splenic tissue is absent due to surgery or atrophy.5 In case 10 the spleen was not visualized and the red cells were not clearly sequestered by the liver. Although asplenia would appear probable, the study was considered inconclusive. The technic thus appears useful in the localization of the spleen and in confirmation of the diagnosis of asplenia.

Pitfalls in this test may occur if the red cells are heated for too long a time; if this occurs they may be taken up by the liver and an erroneous diagnosis of asplenia made.

Radiation dosage by the above technics is small. The dose to the liver from colloidal gold (Au198) is 4 rads, to the spleen from Cr51-labeled red cells 4.7 rads. More recently the use of I131-labeled, aggregated human serum albumin rather than colloidal gold for liver
scanning has reduced the radiation dose to the liver by a factor of 100 to 200. The total body radiation from these procedures is 0.05 rad, which is less than many routine radiologic studies. No complications or untoward effects were observed in the present small series.

Summary and Conclusions

Radioisotope scanning of the liver and spleen was undertaken in 10 patients: five had dextrocardia and five situs inversus with levocardia. All had complicated cardiac malformations.

A liver scan with colloidal gold was performed in two patients and in association with a spleen scan in three. The liver was right sided in two patients with dextrocardia without situs inversus and both left sided and trilobed in one with dextrocardia, situs inversus, and a severely malformed heart. In 2 patients with splenic agenesis the liver appeared bilobed and symmetrical.

A splenic scan was performed in eight patients, with their own chromium-tagged, heated red cells in seven and N-ethyl malleimide-damaged red cells in one. A normal left-sided spleen was demonstrated in one patient without situs inversus; in three with situs inversus the spleen was right sided and of normal size. In two proved and one probable case of congenital asplenia no spleen was visualized, and the tagged red cells were sequestered by the liver: these findings are similar to those in absent spleen from other causes except that in congenital asplenia the liver is bilaterally symmetrical. In one case of possible asplenia the scan was inconclusive. The technic appears of value in demonstrating unusual variations of lobularity of the liver and in demonstrating the presence or absence of the spleen.

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SCANNING RADIOISOTOPE


Scientific Methodology

The theory of relativity is a fine example of the fundamental character of the modern development of theoretical science. The hypotheses with which it starts become steadily more abstract and remote from experience. On the other hand it gets nearer to the grand aim of all science, which is to cover the greatest number of possible number of empirical facts by logical deduction from the smallest number of hypotheses or axioms. Meanwhile the train of thought leading from the axioms to the empirical facts or verifiable consequences gets steadily longer and more subtle. The theoretical scientist is compelled in an increasing degree to be guided by purely mathematical, formal considerations in his search for a theory, because the physical experience of the experimenter cannot lift him into the regions of highest abstraction. The predominantly inductive methods appropriate to the youth of science are giving place to tentative deduction. Such a theoretical structure needs to be very thoroughly elaborated before it can lead to conclusions which can be compared with experience. Here too the observed fact is undoubtedly the supreme arbiter; but it cannot pronounce sentence until the wide chasm separating the axioms from their verifiable consequences has been bridged by much intense, hard thinking. The theorist has to set about this Herculean task in the clear consciousness that his efforts may only be destined to deal the death blow to his theory. The theorist who undertakes such a labor should not be carped at as "fanciful"; on the contrary, he should be encouraged to give free reign to his fancy, for there is no other way to the goal. His is no idle daydreaming, but a search for the logically simplest possibilities and their consequences.—ALBERT EINSTEIN. Essays in Science. New York, Philosophical Library, Inc., 1934, p. 69.
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